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The Tulsa 1000: A naturalistic study protocol for multi-level assessment and outcome prediction in a large psychiatric sample

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ABSTRACT

Introduction: Although neuroscience has made tremendous progress in understanding the basic neural circuitry that underlies important processes such as attention, memory, and emotion, little progress has been made in applying these insights to psychiatric populations in order to make clinically meaningful predictions. The overall aim of the Tulsa 1000 (T-1000) is to use the NIMH Research Domain Criteria (RDoc) framework to establish a robust and reliable dimensional set of variables that quantifies the positive and negative valence, cognition, and arousal/interoception domains to generate clinically useful treatment predictions.

Methods and Analysis: The Tulsa 1000 is a naturalistic study that will recruit, assess, and longitudinally follow 1,000 participants, including healthy controls and treatment-seeking individuals with mood, anxiety, substance use and eating disorders. Each participant will undergo approximately 24 hours of testing over the course of a 1-year time period. The goal of the study is to determine how disorders of affect, substance use, and eating behavior organize across different levels of analysis (genes, molecules, cells, neural circuits, physiology, behavior, and self-report) to predict long-term prognosis, symptom severity, and treatment outcome. The data will be used to generate computational models based on Bayesian statistics. The final end-point of this multi-level latent variable analysis will be a set of standardized assessments that can be developed into a clinical tool to help clinicians predict outcome and select the best intervention for an individual patient, taking psychiatry a step closer toward personalized medicine.

Ethics and Dissemination: Ethical approval was obtained from Western Institutional Review Board (WIRB) screening protocol #20101611. The dissemination plan includes informing health professionals of results that may be used in clinical practice, submitting results to journals for peer-reviewed publication, presenting results at national and international conferences, and making the dataset available to other researchers and mental health professionals.

Trial registration number: NCT02450240

STRENGTHS AND LIMITATIONS

Strengths

- The study uses multiple units of analysis for phenotyping.
- The study explores dimensional psychopathology that is representative of clinical populations.
- The study includes a clear and cohesive statistical analysis plan for a large and complex dataset.

Limitations

- The study does not include controlled treatment interventions.
- The study is a longitudinal observational study.
- The study is representative of a local Midwestern community that may not generalize to populations in different parts of the country or world.

INTRODUCTION

Mood [1] and anxiety [2] disorders are the most common form of mental illness and represent one of the biggest health issues worldwide, accounting for approximately $16 trillion in lost productivity or 25% of the global GDP over the next 20 years [3]. Epidemiological data estimate the lifetime prevalence of Major Depressive Disorder (MDD) at about 18% and the 12-month prevalence at 7% [4]. Both MDD and anxiety disorders are associated with significant medical comorbidities [5] including substance use and eating disorders, which further exacerbate the cost and suffering associated with these disorders. The heterogeneity of mood and anxiety disorders and the limited ability to identify broadly efficacious interventions have provided an impetus to utilize dimensional approaches to help delineate distinct syndromes of mood and anxiety that better reflect the underlying neurobiology [6].

Although neuroscience has made tremendous progress in understanding the basic neural circuitry that underlies important processes such as attention, memory, and basic emotion processing, little progress has been made in applying these insights to psychiatric populations in order to make clinically meaningful predictions. This may be because the diagnostic system that is currently used for mental disorders is based on verbal report, observable behavior, and clinical phenomena that have been aggregated based on statistical approaches to provide reliable categories [7]. Unfortunately, the connection between psychiatric disorders and their underlying neurobiology has been difficult to establish. The NIMH Research Domain Criteria (RDoC) framework was developed as a heuristic approach to better integrate pathophysiology with psychopathology [6]. The RDoC initiative highlights two important goals for this objective: (1) psychiatric studies should transcend traditional diagnostic groups in order to adequately capture the inherent heterogeneity of symptomatology, and (2) clinical neuroscience and advanced statistical approaches should be used to determine the relationship between different units of analyses (self-report, behavior, physiology, neural circuitry, genetics, and clinically relevant psychopathology). The Tulsa 1000 aims to address these needs by determining how biological and objective behavioral measures can contribute to improving assessment and treatment of mental illness.

