Title:	Brain Emotion Circuitry-Targeted Self-Monitoring and Regulation Therapy (BE-SMART)
HIC Protocol Number:	0407026910 Version: 6/20/22
IND #:	NCT03183388
Principal Investigator:	Hilary Blumberg, MD The John and Hope Furth Professor of Psychiatric Neuroscience, Professor of Psychiatry, Diagnostic Radiology & the Child Study Center Yale University School of Medicine 60 Temple St. Suite 6B New Haven, CT, 06510 Ph: 203-785-6180 Email: hilary.blumberg@yale.edu
Funding Sources:	**National Institute of Mental Health (NIMH)**

YALE UNIVERSITY SCHOOL OF MEDICINE
YALE NEW HAVEN HOSPITAL
HUMAN INVESTIGATION COMMITTEE

Application to Involve Human Subjects in Research

Title of Research Project: Genes and Brain Development in Disorders of Mood and Attention			
Principal Investigator: Hilary P. Blumberg, MD		**Yale Academic Appointment** The John and Hope Furth Professor of Psychiatric Neuroscience, Professor of Psychiatry, Diagnostic Radiology & the Child Study Center	
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SECTION I: PRINCIPAL INVESTIGATOR/FACULTY ADVISOR AGREEMENT

As the Principal Investigator or Faculty Advisor of this research project, I certify the following:

- The information provided in this application is complete and accurate.
- That I assume full responsibility for the protection of human subjects and the proper conduct of the research.
- That subject safety will be of paramount concern, and every effort will be made to protect subjects' rights and welfare.
- That the research will be performed according to ethical principles and in compliance will all federal, state and local laws, as well as institutional regulations and policies regarding the protection of human subjects.
- That all members of the research team will be kept apprised of research goals.
- That I will obtain approval for this research study and any subsequent revisions prior to initiation.
- That I will report to the HIC any serious injuries or other unanticipated problems involving risk to participants.

SECTION II: GENERAL INFORMATION

1. **Choose all that apply:** *(* See indicated section in HIC Guidelines for Investigators)*

☒ Children/minors* (Section E.1)
☐ Decisionally impaired* (Section E.2)
☒ Females of childbearing potential
☐ Radioactive Materials
☐ IND # _____
☐ Pregnant women/fetuses/placenta
☐ Prisoners
☐ Non-English Speaking
☐ Use of Employees
☐ Students

APPROVED BY THE YALE UNIVERSITY IRB 6/15/2023

☐ IDE # _____A or B (Section C.1)

2. Will this research study require the rendering of clinical care services to human subjects that may be billable to the subject, the sponsor or other third party payer?
   Yes ☐ No ☒ If you answered "yes", please register this study in the IDX/GE system at http://www.yalemedicalgroup.org/comply/alert/formtrain/NewStudyRequest.pdf

3. **Location of study:** Please identify the hospital, in-patient or outpatient facility, school or other agency that will serve as the location of the research.

☐ APT Foundation, Inc. ☐ Connecticut Mental Health Center ☒ Department of Veterans Affairs, West Haven
☐ Haskins Laboratories ☐ John B. Pierce Laboratory, Inc ☒ Magnetic Resonance Research Center (MR-TAC)
☐ PET Center ☐ Yale Cancer Center ☐ Yale New Haven Hospital HRU
☐ YCCI/Church Street Research Unit (CSRU) ☒ YCCI/Hospital Research Unit
☐ YCCI/Keck Laboratories ☒ Other locations, Specify: Mood Disorders Research Program, 60 Temple St. Suite 6B New Haven CT 06510

Please indicate the location(s) within the hospital and/or Medical School where the research will take place:
Scanning will take place at the Anlyan Building MRI Center, Interviewing at the Yale University School of Medicine, and the blood draw at the YCCI/Hospital Research Unit (HRU).

Please note: when other institutions are engaged in the research, it may be necessary to secure the approval of their Institutional Review Boards (IRB) and/or to insure that the institution has obtained a Federal Wide Assurance (FWA). Institutions may not list the Yale HIC as their IRB of record unless the Federal government has approved their FWA and they have in place a fully executed IRB Authorization Agreement between their institution and Yale University.

4. **Probable Duration of Project**: Please state the expected duration of the project, including all follow-up and data analysis activities. Sample collection will take place over a period of at least 20 years 7 months and probably considerably longer. DNA will be retained indefinitely.

5. Number of Subjects: Please state the number of subjects to be enrolled at Yale. For multi-center studies, indicate the total number of subjects to be enrolled across all sites. If different subject populations will participate, state the anticipated number in each group.
The total is 1029:

396 participants with mood disorders, 50 participants with an attention deficit disorder and 300 healthy comparison participants are anticipated to be enrolled overall. Exclusion criteria are more stringent for the imaging component and thus only a subset will be eligible for the imaging component.

Also, a subgroup of 100 adolescents, ages 13-17 years, will be recruited from a well-characterized cohort from a longitudinal study conducted by Linda Mayes, MD HIC #5149 "The Long Term Impact of Intrauterine Cocaine Exposure" (also known as "The Infant and Young Children's Follow-Up Project").

In addition, a subgroup of 12 subjects who do not meet criteria for bipolar disorder, but who are "at-risk" for bipolar disorder (as they have at least one first degree relative with bipolar disorder) although they do not meet criteria for having the disorder.

Also, 20 subjects (comprised of both healthy control subjects and subjects diagnosed with mood disorders) for a pilot study utilizing the 7T scanner. In addition, for the R21, 26 subjects with bipolar disorder and 26 healthy comparison subjects, ages 16-23 years, to undergo the 7T imaging. There will be no increase to the target enrollment with the addition of the psychotherapy pilot study. Subjects already participating in the imaging component of the study are invited to participate in a pilot treatment study, with initial aim of 10 pilot subjects.

For a combined psychotherapy (BE-SMART) and imaging study, 66 subjects who meet criteria for BDI, BDII, BD-OS for an R61 grant, and 20 additional subjects in the R61 Supplement, ages 16-29 years, who will receive, along with the psychotherapy, the wireless actigraphy device (e.g. GENActiv) that is worn on the wrist and monitors a person's activity when in motion or at rest/sleep and Ecological Momentary Assessment (EMA) electronic diary in which subjects enter their ratings into a handheld electronic device each day on their emotions, behavior, and activities.

In addition, 13 "at risk" subjects for bipolar, ages 13-21 years with DSM-5 diagnosis of MDD and a parent with BDI or BDII. These subjects will not be randomized but will participate in the down regulation BE-SMART therapy for the KGTF grant.

SECTION III: RESEARCH PLAN

1. **Statement of Purpose:** What are the scientific aims of the study, or the hypotheses to be tested?

Purpose of the Genetic Component (formerly HIC Protocol 22336): The purpose of this protocol is to collect blood or saliva for genetic and biochemical (to include neurotrophic and immune factors recently associated with mood disorders) analysis from individuals with mood disorders or an attention deficit disorder and healthy controls in order to look at associations between regional brain abnormalities and specific genotypes and biomarkers that may be associated with mood disorders or attention deficit disorder. The long term scientific goal of the project is to identify genetic loci, and alleles at those loci, that influence vulnerability to mood disorders, attention deficit disorder and related phenotypes, such as prefrontal dysfunction. In addition, study across the lifespan will help to contribute to our understanding of the interaction of genetic vulnerabilities with abnormalities in brain development associated with the onset of the disorders. Prior to 5/11/2023, a sample from this study may have been obtained and submitted to a data repository run by the National Institute of Health. Samples/data from subjects newly enrolled after 5/11/2023 were no longer shared and will continue not to be shared unless NIH funding becomes available. Only data/specimens collected during the NIH funding period will be shared with NIH.

Purpose of the Imaging, and Integrated Imaging and Genetic Components (contains components of former HIC Protocol 11005):

Primary Aims:

Aim #1: Use a prospective longitudinal design and structural MRI to examine age-related changes in amygdala (AMYG) and orbitofrontal cortex (OFC) volumes and to examine ventral prefrontal-amygdala neural system regional brain morphology and chemical patterns in children with mood disorders compared to a healthy comparison group of children.

Hypothesis1A: At both baseline and follow-up, AMYG volumes will be lower in children with mood disorders compared to healthy comparison (HC) children.

Hypothesis 1B: Age-related OFC volume reductions will be greater in children with mood disorders than in HC.

Exploratory analyses will also be conducted to explore the possibility of volumetric differences across diagnostic groups and in other brain regions not hypothesized *a priori*.

Aim #2: Use a prospective longitudinal design and fMRI to examine age-related changes in AMYG and

OFC function in children with mood disorders compared to HC.
Hypothesis 2A: At both baseline and follow-up, AMYG activation will be greater in children with mood disorders compared to HC.
Hypothesis 2B: Age-related OFC activation increases will be lower in magnitude in children with mood disorders than in HC.
Aim #3: Use a prospective longitudinal design and diffusion tensor imaging (DTI) to examine age-related changes in AMYG and OFC connectivity in children with mood disorders compared to HC.

Exploratory analyses will also be conducted to explore the possibility of functional and connectivity differences across diagnostic groups, and in a small sample at "high-risk" for bipolar disorder, and in other brain regions not hypothesized *a priori* and structure-function relationships.

Exploratory Aims:
Exploratory Aim #4: Use structural MRI, in combination with study of allelic variation in genes and associated biochemical factors associated with mood disorders (or behaviors that might contribute to or be related to mood disorders), to examine the potential modifying influence of genetic factors on volume abnormalities in children with mood disorders.
Hypothesis 4: The presence of the serotonin transporter (SLC6A4) promoter short ("s") allele will be associated with greater AMYG volume increases in children with mood disorders than in HC.
Exploratory Aim #5: Use fMRI, in combination with study of allelic variations in genes and associated biochemical factors associated with mood disorders (or behaviors that might contribute to or be related to mood disorders), to examine the potential modifying influence of genetic factors on functional abnormalities in children with mood disorders.
Hypothesis 5: The presence of the serotonin transporter (SLC6A4) promoter short ("s") allele will be associated with greater AMYG activation increases in children with mood disorders than in HC

In addition, we will study effects on MRI measures of allelic variation at other strongly favored candidate loci, including, for example, any specific mood disorder risk loci that may be identified over the course of the study. Exploratory analyses will also be performed for the potential modifying influence on AMYG and OFC structure and function of other demographic and clinical factors such as sex, medication exposure, current medications, presence of rapid-cycling, duration of illness, smoking history, family-loading for mood disorders, stressors and socioeconomic status.
Exploratory Aim #6: Use MRI, in combination with the study of allele variation in genes and associated biochemical factors and assessments of stress, to examine the potential interaction between genes and stress in influencing the development of AMYG-OFC circuitry and the emergence of disorders of mood and impulse regulation (ADHD and substance use disorders).
Hypothesis 6A: Adolescents with high stress exposure, as compared to adolescents with low stress exposure, will show heightened AMYG and ventral striatum response and diminished OFC response to emotional face stimuli.
Hypothesis 6B: Abnormal response in the AMYG-ventral striatum-OFC neural system will be associated with impulsive and addictive behaviors.
Hypothesis 6C: Adolescents with high stress exposure who are 5-HTTLPR (SLC6A4) "s" carriers will show both the greatest magnitude of circuitry dysfunction and addictive behaviors.
Exploratory Aim #7: Investigate changes in corticolimbic system functioning during emotional regulation and to use fMRI, before, at mid-point, and after an emotional regulation intervention, to assess intervention-associated changes in AMYG and OFC responses to emotional stimuli and functional connectivity and if incorporating actigraphy, investigate objective cross-domain peripheral measures of daily rhythm regularity at high temporal resolution.
Hypothesis 7A: The emotional regulation psychotherapy treatment will be associated with "normalization" of the circuitry and symptom improvement.

Hypothesis 7B: Integrating actigraphy and EMA will provide objective and high temporal resolution data about how daily rhythm's change with BE-SMART behavioral therapies.
Exploratory Aim #8: Use 7T MRI and magnetic resonance spectroscopy (MRS) to investigate amygdala anatomy at high resolution and to study glutamate neurotransmitter levels in the amygdala
Hypothesis 8: The volume of the lateral nucleus of the amygdala will be decreased, and there will be differences in amygdala glutamate levels, in adolescents with mood disorders.

2. **Background:** Describe the background information that led to the plan for this project. Please provide references to support the expectation of obtaining useful scientific data. When available, previous work in animal and/or human studies should be included.

Prevalence and Problems of Early Misdiagnosis:

Lifetime prevalence for mood disorders is approximately 10%. Onset of mood disorders is increasingly recognized in childhood. Unfortunately, misdiagnosis is still common especially e.g. with attention deficit hyperactivity disorder (ADHD), as psychomotor and attentional symptoms of ADHD can be similar to symptoms of pediatric mood disorders. Misdiagnosis may have profound consequences, e.g. the exposure to stimulants or antidepressants in the children with a bipolar disorder diathesis may be associated with increased risk of mixed episodes, rapid-cycling, treatment resistance and impaired prognosis. Suffering endured by individuals with mood disorders, as well as their families and communities is great owing to relationship loss, disruption of school or job loss. Importantly, the risk of suicide in mood disorders is highest from amongst pediatric psychiatric disorders. Despite the serious consequences of pediatric mood disorders, their pathophysiology is not understood. There is a paucity of study of mood disorders in children; yet the high rate of the onset of the disorders during this developmental stage suggests that understanding brain changes in mood disorders during this period may be pivotal to understanding their biology. Moreover, diagnosis and treatment of mood disorders in children are extrapolated from adults; yet, the potential biological differences between adolescents and adults with mood disorders are not known. Thus understanding of mood disorders in children is important because it could contribute: key information to understanding the pathophysiology of mood disorders; to improved early detection, minimizing misdiagnoses and deleterious medication exposure; to understanding of potentially unique characteristics of mood disorders in children, as compared to mood disorders in adulthood, so that treatment strategies may be more specifically targeted; to early detection and targeted early interventions that could improve lifetime prognosis; and, as we have argued, the understanding of brain structure and function in children attainable through neuroimaging studies, may be critical for understanding pediatric mood disorders. This work could also have broad implications as it could contribute to understanding of normal and disordered developmental trajectories of amygdala-OFC neural systems in childhood for which little human data is available, and that is especially important as adolescence is associated with a sharp increase in the risk for many other psychopathologies as well as suicide.

MRI Studies in BD to Implicate Amygdala and Orbitofrontal Cortex in Mood Disorders:

Abnormalities in AMYG and OFC volume in adult mood disorders have been reported; however, studies of pediatric mood disorders are rare. We recently reported AMYG volume decreases in adolescents and adults with bipolar disorder (BD) (Blumberg et al. 2003), suggesting that AMYG volume deficits are early and stable abnormalities in BD. In adults with mood disorders, increased AMYG activity has been reported in subjects at rest as well as during emotional face recognition. Decreased OFC activity at rest and a relative failure of right OFC activation in mania have been demonstrated during word generation and decision-making tasks (Blumberg et al. 1999). Recent fMRI work by our group replicated the relative failure of right caudal OFC activation in BD mania, and found a shift in abnormalities to the left caudal OFC in association with depression. Furthermore, we found a relative failure of rostral OFC to

activate that persisted across elevated, depressed and euthymic mood states (36 BD vs. 22 healthy subjects, $p<0.005$) suggesting that impaired function in this region may represent a diathesis to developing BD (Blumberg et al. 2003). In adolescents, our fMRI data support activation increases in subcortical components of OFC neural systems, and emerging abnormalities in OFC, in adolescents with BD (Blumberg et al. 2003).

Pilot MRI Data:

Longitudinal Within-Subject Structural MRI Pilot Data:

Amygdala: 10 BD and 9 HC adolescents were scanned twice over an approximately 2-year interval. Consistent with the cross-sectional data, AMYG volumes did not decrease significantly during the 2-year interval and the diagnosis effect remained consistent, i.e. at each time point AMYG volumes were smaller in BD than in HC ($p<0.05$).

OFC: We used nonrigid registration methods to examine local volume changes between first and second scans within and across diagnostic groups. Consistent with our hypotheses, as well as our cross-sectional pilot data, we observed greater interval-related decreases in volume in the OFC in BD as compared to HC adolescents. Whereas HC (N=9) showed approximately 1% decrease in VPFC volume in the 2year period during adolescence (consistent with the literature on prefrontal change during this developmental period), BD (N=10) showed from 3-6% decreased in this region. Moreover, this new technique permitted us to examine whole brain to observe the particular regions of group differences. The localization of significant group differences encompassed the same regions where we have previously observed age-related changes in adolescence and functional deficits in patients with BD on both emotional and cognitive tasks.

Functional MRI Pilot Data:

Amygdala: In an fMRI study, we employed an emotional face task (happy, sad, fearful and neutral face conditions). Comparing 17 HC and 5 BD subjects we found significantly elevated activation ($p<0.05$) in right AMYG in BD, and interestingly the group x condition interaction was significant with the greatest group differences in the happy condition. This interaction is of interest as the processing of positively valenced emotional stimuli has been theorized to distinguish pediatric BD from other psychiatric disorders.

OFC: In the first published study of fMRI in adolescent BD, we observed age-related increases in OFC engagement during task performance in HC adolescents. This age effect was diminished in adolescents with BD suggesting that abnormalities in the development over adolescence of OFC function contribute to OFC deficits observed in adults with BD (Blumberg et al. 2003). Pilot data with the emotional face fMRI paradigm demonstrated OFC activation of decreased magnitude in BD compared to HC ($p<0.005$), consistent with our previous findings in BD, and within the region where the longitudinal structural data demonstrate accelerated volume loss.

Genetic Factors with the Potential to Modify Regional Brain Volume in BD:

A phenotype provided by neuroimaging that is associated with a particular genotype may be considered an "intermediate" phenotype, possibly an endophenotype, which reflects the effect of the functional variant more directly than DSM-IV diagnosis. The identification of a neural endophenotype could therefore help to clarify classification and diagnosis, as well as develop animal models an important issue in BD for which no good animal model is available. The particular genetic variation with which the endophenotype is associated provides a biochemical mechanism that can be further studied for its influence on the pathophysiology of the disorder as well as a mechanism to target with new treatments.