We use the RDoC framework as a heuristic to recruit, assess, and follow up a group of treatment-seeking individuals with various mental health disorders. Within these groups we aim to determine how affective, addictive, and feeding abnormalities organize across different

levels of analysis and subsequently identify whether these latent factors can be used to generate clinically useful predictions. We aim to establish a robust and reliable dimensional set of variables that quantify the positive and negative valence, cognition, and arousal/interoception RDoC domains based on a latent variable approach [8-10]. These variables will be used to determine whether (a) measures of each domain (across different units of analyses) consistently relate to one another, (b) they predict the progression of symptoms over time (including natural recovery or worsening of symptoms), (c) they predict response to independently-sought pharmacological or behavioral treatments, and (d) they can be used in subsequent computational models of mental health to gain a more fundamental understanding of the pathology and predict illness course and recovery.

Overview of RDoC domains

Affect, or the tendency to experience a given emotion, is often subdivided into two domains [11]. Positive affect is the experience of positive emotions, such as happiness, excitement, elation, and enthusiasm. Negative affect is the experience of negative emotions, such as anger, resentment, sadness, anxiety, and fear. Positive affect and negative affect systems represent dimensions of psychopathology identified by the RDoC work groups [12, 13]. High negative affect is common to anxiety and depression [14-16] and comorbid anxiety and depression is associated with more negative affect than each disorder alone [17]. Low positive affect is relatively specific to depression, with some evidence of low positive affect in social anxiety as well [14, 18]. In addition, psychophysiological and neurobiological data indicate that the negative affect system is closely tied to threat sensitivity whereas the positive affect system is closely tied to reward sensitivity.

Positive Valence System

A central construct of the positive valence system is *approach motivation*, which can be defined as processes that regulate the direction and maintenance of approach behavior. The constructs of *reward seeking* and *reward sensitivity* are components of approach motivation. Reward sensitivity refers to the anticipation and receipt of positive stimuli. The primary neural mechanisms of reward sensitivity involve the ventral striatum (VS) and orbitofrontal cortex (OFC). These structures are involved in the processing of primary rewards, such as pleasant tastes [19], smells [20] or sights [21], as well as secondary (monetary) rewards [21-23]. The VS plays an important role in the anticipation of reward [24, 25] as well as the receipt of reward [22, 26]. The VS is part of a larger fronto-striatal circuit subserving reward-related processing that also includes the OFC, a subregion of the prefrontal cortex [27]. An important functional coupling exists between the VS and OFC [28]. Reward-processing also involves other neural regions, including the amygdala [29-31], dorsal anterior cingulate cortex (ACC) [32] and the hippocampus [33].

Relationship between reward sensitivity and the positive valence system: Extant evidence shows that individuals have deficits in positive affect (i.e., individuals with depressive disorders) show deficits in reward processing, at both the behavioral [34] and the neural levels [35]. At the behavioral level, individuals with major depression are less responsive to reward-relevant stimuli than non-depressed individuals and deficits in reward responding are associated with deficits in positive affect or the ability to experience pleasure [34, 36]. At the neural level, depression is associated with reduced activation in fronto-striatal circuits, namely the VS and caudate, during reward processing compared with healthy controls [35]. Anhedonia [37, 38] (or, the inability to experience pleasure) and reward-related processing [39] have been considered critical factors in the development of depression. Reward sensitivity in anxiety disorders has been less well studied. Similar to depression, evidence of reduced striatal activation during reward processing has been found in individuals diagnosed with posttraumatic stress disorder (PTSD) compared with healthy controls [40, 41], particularly in relation to anhedonic features of PTSD (e.g., emotional numbing). Other studies, however, find evidence of heightened striatal activation during reward anticipation in some anxiety disorders [42]. This heterogeneity underscores the potential value of moving towards a dimensional understanding of reward sensitivity and positive valence system functioning in anxiety, mood, substance and eating disorders.