Modifying Influence of Genotypes on Amygdala Function in BD: Pilot Data:

The data above was examined for potential increases in AMYG activity in association with the serotonin transporter promoter protein SLC6A4 "s" allele. We found that BD subjects who are "s" carriers (i.e. "ss" or "ls") have significantly higher left AMYG volume as well as activation ($p<0.05$) than those with "ll" genotype. This suggests that the "s" allele may influence a shift in neuroprotection towards greater

volume but that volume increases may be associated with some maladaptive functional features such as abnormal emotional processing.

Note: While we have focused on the AMYG and OFC in this proposal, other brain structures including medial temporal regions such as the hippocampus and other frontocortical structures have also been implicated in BD. Exploratory analyses will be performed to investigate potential group differences in these and other brain regions identified as potential regions of difference on whole brain structural and functional analyses.

Salutary Effects of Psychotherapy:

New treatments to help to reduce the emotional dysregulation of mood disorders are critically needed. We are continuing to study an emotional dysregulation psychotherapy treatment in which subjects learn skills to help to down-regulate maladaptive emotional responses and learn beneficial, healthy sleep and activity habits. We repeat scanning and symptom and behavioral assessments at the midpoint, and after the psychotherapy is completed. This collected information will demonstrate that the treatment can help subjects to better self-regulate their emotional responses and behaviors, reducing abnormalities in neural circuitry responses and their symptoms.

Incorporating the actigraphy device and EMA data has potential to generate novel scientific insights into the brain and behavioral mechanisms underlying beneficial effects of daily rhythm regularization on the emotional circuitry target.

3. **Research Plan:** Please provide an orderly scientific description of the study design and research procedures as they directly affect the subjects. *Please note: Investigators should take care to distinguish clearly between any procedures that are experimental and those that are part of subjects' standard clinical care.*

Procedures:

After written informed parental permission is obtained from a parent/guardian of subjects under age 18 years or written informed consent from subjects 18 years old or greater (and written informed assent in subjects <18 years of age), interviews (about 3 - 4 and ½ hours) will be performed at the Yale University School of Medicine, blood draws for genetic and biochemical (to include levels of neurotrophic and immune factors) testing will be performed by a certified phlebotomist at our lab or at the YCCI HRU, and urine toxicology will be performed at either the YCCI HRU or at the Yale University School of Medicine. (Obtaining blood and urine will take about 15 minutes if done at our lab and ½ hour if taken from YCCI HRU which includes the walk to the 10th floor at YCCI HRU and the return walk to Anylan Center). For the Mayes sample, the blood sample may already have been obtained for genetic study, and therefore a blood sample may not need to be redrawn. Results of the urine toxicology will be discussed only with the subject, including if the subject is a minor. Subjects who are unable to give a blood sample but wish to participate in genetic testing may opt to give a saliva sample by spitting into a tube until it is filled to a certain level. The saliva sample process may take up to 20 minutes. Children and their parents will be interviewed separately and together. Scanning will be performed on the 3T system at the Anlyan Center at the Yale University School of Medicine. The scanning session will be 90 minutes long. Further interview information will be collected from the parent during the scanning session in an office on the same level as the scanner in case the child requests their parent during scanning. For follow-up subjects, assessments will follow similar procedures, including pregnancy tests for menstruating females; however, interviews are anticipated to be brief. Diagnosis will be confirmed and clinical changes recorded such as interim episodes, treatment changes and social changes that might affect SES. Genetic testing need not be repeated. We anticipate that total participation will take approximately 4 and ½ - 6 and ½ hours to complete. This time can be divided into different days if preferred by the subject.

The 7T study procedures were the same as for subjects being scanned on the 3T system, except that they were scanned with the 7T MRI system.

Clinical Assessments:

- *Altman Self-Rating Mania Scale (ASRM):* The ASRM (Altman et al. 1997) is a 5-item weekly self rating designed to assess the presence and/or severity of manic symptoms
- *Barratt Impulsiveness Scale-11 (BIS)*: The BIS (Patton et al., 1995) will measure trait impulsiveness, we observed increased in adolescents with BD.
- *Beck Anxiety Inventory (BAI):* The BAI (Beck et al 1988) is a 21-question, self rated, multiple-choice scale, used to measure the severity of anxiety in children and adults.
- *Beck Hopelessness Scale (BHI):* The BHI (Beck 1974) consists of 20 true or false statements designed to assess the extent of positive and negative beliefs about the future.
- *Brief Social Rhythm Scale (BSRS):* The BSRS (Margraf et al., 2016) is a self rated and used to assess the regularity with which one engages in social activities throughout the week.
- *Clinician-Administered Rating Scale for Mania (CARS-M):* CARS-M (Altman et al. 1994) is a 15 item clinician administered rating used to assess the severity of manic symptomatology.
- *Child Depression Rating Scale - Revised (CDRS-R):* The CDRS-R (Pozanski et al., 1982) is a 17-item clinician administered depression severity rating scale.
- *Child Global Assessment of Functioning (C-GAF):* as adapted for use with children rates the child's level of function on a 100point scale at the end of the K-SADS for the present, period of highest functioning, and of most severe psychiatric impairment.
- *Childhood Trauma Questionnaire (CTQ):* The CTQ (Scher et al 2001), is a 28 item, self rated scale, that measures 5 types of maltreatment.
- *Client Satisfaction Questionnaire (CSQ):* The CSQ is a rating completed after the psychotherapy portion and used to assess the treatment satisfaction.
- *Cognitive Testing:* intelligence quotient estimates as well as measures of cognitive performance will be obtained with standard instruments such as the *Wechsler Intelligence Scale for Children (WISC)* block design and vocabulary subtests.
- *Columbia Suicide History Form (CSHF):* The CSHF (Posner et al 2007) is an interviewer-administered scale to gather lifetime history of suicidality as well as any recent suicide ideation and/or behavior.
- *Columbia Suicide Severity Rating Scale (C-SSRS):* The C-SSRS is a questionnaire assessing suicidality since the last subject visit.
- *Concise Health Risk Tracking Scale (CHRT-SR):* The CHRT-SR (Trivedi et al., 2011) is a brief self report used to monitor suicidal risks.
- *Difficulties in Emotion Regulation Scale (DERS):* The DERS (Gratz et al 2003), is a self rated measure used to assess the emotion regulation problems among adolescents and adults.
- *Edinburgh Handedness Inventory (EHI):* The EHI (Oldfield et al. 1971) is a 10-item questionnaire that assesses right- and left-hand preference with good test re-test reliability.
- *Emotion Reactivity Scale (ERS), Difficulties in Emotion Regulation Scale (DERS):* will assess regulation of subjective/behavioral reactions to emotional stimuli, and the *Difficulties in Emotion Regulation Scale Positive(DERS-P)* focuses on positive emotions.
- *Hamilton Psychiatric Rating Scale for Depression (HRSD*): is a clinician-administered scale validated for use in adults. A modified version has been validated for use in children will quantify depressive symptoms.
- *Medical Lethality Suicide Scales:* are interviewer-administered scale that measures the medical severity of suicide attempts (Beck et al 1975).
- *Modified Fagerstrom Tolerance Questionnaire (mFTQ):* the 6 item mFTQ has been validated for use in adolescents, with total scores reflecting smoking rates.

- *Multidimensional Anxiety Scale for Children (MASC):* The MASC (March et al 1997) is a self rated assessment on anxiety in youth.
- *National Institute of Health Life Chart Methodology for Recurrent Affective Illness - Clinician and Parent, Retrospective and Prospective versions:* the LCM provides a systematic method for the collection of detailed (coded by month) information regarding the type and severity of mood episodes, as well the type, dose and duration of treatments (specific medications and psychotherapy), type and severity of psychosocial stressors (life events) and comorbidities.
- *Pittsburg Sleep Quality Index (PSQI):* The PSQI (Buysse et al.1988) is a clinician administered instrument used to measure the quality and patterns of sleep.
- *Positive and Negative Affect Schedule (PANAS):* The PANAS (Watson et al 1988) is a clinician administered scale that measures both positive and negative affect.
- Perceived Stress Scale (PSS) (Cohen et al 1983), The PSS (Cohen et al 1983) is a 10 item self rated assessment used to measure the perception of stress.
- *Quick Inventory of Depression Symptomatology Self-Report (QIDS-SR):* Self rated weekly mood scale to assess safety (eg., follow mood for worsening) in the psychotherapy subjects.
- *Scale for Suicide Ideation:* is a 21-item, interviewer-administered scale that evaluates the intensity of the participant's specific attitudes, behaviors, and plans to commit suicide, as well as the incidence and frequency of past attempts, which has been used in adult and adolescent samples (Beck et al 1979, Molock et al 1994). It is one of the most widely used measures to assess suicidality.
- *Schedule for Affective Disorders and Schizophrenia for School Aged Children - Present and Lifetime Version (K-SADS -PL):* is 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 parent separately. Final diagnoses are made by incorporating all sources of data and using best estimate procedures.
- *Sexual Orientation and Gender Identity (SOGI):* is a 3 question self-report used to identify sexual and gender minorities (SGM).
- *Socioeconomic Status (SES):* will be estimated with the Hollingshead Index of Social Status.
- *The Structured Clinical Interview for DSM-5-RV for Adults Aged 18 and Over – Present and Lifetime Research Version (SCID-5-RV):* is a structured diagnostic interview that provides assessment o present episode and lifetime history of psychiatric illness in adults according to DSM-5 criteria. It is completed by interviewing the adult subject.
- *The Structured Diagnostic Interview for Sleep Patterns and Disorders (DISP):* The DISP is a characterization of sleep history which includes information on insomnia, hypersomnia and chronotype.
- *The Young Mania Rating Scale (YMRS): A* clinician administered tool used to rate the severity of symptoms of mania (11 items)
- Subjects will complete a subset of self-reports (from list above), dependent on the part/s of the study they have consented/assented to participate in.

We will use the Yale licensed HIPAA approved web-based survey tool (from Qualtrics) for subject reminders and electronic access for subjects to fill out their self-reports and weekly ratings.

Medical History:

With a subject's assent and guardian's permission, the study staff may contact the subject's treater to clarify diagnosis and the psychiatric medical records of the patients may be reviewed for diagnostic and treatment history information.

Assessment for Ferromagnetic Objects:

All subjects will be screened for implanted foreign metal objects by the same questionnaire used for

routine clinical scanning. Subjects having or suspected of having foreign metal objects will be excluded. This may be confirmed, with a subject's assent and guardian's permission, either by examining the subject's medical chart and/or contacting their physician if there is any question.

Assessment of Pregnancy:

The risks of study with pregnancy and the possibility of pregnancy will be discussed with each menstruating female subject by an investigator of the study. A urine screening will be performed within 24 hours of scanning to determine the pregnancy status. If there is any question that a pregnancy could exist but be at too early a stage for detection by this test the woman would also be excluded from study.

Female subjects of childbearing potential will require urine pregnancy testing prior to MRI scanning. Because full confidentiality regarding pregnancy cannot be entirely guaranteed, these testing requirements and the limited scope of confidentiality will be made known to all subjects during the consent procedure. In this manner, young women who would not be comfortable with pregnancy testing or sharing the results of such testing can opt out of the study at the time of the initial consent, without having to declare specific reasons. Subjects 13 or older will be told the results.

Females of child bearing potential will be notified that it may not be safe to participate while pregnant and if pregnant will not be enrolled. If they would like to become pregnant during the course of the study, then they should not participate. Pregnancy testing will be done prior to scanning on all female subjects and any positive tests will exclude further participation.

FMRI Paradigm-Related Behavioral Testing:

Before scanning, subjects will be asked to practice paper and computerized versions of the tasks that will be given to them in the scanner to familiarize them with the neuropsychological stimuli. Accuracy and response time data will be collected. Further testing, e.g. regarding memory for stimuli during scanning may be administered briefly after scanning.

Genotyping and Biochemical Analysis: All blood tubes or saliva samples will be labeled with a code that contains no personal identifying information. DNA extraction and genotyping will be performed in Dr. Gelernter's laboratory. DNA will be extracted from 10 ml whole blood or saliva samples using standard methods. Pre-existing subjects who had consented to share their samples and data may have their de-identified information in computer files about their processed samples along with their post processed MRI data sent to the University of Iowa as part of a GWAS. Yale is not receiving information from University of Iowa for this study.

Magnetic Resonance Imaging Acquisition:

MRI scans will be obtained using the 3T scanner in the MR Center in the Yale Anlyan building. Head position will be secured with foam pads and Velcro strap across the forehead and standardized using canthomeatal landmarks. A 90 minute protocol will include acquisition of high resolution structural MRI data, MRS, fMRI data and DTI data. With exception of the fMRI component, subjects will lie still with their eyes closed. During the fMRI component subjects may perform a neuropsychological task. These tasks will involve the presentation of visual or auditory stimuli related to cognitive or emotional functions. They will not include material that would be considered offensive, threatening or degrading. Visual stimuli may be words, stars, picture of objects or human faces standardized by computer and back-projected using an active matrix LCD projection system. The subjects view the images using a mirror system. Tasks may alternate to provide information at baseline (e.g. while passively viewing a cross hatch on a screen), during an activation task of interest (e.g. during a Stroop interference task while naming the color of the letters in words when the words do not match the color such as "blue" written in

green letters or responding to emotional stimuli) and may include a sensorimotor control (e.g. during a Stroop task naming the color of words presented in the congruent colors such as "blue" in blue letters) and responses will be made by silent verbalization or by button press using a fiber optic response box. If a response box is used, accuracy and time of response will be recorded.

For the pilot study subjects and the 52 subjects enrolled in the NIH-funded R21 on the 7T scanner: At 7T, high-resolution images were implemented with the goal of differentiation of the internal regions of the amygdala. These were T1-weighted, T2-weighted, diffusion-weighted, or another approach, as necessary was used to achieve the sensitivity and contrast required for visualization of the amygdala's substructures. SAR and gradient strengths were maintained within FDA limits. Scan times were limited to 90 minutes, with attempts to achieve the sensitivity and contrast in less time.

MRS Acquisition:

Total 7T scanning time, including MRS, was 90 minutes. Single- or multi-voxel H-MRS scans were used to obtain proton spectra from regions of the frontal and/or occipital lobes and possibly other regions, as well, using surface coils or volume coils. The single voxels measure 4-27 cubic centimeters in size and located based on the structural scans. Details of voxel construction and placement evolved as the MRS physicists of the Yale Magnetic Resonance Center developed new MRS acquisition protocols. MRS spectra was collected from the voxel(s) of interest. GABA was acquired using PRESS localization and J-editing, using an echo time of as close to 68ms as possible. Glutamate was measured using short-echo MRS, with an echo time as low as possible, ideally less than 15ms.

BE-SMART Psychotherapy Treatment:

Subjects with or "at-risk" of mood disorders are invited to participate in the psychotherapy treatment trial. The testing assesses acceptability to subjects and ability to engage the brain targets, and the treatment will be adapted to optimize helpfulness to the subjects, as compared to burden. Subjects participating in our scanning studies frequently request opportunities to participate in treatment studies. This provides free, non-medication treatment. The treatment is overseen by a licensed mental health professional. The treatment is designed to increase healthy emotional regulation and behavioral habits (such as sleep and activity). *The treatment provided in this study will be in addition to subjects' current treatment, as the study treatment is considered an adjunctive treatment.*

Subjects may participate in 12 therapy sessions, at a rate of 1 session every one to two weeks. Sessions are anticipated to last about 1 hour each. These therapy sessions may be videotaped and audiotaped (only with the written consent of the subject, and when appropriate, the subject's parent or guardian). Subjects may be asked to complete weekly worksheets (either through qualtrics or by pen and paper) and practice the skills learned from these sessions and they may be asked questions about how they are feeling. There may be an interview assessment and scan performed at baseline, midpoint and at the completion of the psychotherapy sessions to review progress for the BE-SMART subjects. As it is often challenging for subjects to come to the site, we will conduct sessions by videocommunication (Zoom) and plan that approximately 50-75% of the sessions will occur via such methods.

Subjects participating in the R61 Supplement will receive the psychotherapy treatment the actigraphy and EMA electronic diary devices. We ask that subjects use the provided actigraphy device in place of any current personal activity tracker they may be using, or if not cumbersome, in conjunction with their own device for the duration of the study. The actigraph is widely used in research settings, including with our NIMH intramural collaborators on this funded Supplement with whom we will be sharing deidentified information with their computational team. The EMA electronic diary will allow us to monitor changes in subject's emotions, behavior, and activities and show us how these measures change

during the day and vary from day to day during their psychotherapy and will be evaluated together with the other study data obtained.

When the subject is given the EMA diary, it will signal 4 times each day. The electronic diary will alert the subject by ringing when the questionnaires are available for completion. The device will ring every 2 minutes until the "Press here to start Questions" has been activated or will time out after 10 minutes without any user interaction in which this set of questionnaires would be considered as missed.

Included in the daily events to be rated, participants 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). For negative endorsed events (scores of 5-7) the additional question will be activated, 'Were these thoughts about things that could be dangerous for you physically?' If 'YES' is endorsed, we plan to use methods adopted by the 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. Subjects will receive the following alert on their device that will provide specific instructions and phone numbers to contact (as agreed in the parent 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 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).

*Complete list of EMA questions can be found in IRES IRB Documents 'EMA_Schedule'.
These devices do not have internet capability, do not hold PHI, and information can only be entered when prompted by an alert from the device. If a device is lost or stolen, there is no way to link the stored data to its user.

MRI Data Processing:
Image processing and analysis will be performed at the Yale MR Center on UNIX workstations using standard as well as locally developed software. Data are stripped of all identifying information and assigned a numerical code so that image processors are blind to subject information. Processing will include transformation of brains across subjects into common stereotactic space. Pre-existing subjects who had consented to share their samples and data may have their post processed MRI data along with de-identified information in computer files about their processed samples sent to the University of Iowa as part of a GWAS. Yale is not receiving information from University of Iowa for this study.

4. Statistical Considerations: Describe the statistical analyses that support the study design. This section should include:

- The number of subjects expected to enter the study.
- A statement about the statistical power of the study to test the major hypothesis.
- A summary of the plans for data analysis.