Negative Valence System

Responses to *acute threat* (fear) and *potential harm* (anxiety) were considered by the RDoC workshop committee to be central constructs within the negative valence system. One approach to measuring response to threat is via fear conditioning, which involves excitatory learning of conditioned stimulus vs. unconditioned stimulus (CS-US) associations [43, 44]. Research on fear learning uniquely adapts to translational neuroscience contexts because we understand with great precision the relevant neural processes in many species, including humans. The brain regions that have most consistently been associated with fear conditioning are the amygdala [45-49] and insular cortex [50]. In healthy adults, increased activity in the amygdala and insula is typically observed in response to the CS during conditioning. Response to loss was cited by the RDoC committee as another critical component process of the negative valence system, and may be particularly related to depression. Reward paradigms that include loss or punishment trials (e.g., losing money for incorrect responses [51-53]) can be used to measure behavioral and neural responses to loss anticipation and outcome. Research in healthy adults suggests that the ventral and dorsal striatum (caudate) are associated with anticipation and receipt of loss or punishment using these paradigms [51, 52].

Cognitive System

The major constructs that were considered by the RDoC committee on cognitive systems

included: (1) *attention,* i.e. a set of processes that regulate access to capacity-limited systems, such as awareness, higher perceptual processes, and motor action; (2) *perception*, i.e. process(es) that perform computations on sensory data to construct and transform representations of the external environment to make predictions and guide action; (3) *declarative memory*, i.e. the acquisition or encoding, storage, consolidation, and retrieval of facts and events; (4) *language*, i.e. a system of shared symbolic representations of the world, the self and abstract concepts that supports thought and communication; (5) *cognitive control*, i.e. a system that modulates the operation of other cognitive and emotional systems, in the service of goal-directed behavior, when prepotent modes of responding are not adequate to meet the demands of the current context; (6) *working memory*, i.e. the active maintenance and flexible updating of goal/task relevant information (items, goals, strategies, etc.) in a form that has limited capacity and resists interference.

The T-1000 will focuses primarily on two constructs within the cognitive system (a) *cognitive control* and (b) *attention*. Inhibitory control, the ability to withhold a prepotent action, is an important cognitive control process, and is hypothesized to be dysfunctional in individuals with substance use problems [54]. However, it is unclear how dysfunctional cognitive control previously associated with continuing substance use, and how this effects relapse following a period of recovery from substance use. Prior investigations have shown inhibitory control deficits in stimulant dependent individuals and moderate correlations with drug use indices [55-60]. Stimulant dependence has been linked to reduced functioning of dopamine transporters as well as hypo-metabolism in various regions critical to inhibitory control, including basal ganglia, anterior cingulate cortex and other prefrontal areas [61-64]. During inhibitory control tasks, such as go/no-go and Stroop paradigms, cocaine abusers also show hypoactivity in the ACC, pre-supplementary motor area, superior frontal gyrus, and insula [65-67]. In contrast to dependent users, there are relatively few studies on occasional users, although some behavioral studies suggest subtle impairments in inhibitory response and error monitoring [68, 69].

In this study protocol, we will combine Bayesian ideal observer model-based analysis with fast, event-related functional magnetic resonance imaging (fMRI) data, to investigate subtle behavioral and neural differences among the target populations. Bayesian ideal observer models have been applied widely to the study of choice in uncertain environments, and to identify potential neural markers of the iterative processes of belief update underlying such models [70, 71]. Subsequent modeling studies have shown that such a framework is readily adapted to various aspects of executive function, including attentional and inhibitory control [72-75]. In particular, this literature suggests that apparently distinct faculties in inhibitory control can be folded into a single framework where subtle differences in task contexts are

reflected in their influence on components of the framework, giving rise to the diversity of observed behavior.

Arousal/Interoceptive System

Arousal is defined as a continuum of sensitivity of the organism to stimuli, both external and internal. Interoception refers to how the brain receives, processes, and integrates internal signals from the body to affect motivated behavior [76-78]. One important aspect of the arousal domain is the link to homeostatic drives and interoception. Different conceptualizations of interoception have included its definition as the state of the individual at a particular point in time [79], or as the sensing of body-related information in terms of awareness [80], or as the accuracy of the sensing process [81], or as a trait phenomenon [82]. It is therefore a multifaceted process operating across numerous physiological and neural organ systems [83, 84]. Interoception provides an anatomical framework for identifying pathways focused on modulating the internal state of the individual. This framework comprises peripheral receptors [83], c-fiber afferents, spino-thalamic projections, specific thalamic nuclei, posterior and anterior insula as the limbic sensory cortex, and ACC as the limbic motor cortex (for reviews see [85, 86]). Central to the concept of interoception is that body-state relevant signals comprise a rich and highly organized source of information that affects how an individual engages in motivated behavior. Importantly, interoception is linked to homeostasis [87], which implies that an individual's motivated approach or avoidance behavior toward stimuli and resources in the outside world is aimed at maintaining an equilibrium in the inside world of the organism. For example, a person will approach a heat source in a cold environment but avoid it when the ambient temperature is high.