Hypothesis testing will be performed with region of interest measures as the dependent variables, analyzed in mixed models in consultation with a statistician, e.g. with current collaborators such as Ralitza Gueorguieva, PhD (EPH) and James Dziura, PhD (GCRC). For example, to test hypothesis #1: diagnosis will be the between subject's variable. Hemisphere (right vs. left) and time (1st scan vs. 2nd scan) will be the within-subject variables and there will be a random subject effect. Repeated measures will be performed over the spatial domain of hemisphere. Total brain volume will be included as a covariate to control for general scaling effects. Terms that are not significant ($p>0.05$) will be eliminated via a backward stepwise algorithm, with the constraint that the model at each step is hierarchically well-formulated. Least squares means (ls means) and standard errors (SE) will be calculated in the mixed model and plotted to interpret significant interactions.

Whole brain analyses will also be performed to examine for group differences in regions not hypothesized *a priori*. These will be performed with widely available software such as SPM software as well locally developed software.

Power:

Effect sizes, calculated based upon pilot data, are large for testing of main hypotheses. For example, the mean difference in AMYG volumes between BD and HC subjects was 382 ml, corresponding to an effect size of 1.14. Mean reductions in volume in the OFC ROI of 3.35±1.73% in BD subjects compared to reductions of 0.78±3.40% in HC subjects. The absolute difference of 2.57 corresponds to a standardized effect size (d) of 0.93. A sample size of 50 subjects per group will provide >95% power to detect differences of this magnitude even at attrition rates as large as 30%.

SECTION IV: RESEARCH INVOLVING DRUGS, DEVICES OR BIOLOGICS

Please note: protocols using chemicals, hormones, other natural substances, or devices not regulated by the U.S. Food and Drug Administration (FDA) must still complete this section of the application form. Based upon the information provided in items 1-4, the HIC will determine whether an Investigational New Drug (IND) or Investigational Device Exemption (IDE) application must be submitted to the FDA.

This section is not applicable to this study.

SECTION V: HUMAN SUBJECTS

1. **Recruitment Procedures:** How will potential subjects be identified, contacted and recruited? Attach copies of any recruitment materials – such as flyers, telephone scripts, or introductory letters that will be used.

   Please note that a researcher may not use an individual's Protected Health Information (PHI) for recruitment into research without first obtaining an authorization from the individual, or a Waiver of Authorization from the HIC. A treating provider does, however, have the option to:
   - Discuss with his/her own patients the option of enrolling in a study.
   - Obtain written authorization from the patient for referral into a research study.
   - Provide background information about the study to the patient so that the patient can initiate contact with the researcher.
   - Provide the individual's PHI to a researcher without authorization when the researcher has obtained an approved Waiver of Authorization for recruitment purposes from the HIC.

   If PHI will be accessed without subject authorization, please state whether any member of the research team has an existing clinical relationship with the potential subject. Researcher-clinicians are

permitted to access the PHI of their own patients, or patients of co-investigators listed on the protocol, for recruitment purposes. Alternately, please submit a completed Yale University Request for HIPAA Waiver of Authorization for Research Form (available at http://info.med.yale.edu/hic/hipaa/. *For further information, see the Yale HIPAA website at* http://info.med.yale.edu/hipaa/.

Overall Recruitment Efforts: Through a variety of efforts, subjects will be informed about our study. These efforts will include educational presentations, and websites (e.g. Craig's List, FaceBook, YCCI website, and the Yale University Department of Psychiatry website).
The flyers will be widely distributed (e.g., within school systems given prior authorized permission to do so) and placed at varied locations throughout the community. 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).
Potential subjects or their referrers may call the research staff directly. A telephone screen is administered with the study procedures and potential risks and inclusion and exclusion criteria explained in detail over the telephone to the referrer or parent/guardian and the child. If eligible and interested, an in-person appointment will be scheduled to obtain written informed consent and assent. If the parent/guardian agrees to consider having their child participate then a follow up in-person appointment will be scheduled to obtain written informed consent and assent.
Additional Methods of Recruitment of Individuals with Mood Disorders and/or ADHD: Study inclusion and exclusion criteria and procedures will be discussed with clinicians from the Yale Medical Center and the Yale Child Study Center (CSC) as well as treaters in the surrounding community. We will recruit through referral sites of the CSC including satellite programs such as Cedarhurst therapeutic school and affiliated hospitals throughout CT, including Bridgeport Hospital. We have clinicians who are collaborators on both inpatient and outpatient adolescent and young adult clinical programs of Yale New Haven Psychiatric Hospital. We will provide written information about the study to inform them, and so that they may provide the written materials to parents/guardians of potential subjects. The parent/guardian would then be able to contact the research staff directly. However, if the treating clinician is one of the study investigators, the treating clinician will be able to enroll the participant directly. Participants may also call the research coordinator after viewing the HIC approved advertisement for this study.

Additional Methods of Recruitment of Healthy Participants: Controls will be recruited through word-of-mouth, and advertisement.

2. **Inclusion/Exclusion Criteria:** What are the criteria for subject inclusion or exclusion? How will eligibility be determined, and by whom?

Eligibility:
Eligibility will be determined by the staff consenting subjects, under the supervision of the Principal Investigator.

Inclusion Criteria:
All Subjects: 1. ages 13 to 30
2. subjects from all racial and minority groups
Subjects with Mood Disorders and/or ADHD
1. subjects with Bipolar Disorder, Major Depressive Disorder, and/or Attention Deficit Hyperactivity Disorder,
Control Subjects

1. no lifetime history of major Axis I disorder

Subjects in the Psychotherapy Pilot Study:

1. subjects must have a current mood disorder, be age 13-17 years old, with a current outpatient clinician.

Subjects in the BE-SMART Psychotherapy Study and Supplement**:**

1. subjects must be age 16-29 years old meeting DSM5 criteria for BDI, BDII, BD Other Specified Bipolar (BD-OS).
2. subjects participating in the Early Targeted Psychobehavioral Treatment for Depressed Adolescents at High-Risk for Bipolar Disorder, must be age 13-21 years old and can meet for DSM5 criteria for MDD.
   subjects with mood symptoms, such as Ham-D score ≥ 15 and/or for hypomania/mild mania YMRS ≥ 12.

Exclusion criteria:

For all subjects to participate in the interview, genetics and scanning, subjects must not have:

1. diagnosis of schizophrenia
2. mental retardation (IQ < 70)

Subjects in the BE-SMART Psychotherapy Study:

1. current psychosis or substance abuse disorders in #2
2. alcohol/substance use may be permitted if subject does not meet for more than one DSM-5 use disorder threshold criteria, except for craving, in the past 3 months (excluding nicotine and caffeine). THC may be permitted if DSM-5 score for THC use is not severe.
3. Receiving structured psychotherapy (e.g. family, cognitive behavioral, interpersonal/social rhythm, dialectical), or other treatments that may affect brain functioning such as rapid transcranial magnetic stimulation and electroconvulsive therapy (ECT, excluded for if in prior 6 months); however, BE-SMART is designed to be adjunctive and subjects may continue outside treatments such as pharmacotherapy
4. active suicidal or homicidal ideation
5. Alcohol or illicit substance use in the week prior to study (excluding nicotine and caffeine and THC may be permitted). Subjects will be excluded for a positive screen with exception of THC as urine toxicology screens remain positive for up to a month after THC use, they cannot accurately reflect current use.

For Healthy Control Subjects to participate in interview, genetics and scanning, subject's must not have:

1. history of a mood disorder in a first-degree relative
2. history of prescribed psychotropic medication

<u>For all subjects to participate in scanning session, subjects must not have:</u>

i. history of structural brain disease, mass lesion, stroke or epilepsy
ii. history of loss of consciousness greater than 5 minutes
iii. significant medical illness e.g. insulin dependent diabetes milletus
iv. any possibility of pregnancy
v. presence of ferromagnetic devices e.g. pacemakers, reactive metallic implants or fragments
vi. alcohol/substance use may be permitted if subject does not meet current DSM-5 use disorder (excluding nicotine and caffeine).

vii. orthodontic braces
viii. history of claustrophobia

Follow-up visit:

Subjects will be instructed not to drink any alcohol or use any other substances within 1 week of the scanning session that could change brain function aside from use of their prescribed medication. They will be instructed to restrict caffeine use to 5 hours prior to scan. Subjects that smoke will be instructed to complete smoking cigarettes one hour prior to scanning and to then abstain from smoking until scanning has been completed.

3. **Subject Population:** Provide a detailed description of the proposed involvement of human subjects. Describe the characteristics of the subject population, including their anticipated number, age range and health status.

The selection of subjects should be equitable. Generally speaking, subject selection should reflect a reasonable cross-section of the population that is being studied. In research that requires a more restricted population, the rationale for this need should be fully justified. Investigators must also provide scientific justification for the exclusion of underrepresented populations such as women, children, or minorities.

Subjects will be age 13 years or older but under age 31. We plan to include equal numbers of males and females (inclusion of sex assigned at birth) and minority subjects in proportions representative of the population in the greater New Haven area. However, specifically for the Mayes sample, the adolescent cohort is primarily minority, with 60% African-American, 14% Hispanic, and 26% Caucasian.

There will be no increase to the target enrollment with the addition of the psychotherapy pilot study. Subjects already participating in the imaging component of the study will be invited to participate in a pilot treatment study, with an initial aim of piloting 10 subjects.

There will be an increase of 86 BD adolescent/young adult subjects to the target enrollment with the addition of the BE-SMART and Supplement. These subjects will be 16 to 30 years old at entry and will participate in open trials, 50% randomized to either the BE-SMART-DR or BE-SMART-ER. With an estimate of 20% attrition, there will be 26 completers per group. An additional 13 "at risk" for bipolar disorder adolescent subjects, who will not be randomized, but participate in the BE-SMART-DR psychotherapy.

4. **Vulnerable Subjects:** Certain populations are considered vulnerable and require special protections when asked to participate in a research study. (Vulnerable populations include, but are not limited to pregnant women, fetuses, human embryos, prisoners, children, and cognitively impaired individuals or persons with questionable capacity to consent. Others which may require special consideration include elderly persons, economically disadvantaged persons and educationally disadvantaged persons.)

Children include all persons who have not attained the legal age for consent to treatments or procedures involved in the research under the applicable law of the jurisdiction in which the research will be conducted (the age of majority is 18 years in the Connecticut). Parental permission and the child's assent are required for participation in the study. (Assent is defined as "a child's affirmative agreement to participate in research" and should be sought in addition to parental permission when the minor subject is sufficiently mature to understand the nature of his or her participation in a Research study.) Please refer to the HIC Guidelines for Investigators at http://www.med.yale.edu/hic/forms/forms/guidelines.pdf

Will vulnerable subjects be enrolled in the study? If so, identify the vulnerable population and provide a justification for their involvement. Also, address any additional safeguards necessary to protect the rights and welfare of vulnerable subjects.

All study personnel working with this child/adolescent/adult population will have completed Good Clinical Practice trainings. Both written parental permission and the child's assent will be obtained for all minor subjects under the age of 18 who were invited to participate. Literature supports that although the age range encompasses a period of neurodevelopmental change, some subcortical system components are relatively stable by this point in development. The amygdala, a key target, has a developmental peak by age 16 years, and can be expected to be relatively stable in structure and function levels in the child/adolescent/young adults. We reported amygdala volume decreases and associated activation increases to emotional faces in adolescents with BD in this age range, considered some of the most replicated biological findings in BD. It is possible that the magnitude of target engagement could vary by age, and this would be important to study. This would be in-line with our overall program of research.

SECTION VI: CONSENT/ASSENT PROCEDURES

1. **Consent Personnel:** Please list all personnel who will be obtaining consent.
   SEE IRES RECORD

2. **Assessment of Capacity to Consent:** For research involving subjects with limited decision-making capacity, how will the capacity to consent be assessed?
   All guardians and subjects 18 years of age or older must be capable for providing informed consent and subjects under 18 years of age of informed assent.

3. **Process of Consent:** Describe the setting and conditions under which consent will be obtained, including the information that will be communicated to the subject, any steps taken to minimize undue influence, and any steps taken to enhance subjects' independent decision-making (such as a waiting period between the consent discussion and obtaining consent).
   Subjects are consented on a 1:1 basis with a member of the study team as above. The staff member reads the consent form aloud with the subject and the parent/guardian. The subject and parent/guardian are encouraged to stop the staff member and ask questions along the way. In addition, the staff member anticipates questions and describes anything that seems unclear in more detail. After reading the consent form, the subject and parent/guardian are asked again if they have any questions. Any questions are answered. Then they are asked by the staff member whether the parent/guardian will permit the child to participate and the child whether he/she wishes to participate in the study. This enhances independent decision-making by never assuming the subject automatically wants to participate after reading the consent form. We will require written informed permission by a parent or guardian for their child's participation in this study, as well as written informed assent by the child.

<u>Re-contacting:</u>

Adult subjects, minor subjects and parent/guardian (will initial in their respective consent, assent, parent permission form) if permission is given to be re-contacted in the future for other studies such as genotyping. They will not have to agree to be re-contacted to participate in this protocol.

4. **Non-English-Speaking Subjects:** For research involving non-English-speaking subjects, fully explain provisions in place to ensure comprehension. In addition, please submit translated copies of all consent materials.
   Not applicable.

5. **Parental Permission and Assent:** For research involving minors, please explain how parental permission and child assent will be obtained.
   We will discuss the study in detail with both the parent/guardian and the child and require written permission from the parent/guardian and written assent from the child.

6. **Documentation of Consent:** Specify the forms that will be used among the following: adult consent form, parental permission form, LAR (Legally Authorized Representative) permission form, and adolescent assent form (ages 13-17 inclusive). Copies of all forms should be appended to the protocol, in the same format that they will be given to subjects.
   During the consenting process, subjects will be asked to initial the parts of the study in which they wish to participate as well as initial additioninitial whether they permit us to stay in contact with them in order to invite them to return for a second assessment and scanning session or to hear about other study opportunities. We will ask subjects who turn 18 years of age while participating to sign an adult consent form.
   Copies of the following forms are attached:

Compound Authorization and Consent Forms:
1. For Parents/Guardians of Children with a Mood Disorder
2. For Parents/Guardians of a Healthy Child
3. For Parents/Guardians of Children for a Psychotherapy Study aged 13-17 with a Mood Disorder
4. For Parents of Children for a Psychotherapy Study - Videotaping and Audiotaping

Compound Authorization and Consent Forms:
1. For Participants with a Mood Disorder Ages 18 and older
2. For Healthy Participants Ages 18 and older
3. For Participants for a Psychotherapy Study ages 18 years and older with a Mood Disorder
4. Audio/Video for Participants Psychotherapy Study ages 18 and older

Compound Authorization and Assent Forms:
1. For Participants with a Mood Disorder Ages 13-17 Years
2. For Healthy Participants Ages 13-17 Years
3. For Participants for a Psychotherapy Study with a Mood Disorder Ages 13-17 Years
4. Videotaping and Audiotaping for a Psychotherapy Study

7. **Waiver of Consent:** Will you request either a waiver of consent, or a waiver of signed consent, for this study? If so, please address the following:
   Not Applicable.

8. **HIPAA Authorization:** If the research involves the creation, use or disclosure of PHI, separate authorization is required under the HIPAA Privacy Rule. Please provide the HIPAA Research

Authorization Form and/or a request for waiver of HIPAA authorization. *(For further information, see the Yale HIPAA website at* http://info.med.yale.edu/hipaa/).
HIPAA Authorizations are combined in the Consent and Assent forms .

SECTION VII: PROTECTION OF RESEARCH SUBJECTS

1. **Risks:** What are the reasonably foreseeable risks, discomforts, or inconveniences associated with participation in the research?

   Please note: Potential research risks include more than physical harm; risks may also include, for example, emotional or psychological harm, risk of social stigmatization, economic or legal risk.

Diagnostic Assessment, Symptom Rating and Neuropsychological Testing
Discussing symptoms or past experiences, seeing emotional stimuli or taking cognitive tests can sometimes be stressful.

Blood Draw
Pain, bruises, inflammation, blood clot, bleeding, and/or infection can sometimes occur at the phlebotomy site. Very rarely syncope can occur during phlebotomy.

Saliva Sample
Donating saliva is not harmful. If a subject gives a saliva sample, their mouth may become dry from spitting into the tube.

Confidentiality
Loss of confidentiality is another potential hazard of any research protocol. Specific confidentiality concerns are associated with genetic information. The investigators follow a system of specific precautions to ensure the confidentiality of genetic data generated by use of the DNA collected in this protocol; see Section VIII "Confidentiality of Data" below.
We were issued a Certificate of Confidentiality on 5/24/23.

Subjects in Psychotherapy and Supplement Study:

The therapy is designed to help to develop more healthy ways to regulate emotions and more healthy sleep and activity patterns. It is possible that the subject could feel worse during the treatment. If the subject does, the subject is free to stop at any time. If the subject wishes, we can help to inform their treater.

The subject may be asked to utilize a computer or phone for sessions via videotelecommunication, wear the actigraphy device, use the EMA electronic diary and fill out self-reports through Qualtrics. There is a risk of loss of confidentiality with use of the internet. 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 device or EMA diary device and neither have GPS or any other location recording capability. Deidentified raw activity, emotional, and behavioral data is downloaded to a desktop app and converted to a .csv file that only the researchers on this project can match to subjects. The subject may find that the actigraph provided to them is uncomfortable to wear on their wrist. If this occurs, the subject can opt not to wear the device without this affecting their participation in the other parts of the study. If the devices are lost, there is no way to track the device back to the user as neither holds personally identifying information.

2. **Minimizing Risks:** How will the above-mentioned risks be minimized?

Diagnostic Assessment and Symptom Rating

Discussing symptoms or past experiences can sometimes be stressful. These procedures will be described to the subject, and if applicable, to the parent/guardian. Not all subjects are referred by treaters, but if they are, these procedures will also be explained to the referring treater as well. A subject will be excluded from study if there is a contraindication to these procedures. Interviewers will be specifically trained to collect only information necessary for the purposes of this study. Interviews are to be conducted in a professional and skillful manner.