The insular cortex is a complex brain structure, which is organized macroscopically along an anterior-posterior [76] and superior-inferior axis [88] and cytoarchitectonically as granular, dysgranular, and agranular from posterior to anterior insula, respectively [89, 90]. The anterior insula is predominately activated by effortful cognitive processing, whereas the posterior region is mostly activated by interoceptive sensory signals [91]. Moreover, the anterior insula, potentially together with the ACC, appears to pivotally influence the dynamics between default-mode and executive control networks [92]. The insula is thought to be the central nervous system hub for interoceptive processing, such that somatosensory relevant afferents enter the posterior insula and are integrated with the internal state in the mid-insula, and re-represented as a complex feeling state within the anterior insular cortex. There is an emerging generalized view that the ACC, among other functions, orchestrates approach or avoidance behaviors in response to particular internal body states that involve homeostatic perturbations [93]. This function of the ACC is supported by the strong functional [94] and anatomical [95] connections between the anterior insula and the ACC. This view is also aligned with a prediction error-based conceptualization of the specific computational processes that may be carried out within

the insula and ACC [96]. Taken together, the insula and ACC receive information about the individual's current body state and use this information to predict future body states and select actions that will help maintain bodily homeostasis.

The primary units of analyses are (a) symptoms, (b) paradigms / behavior, (c) physiology, (d) circuits, and (e) molecules. However, there are several new emerging areas that either provide opportunities to examine how individual domains are affected by biological influences other than the individual or have the potential to yield cellular models of diseases. Next, these other units of analysis are described further.

Microbiome

The human body can be considered a super-organism composed of 10 times more microbial cells than our body cells. A meta-genomic study of the human microbiome has shown that microbial cells contain 150 times more genes than our own genome and make up an extraordinarily diverse set of over 1000 bacterial species [97]. Our understanding of the vast collection of microbes that live on and inside us (*microbiota*) and their collective genes (*microbiome*) has been revolutionized by culture-independent 'metagenomic' techniques and DNA sequencing technologies. Gut microbiota play an important role in health and disease and can be considered a 'microbial organ' [98]. Each individual's microbiota shows significant variability across body habitats and time, which may provide clues as to how microbiome changes cause or prevent disease [99].

The interaction between microbiota and human organs has been extended recently to brain-gut interactions [100]. The brain can influence enteric microbiota indirectly, via changes in gastrointestinal motility and secretion, and intestinal permeability, or directly, via signaling molecules released into the gut lumen from cells in the lamina propria [101]. There is emerging preclinical evidence that variations in the composition of gut microbes may be associated with changes in the normal functioning of the nervous system [102]. For example, introducing *Citrobacter rodentium* in both C57BL/6 mice and germ-free Swiss-Webster mice resulted in memory dysfunction [103]. Conversely, early life stress alters fecal microbiota [104]. Germ free mice display increased motor activity and reduced anxiety, compared with specific pathogen free mice with a normal gut microbiota [105]. Moreover, germ-free mice also show a decrease in the N-methyl-D-aspartate receptor subunit NR2B mRNA expression in the central amygdala, increased brain-derived neurotrophic factor expression and decreased serotonin receptor 1A (5HT1A) expression in the dentate granule layer of the hippocampus [106]. Taken together, the human microbiome serves as the interface between our genes and our history of environmental exposures. Better understanding of microbiome-encoded pathways for xenobiotic metabolism also has important implications for improving the efficacy of pharmacologic interventions with neuromodulatory agents. Explorations of the microbiome thus offer new insight into our neurodevelopment, behavioral phenotypes, and perhaps disorders affecting complex processes,

such as cognition, personality, mood, sleep and eating.