If there is an acute concern that a subject could be a danger to himself/herself or others, he/she will be escorted to the emergency room, or if necessary the study staff will activate the EMS system/Police (911). If it is the opinion of an investigator that a subject is in need of psychiatric care, a referral will be given to that subject. If a subject asks that information from the diagnostic interview be communicated to his/her outside treater, an investigator from the study will provide the requested information to the treater.

If an individual contacts our program and asks for a referral, or, if an enrolled subject is in need of psychiatric care, we provide names and phone numbers of referrals. If the person wishes, we are happy to facilitate the intake. If a subject/parent/guardian expresses significant distress during the screening process, we obtain their contact information and address and try to keep them on the phone for the PI or clinician of the program to speak with them. If the subject/parent/guardian has an outside clinician it will be recommended that they talk with their clinician and, if they wish, we will speak with the clinician. If the subject/parent/guardian is judged by the clinician to be in imminent danger then the subject/parent/guardian will be told to contact their outside clinician if they have one, go to the emergency room, or if unwilling, the outside clinician and 911 may be called.

If a parent/guardian of a subject requested a referral for themselves, and/or appeared in need of psychiatric care, we provide names and phone numbers of referrals. If the person wishes, we are happy to facilitate the intake. If a parent/guardian expresses distress and/or suicidal ideation, then the PI will be contacted and the PI and/or a licensed clinician of the program will evaluate the situation. If the subject/parent/guardian has an outside clinician it will be recommended that they talk with their clinician and, if they wish, we will speak with the clinician. If the parent/guardian is judged by the clinician to be in imminent danger then the parent/guardian will be escorted to the emergency room, or if unwilling the outside clinician and 911 may be called.

Neuropsychological Task

The content of the stimuli and task will be explained to the subject, and if applicable, to the parent/guardian. If there is any question as to whether a subject might find such stimuli or task disturbing, they will not be exposed to the stimuli.

Magnetic Resonance Imaging and Spectroscopy (MRI and MRS)

Magnetic resonance (MR) is a technique that uses magnetism 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 to the subject, they may ask to stop the study at any time and we will take them out of the MR scanner. On occasion, some people might feel dizzy, fatigued, get an upset stomach, have a metallic taste or feel tingling sensations or muscle twitches, possible headaches from the noise, back/neck aches from lying still. These sensations usually go away quickly but the subject is asked to tell the research staff if they have any of these symptoms. The subject is given a rubber ball to hold in their hand during the

scanning process. Once this ball is squeezed it sets off an alarm notifying the technician that the subject needs immediate attention.

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. To reduce this risk, we require that all people involved with the study remove all metal from their clothing and all metal objects from their pockets to help prevent against the potential risk of metal objects being pulled into the magnet and causing injury. All subjects involved with the study walk through a detector designed to detect metal objects prior to entering the scanner. 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.

We want the subject to read and answer very carefully the questions on the MR Safety Questionnaire related to their personal safety. The subject will take a moment to be sure that they have read the MR Safety Questionnaire and be sure to tell us any information about them that they think might be important.

This MR study is for research purposes only and is not in any way a clinical examination. The scans performed in this study are not designed to find abnormalities. The primary investigator, the lab, the MR technologist, and the Magnetic Resonance Research Center are not qualified to interpret the MR scans and are not responsible for providing a diagnostic evaluation of the images. If a worrisome finding is seen on the subject's scan, a radiologist will be asked to review the relevant images. Based on his or her recommendation (if any), the primary investigator or consulting physician will contact the subject, inform them of the finding regarding their scan, and recommend that the subject seek medical advice as a precautionary measure. The decision for additional examination or treatment would lie solely with the subject and their physician. The investigators, the consulting physician, the Magnetic Resonance Research Center, and Yale University are not responsible for any examination or treatment that the subject receives based on these findings. The images collected in this study are not a clinical MR exam and for that reason, they will not be made available for diagnostic purposes.

Scanner anxiety will be diminished by discussing the procedure and allowing the subjects to view the scanner prior to entry into it. Every effort will be made to ensure the comfort of subjects while in the MRI scanner. Subjects will be communicated with frequently by intercom and will be able to communicate with the MR staff throughout scanning. Subjects may discontinue at any time if they wish due to any mental or physical discomfort or any other reason. It will be made clear that the participation is completely voluntary and that if the subject is a patient of the Yale Medical Center then his/her decision will in no way affect his/her treatment. A study session will also be terminated if there is unexpected technical difficulty that precludes the safe and efficient performance of the study.

While there are no known risks associated with MRI and pregnancy it is standard clinical practice to avoid MRI scans in pregnancy when possible and therefore there is not a large pool of data. Given this, pregnant subjects will be excluded from study.

Scanning is performed at The Anlyan Center on the campus of the Yale University Medical Center so that emergency medical intervention is available in the event of an adverse event.

Blood Draw

Only personnel from our lab or the YCCI-HRU trained in phlebotomy will perform the blood draws. The YCCI-HRU has agreed to provide nurses experienced in blood draws in children and adults.

Confidentiality of Data

Biological materials (blood or saliva) for DNA studies collected from individuals are identified by a letter and number code rather than by name. For this genetic component, the samples that are brought to Dr. Gelernter's laboratory for storage and analysis are coded with a letter and number code that does not contain personal identifiers. Accompanying demographic information is limited to age, sex, diagnosis,

and ethnicity/race. Scans are also identified by code number. No genotype data are released to subjects or clinicians, or are recorded in the medical record, under any circumstances.

To protect subject confidentiality, subjects will be assigned a letter and number code that will be used when performing data analysis. Paper study documents that contain identifying information will be kept in a locked cabinet in a locked office in the investigator's locked research suite. The letter and number codes with the link to subject 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 on office desktop computers, as well as CDs stored in a locked file cabinet, in a locked office in the investigator's locked research suite. Some subject information will also be stored on unencrypted electronic databases, but these databases will contain only de-identified data. Laptops and computers will be pass-word protected.

After the study is closed and all data analysis is complete, all identifiers will be removed. The code will continue to be stored in a secure location to verify data should that be necessary. All other personally identifying information will be removed and deleted using the appropriate methods (e.g. zeroing). These records will be destroyed according with policies regarding length of time that research documents need to be retained after protocol completion.

Fate of DNA to be studied and issues of DNA "banking": DNA samples from participants will be retained for future study. This is clearly indicated in the informed consent. A subject or the parent/guardian of a minor subject may request that we destroy the code linking the identifiers of the subject with their DNA sample, so that the sample would only be studied anonymously from that point forward.

3. **Data and Safety Monitoring Plan:** Please include a Data and Safety Monitoring Plan (DSMP) that includes an explicit statement of overall risks, addresses attribution and grading of adverse events and describes procedures for monitoring the ongoing progress of the research and reporting adverse events. For more information, please see the HIC website: http://info.med.yale.edu/hic/forms/index.html

This protocol presents greater than minimal risks to the subjects and adverse events are not anticipated but the potential exists for anticipated and/or unanticipated adverse events, 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 adverse events occur, serious unanticipated adverse events 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 adverse event 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 principal investigator 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.

Greater Than Minimal Risk DSMP

1. Personnel responsible for the safety review and its frequency:

The principal investigator 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 principal investigator (monitor) will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. The principal investigator, the Institutional Review Board (IRB) or the HIC or the NIMH have the authority to stop or suspend the study or require modifications

For the psychotherapy study, the Independent Safety Monitor (ISM), Laura Ment, is an independent physician and appropriate expert with relevant expertise whose primary responsibility is to provide independent monitoring of the clinical trial.

2. The risks associated with the current study are deemed for the following reasons: (choose those that apply)

1. We do not view the risks associated with the psychotherapy intervention as minimal risks.
2. We do not view the risks associated with the combined use of (not apply) and (not apply) as minimal risks.
3. Given the now established safety and validity of the current psychotherapy intervention in our prior work, we do not view the proposed studies as high risk.
4. Given our experience with the combined co-administration (not apply), 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 adverse events, 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:

3. Attribution of Adverse Events:

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

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

4. Plan for Grading Adverse Events:

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

1. Mild adverse event
2. Moderate adverse event
3. Severe

5. Plan for Determining Seriousness of Adverse Events:
Serious Adverse Events:
In addition to grading the adverse event, the PI will determine whether the adverse event meets the criteria for a Serious Adverse Event (SAE). An adverse event is considered serious if it:

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 adverse event 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 adverse event may be graded as severe but still not meet the criteria for a Serious Adverse Event. Similarly, an adverse event may be graded as moderate but still meet the criteria for an SAE. It is important for the PI to consider the grade of the event as well as its "seriousness" when determining whether reporting to the IRB is necessary.

6. Plan for reporting UPIRSOs (including Adverse Events) to the IRB

The principal investigator will report the following types of adverse events to the IRB:

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

1. Is unexpected (in terms of nature, specificity, severity, or frequency) given (a) the research procedures described in the protocol-related documents, such as the IRB-approved protocol and informed consent document and (b) the characteristics of the subject population being studied; AND
2. Is 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
3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, legal, or social harm) than was previously known or recognized.

Unanticipated Problems Involving Risks to Subjects or Others (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*. ***Please note*** that adverse events are reportable to the IRB as UPIRSOs **only** if they meet all 3 criteria listed above.