Human induced pluripotent stem (hiPS) cells

The molecular mechanisms responsible for dysregulated mood and anxiety, substance use, and eating behaviors are not well understood and few defining characteristics of diseased neurons have been identified. We intend to address this by generating dopamine cells (or neurons) that have been derived from a subset of individuals with extreme phenotypes of depression and/or anxiety, substance use, or eating behaviors. We aim to create cell-based human models for psychiatric disorders by directly reprogramming blood cells into human induced pluripotent stem (hiPS) cells in both healthy individuals and those with clinically-significant complaints related to affect, substance use, or eating [107-109]. We aim to identify specific neuronal defects associated with dopamine neurons *in vitro* and demonstrate the reversibility of the disease phenotype in human neurons, with the expectation to ultimately screen chemical libraries to identify novel therapeutic targets. The goal of these experiments is to identify key molecular events involved in the dysregulation of these target populations and to exploit these as possible points of intervention.

Genetics and Epigenetics

In humans, there is considerable evidence that anxiety and depression are moderately heritable and influenced by multiple genes. Most experts now believe that it is highly unlikely that there are "genes for psychiatric disorders". Rather, genes involved in susceptibility to psychiatric disorders can best be understood at the level of more basic biological processes (e.g., neuronal cell migrations during development) and/or mental function in the context of particular life experiences that are requisite for the expression of psychopathology. If it is true that no single gene, or group of genes, can explain much of the variance in risk for mood or anxiety disorders, then the rationale for the continued study of genes in anxiety and depression is unclear. Importantly, the relationship between certain heritable quantitative traits and certain psychiatric disorders has been sufficiently well studied that this provides an opportunity to examine associations with quantitative traits that may be closer to the heritable phenotype (endophenotypes) than the categorical construct as outlined in the DSM-V. Furthermore, we and other investigators have identified abnormalities in functioning of key structures (e.g., amygdala and insula) within the brain's anxiety circuitry in anxiety-prone subjects and there is evidence that certain genes influence the extent of activation in these regions. There is ample reason to expect that genetic susceptibility factors for anxiety-related traits can be detected, and that functional neuroimaging techniques can be brought to bear to probe the functional relevance of such variants for anxiety-relevant emotion processing.

Data from twin and adoption studies indicate that major depressive disorder (MDD), addiction disorders, and eating disorders (anorexia nervosa and bulimia) are moderately heritable - in the

region of 40% to 60% - suggestive of a significant genetic contribution [110-112]. Clearly identifying the genetic variants that are associated with risk for developing these disorders would be helpful for predicting who is at risk of becoming ill and increasing our understanding of the pathophysiological basis of these disorders. Unfortunately, given the heterogeneity and complexity of MDD and anorexia nervosa, even well-powered GWAS datasets of ~10,000 cases and ~10,000 controls and ~5,500 cases and ~20,000 controls, respectively, have failed to identify alleles that achieve genome-wide significance [113, 114].

A more tractable approach than the traditional case-control association study is offered by large scale longitudinal designs such as the Tulsa 1000. Here the proposed within-subject genetic analyses will emphasize the prediction of naturalistic clinical outcomes such as response to pharmacological and/or non-pharmacological treatment. Further, the genetic data collected will be stored for future testing and combined with multiple phenotypes (e.g. neuroimaging, clinical, cognitive assessments, and other bioassays) to provide an integrated theoretical perspective on the genetic basis for disorders of mood, anxiety, eating and addiction [115-117].

Immunophenotyping

Data from several different fields of study suggest that at least a subset of individuals with depression and other psychiatric illnesses show immunological dysregulation characterized by activation of the innate immune system together with suppression of elements of the adaptive immune response (reviewed in [118-121]). However, progress has been limited by a disproportionate focus on a static and narrow aspect of innate immunity, i.e. single time-point measurements of CRP or cytokines to the exclusion of other potentially informative markers of innate and adaptive immune function. Here, we will leverage the T-1000 design to obtain a wide-range of immunophenotypes both at baseline and post-treatment. Further, the range of tasks embedded within the T-1000 will provide a rich opportunity to examine the effect of experimental manipulations on immune function. The data obtained will not only further our understanding of the nature of immune dysfunction in psychiatric illness but may lead to the identification of prognostic and/or predictive biomarkers that possess clinical utility.