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 should 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**.** In lieu of a summary of external events, a current DSMB report can be submitted for research studies that are subject

to oversight by a DSMB (or other monitoring entity that is monitoring the study on behalf of an industry sponsor).

7. Plan for reporting adverse events to co-investigators on the study, as appropriate the protocol's research monitor(s), e.g., industrial sponsor, Yale Cancer Center Data and Safety Monitoring Committee (DSMC), Protocol Review Committee (PRC), DSMBs, study sponsors, funding and regulatory agencies, and regulatory and decision-making bodies.
For the current study, the following individuals, funding, and/or regulatory agencies will be notified: (choose those that apply)

- X All Co-Investigators listed on the protocol.
- ☐ Yale Cancer Center Data and Safety Monitoring Committee (DSMC)
- ☐ National Institutes of Health
- ☐ Food and Drug Administration (Physician-Sponsored IND #_____)
- ☐ Medical Research Foundation (Grant_____)
- ☐ Study Sponsor
- ☐ Other Data Safety Monitoring Board (DSMB) or Committee (DSMC)

The principal investigator (Hilary Blumberg, MD) will conduct a review of all adverse events upon completion of every study subject. The principal investigator will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent form are required.

Please note: For any study that may be considered high risk, the IRB will be more focused on the safety requirements for the study and a DSMB will likely be required.

4. **Confidentiality and Security of Data:**
   a) Will private identifiable information about individuals be collected and used? Yes, such data will be collected and recorded during semi-structured interviews with the parent/guardian and the subject. Mood disorders subjects will also be asked to sign a request to obtain/release their specific data they elect to/from Yale and their treatments providers.

   b) How will research data be collected and recorded? *Investigators are reminded that subject identifiers and the means to link subject names and codes with research data should not be stored on unencrypted moveable media, (e.g., laptops, compact discs, jump drives, thumb drives). Identifiers and code keys must be stored in a secure manner, e.g., Yale network servers.*

Biological materials (blood or saliva) for biochemical DNA studies that are collected from individuals are identified by code number rather than by name. For the biochemical and genetic components, the samples that are brought to Dr. Gelernter's laboratory for storage and analysis are coded with a letter and number code that does not contain personal identifiers. Accompanying demographic information is limited to age, sex, diagnosis, and ethnicity/race. Scans are also identified by code number with no

personal identifiers. Data collected via actigraphy applications, ZOOM, and Qualtrics will be identified by code number with no personal identifiers.

Copies of video and audio recordings of Psychotherapy Pilot Study subjects will also be kept in locked cabinets, in a locked room separate from PHI data. Coded subject self-reports completed through Qualtrics will be downloaded to a secure Yale server.

c) How will digital data be stored? ☒CD ☒ ☒DVD ☒Flash Drive ☒☒Portable Hard Drive
☒Secure Server ☒Laptop Computer ☒Desktop Computer ☐ Other Specify: _____

d) What methods and procedures will be used to safeguard the confidentiality of subjects and their data? (Note: data security plan must include methods to secure all information gathered about an individual during the recruitment, screening and participation phases.) *Investigators must use encryption methods to protect access to files that contain identifiable research data that are stored on moveable media. Other data security methods may be appropriate for other, not directly identifiable types of research data.*

Please see *Confidentiality of Data* section above.

e) What mechanisms are in place to ensure proper use and continued protection of these data?

Please see *Confidentiality of Data* section above.

f) Describe any limits to confidentiality, e.g., legal requirements for disclosure of reportable diseases, abuse of child or elder, danger to self or others.

Limits exist for suspicion that the child is in acute danger of harming self or others and for suspected child or elder abuse.

g) What will be done with the data when the research is completed? *Researchers are reminded that subject permission must be obtained to retain personally identifiable research data for future research purposes. Researchers are also reminded that deleting data or reformatting disks is not sufficient for removing personally identifiable information or data. Zeroing, degaussing or other method must be used to remove these types of identifiers or data.*

Please see *Confidentiality of Data* section above. Once all data for this project has been collected and results of these studies published, study data which has been stripped of all subject identifiers will be available to other qualified researchers. Any such request for study data which meets reasonable standards of scientific integrity will be considered.

h) Will any external or internal individuals or agencies charged with monitoring (such as the study sponsor, FDA, QUACS, SSC, etc.) have access to study data?

Records can only be revealed in accordance with Yale HIC policy.

i) If appropriate, has a Certificate of Confidentiality been obtained? For more information, please see the HIC website: http://www.med.yale.edu/hic/policy/CofC.pdf

Yes, this protocol was granted a Certificate of Confidentiality that will be uploaded in IRES.

5. **Potential Benefits:** Please identify any benefits that may be reasonably expected to result from the research, either to subjects or to society at large.

There are no benefits to the subject. However, the prospect of genetic discoveries leading to new understanding of disease, and potentially to new treatments or preventions for disease, is quite real. There are also general benefits to this research with regards to development of new methods for localizing critical brain structures involved in mood disorders.

For the subjects in the BE-SMART and the pilot study involving psychotherapy, there may be potential benefits of the treatment, thus increasing the benefit to risk ratio.

SECTION VIII: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. **Alternatives:** For studies offering treatment, what treatment alternatives are available outside of the research?
   Please note: Some categories of non-treatment research may also require a section outlining alternatives to participation. For example, a study that provides screening for a particular illness or condition should state whether testing is available outside of the research.
   Subjects have the option to decline participation, or if they have initially agreed to participate to withdraw their participation at any time during the study.

2. **Payments for participation (Economic Considerations):** Describe any payments that will be made to subjects (including direct monetary payment, payment in the form of a gift, or reimbursement for costs such as travel, parking, childcare, etc.), and the conditions for receiving this compensation.
   All subjects will be paid for all parts of this study in which they participate. Subjects do not have to do all the parts to participate in this study.

1. Subjects will be compensated $30 for their time participation in the initial interview.
2. Subjects will be compensated $30 for their time participation in cognitive testing.
3. Subjects will be compensated $50 for their time participation in the MRI session.
4. Subjects will be compensated $30 for their time participating in a blood/saliva sample collection for biochemical and DNA study.

   Subjects will additionally be compensated for reasonable travel expenses and if parking at Temple Street or Temple Medical garage the subject will be reimbursed $15 if 3 hours or under and $18 if parking 4 hrs or longer. If a subject participates for more than 3 consecutive hours we will additionally provide lunch or refreshments in the amount of $10 each per parent/guardian and child. If it becomes necessary for subjects to return for an unanticipated, additional visit to complete some part/s of the study the subject will be reimbursed appropriately. Any other reasonable expenses will be made per PI discretion.
   There are no plans at present to use the DNA samples for any commercial uses. However, if a discovery from research on DNA samples results in a patent or becomes commercially useful in any way, subjects will not be notified.

For subjects participating in the Psychotherapy Study the payment schedule is as follows:

1. The subject will be compensated $30 for their time in participation in the Part 1 interview.
2. The subject will be compensated $30 for their time in participation in the Part 1 cognitive testing.
3. The subject will be compensated $50 for their time in participation in the Part 1MRI session.

4. The subject will be compensated $30 for their time in participation in the Part 2 interview assessment.
5. The subject will be compensated $50 for their time in participation in the Part 2 MRI session.
6. The subject will be compensated $30 for their time in participation in the Part 3 interview.
7. The subject will be compensated $50 for their time in participation in the Part 3MRI session.
8. The subject will be compensated $10 for their time in completion of interim assessments at the intervening therapy sessions (total possible, $90 for their time completing 9 separate sets of assessments)
9. The subject will be compensated $10 for their time completing weekly EMA in a digital diary (total possible, $120 for completing 12 weeks)

   Subjects will additionally be compensated for reasonable travel expenses and if parking at Temple Street or Temple Medical garage the subject will be reimbursed $15 if 3 hours or under and $18 if parking 4 hours or longer. Any other reasonable expenses will be made per PI discretion.

   Costs for participation (Economic Considerations): Clearly describe the subject's costs associated with participation in the research. If it is possible that the subject's insurance, health plan benefits, or other third-party payers will not cover research procedures or tests, this should be indicated. Clearly describe the parts of the research visits (drugs, tests, procedures, etc.) that will be provided at no cost to the subjects.
   Please note: If payment will be prorated for subjects who do not complete the study, this should be clearly explained. If payment is conditional on completing the study, this should be clearly explained.

   All research interventions and procedures are free of charge.
   All participation in the psychotherapy study will be free of charge.
   All participants given the actigraph to wear will be free of charge but we ask that you return it to study staff at the end of participation.

3. **In Case of Injury:** Will medical treatment be available if injury occurs? Where and from whom may treatment be obtained? Are there any limits to the treatment being provided? Who will pay for this treatment? How will it be accessed by subjects? (Please refer to the Compensation and Medical Therapy sections of the *HIC Guidance for Investigators Manual* available on the HIC web site: http://www.med.yale.edu/hic/forms/forms/guidelines.pdf)

Medical treatment will be offered to the parent/guardian for any physical injuries sustained as consequence of the participation of his/her child in this research. They will be informed that their health insurance will be charged for this treatment. The parent/guardian will also be informed that in the event of physical injury, no additional financial compensation is available.