METHODS

Aims and Objective

This is a multi-level, longitudinal observational study of healthy controls and treatment-seeking individuals with mental health problems in Tulsa and the surrounding regions of Oklahoma. The overall aim is to obtain a comprehensive assessment based on RDoC principles, in order to:

(1) Determine relationships among variables assessing positive/negative valence, cognition, and arousal/interoception domains in order to derive latent variables that describe psychopathology across units of analysis and diagnostic groups.

(2) Investigate whether latent factors can be used to generate clinically meaningful outcome predictions across different domains and diagnostic groups.

Thus, this study has the potential to substantially improve our understanding of how disorders of mood, anxiety, substance use, and eating behavior are organized across different units of analysis (genes, molecules, cells, neural circuits, physiology, behavior, and self-report) and different domains of functioning (positive and negative valence, cognition, and arousal/interoception). Upon completion, we will have robust and reliable dimensional measures that quantify these relationships among different units of analysis and different domains of functioning. The latent constructs will be the main outcome variables of this protocol. The baseline assessments will be used with individual-based prediction methods (e.g., random forests or support vector machines) to develop predictors. These predictors will be evaluated with test-specific statistics such as positive and negative likelihood ratios and standard measures such as area under the Receiver Operation Characteristic curve and area under Precision-Recall curve to determine which baseline measure or combination of measures best predicts clinical outcomes. Ultimately, the aim is to develop a set of assessments that can be used as a clinical tool to enhance outcome prediction for the clinician. These measures may also serve as an aid to determine who would likely benefit from different interventions.

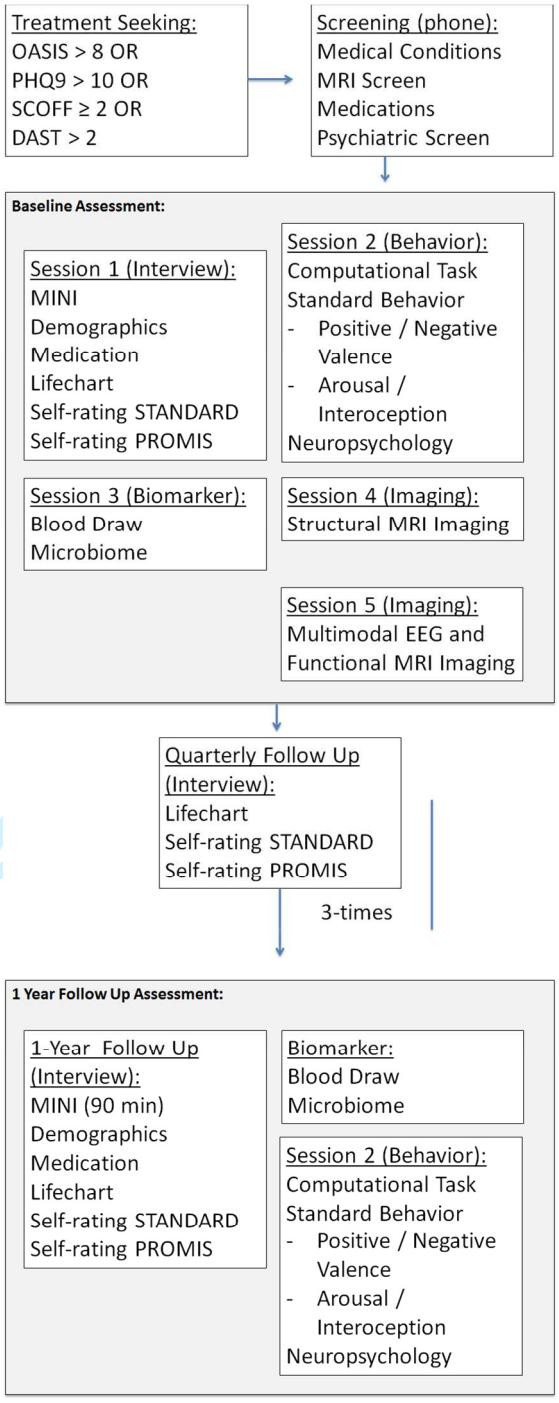
Participants

We propose to collect complete datasets on a total of 1000 participants with approximately 400 mood and/or anxiety, 400 substance use, 50 eating disorder and 150 mentally and physically healthy control participants in their respective categories. In order to obtain 1000 participants who complete the year-long study, we plan to enroll up to 1400 participants. Subjects will be between 18 and 55 years of age and have a body mass index between 17-38kg/m^2. Subjects will be referred from local treatment facilities or seeking treatment for anxiety and/or depressive symptoms, problems related to substance use, or problems related to eating behavior. As part of the inclusion criteria, mood/anxiety, substance, and eating disorder participants must also screen positive for these conditions as indicated by a score on the Patient Health Questionnaire (PHQ-9) ≥ 10 and/or Overall Anxiety Severity and Impairment Scale (OASIS) ≥ 8, Drug Abuse Screening Test (DAST-10) score > 2 or Eating Disorder Screen (SCOFF) score ≥ 2. Participants who meet criteria for one primary domain may also screen positive for one of the other study domains. Healthy control participants will screen negative for these inclusion measures.

Study design

The study's dependent variables will focus on the *positive and negative valence systems, cognition, and arousal/interoception domains* proposed by the RDoC [12, 13]. Using self-report, behavior, physiology, neural circuit, cell, molecule, and gene unit of analysis measures, we will apply these constructs to a clinical population of individuals with dysregulation of affect, substance use, and eating behavior recruited from treatment providers across different sites in the community. Through the application of latent variable analysis, we will derive latent constructs of positive and negative valence, cognition, and arousal/interoception system functioning that cut across units of analyses and diagnostic groups. Subjects will undergo a multi-level assessment based on the RDoC approach that consists of (a) a standardized diagnostic assessment (MINI), (b) self-report questionnaires assessing the positive and negative valence domains as well as interoception, (c) behavioral tasks assessing positive and negative valence, cognition, and interoception, (d) physiological measurements consisting of skin conductance, facial emotion expression monitoring, heart rate, respiration and eye-blink startle response, (e) functional magnetic resonance imaging focusing on reward-related processing, fear conditioning and extinction, cognitive control and inhibition, and interoceptive processing, (f) biomarker assessment, (g) microbiome assessment, (h) blood to derive induced pluripotent stem cells (IPS), (i) and genetic as well as epigenetic assessments. Subsequently, these individuals will be followed up quarterly and for one year. At months 3, 6, and 9, only self-report assessments will be collected, and the participants and will be re-assessed using a multi-domain assessment of functioning, which will include: (a) symptom severity and duration, (b) subjective well-being, (c)

Figure 1. T1000 Workflow Schematic



psychosocial function, (c) occupational function, (d) physical health, (e) utilization of mental health resources (treatment), and (f) adherence to treatment.

The workflow schematic in Figure 1 describes the overall outline of the T-1000 study and the measures obtained at different points in time.

Potential subjects will be screened by phone or in-person using the Western Institutional Review Board (WIRB) screening protocol 20101611. Once an individual has been identified as a potential subject in the T-1000, he or she will complete two to six in-person sessions within a two-week time period. However, completion of these sessions may be broken into more or less visits depending on what works best for the participant's schedule. The order of the baseline assessments may also be modified to ensure timely and efficient completion, given individual differences in completion times for the various measures (e.g., variability in how long individuals may take to complete self-report measures).

Although entry into the study is not based on meeting diagnostic criteria for a particular mood, anxiety, substance use, or eating disorder, it will be important to characterize how our findings map onto the DSM (using DSM-5 criteria). Accordingly, patients will complete a diagnostic interview with study personnel, using an abbreviated version of the Mini International Neuropsychiatric Interview (MINI Version 6.0) [122]. The MINI was chosen over other diagnostic interviews (e.g., SCID or CIDI) because of its relative brevity, good inter-rater reliability, and suitability for use by an interviewer with limited training. We will include sections on panic disorder (PD), social anxiety disorder (SAD), posttraumatic stress disorder (PTSD), generalized anxiety disorder (GAD), eating disorders (ED), obsessive-compulsive disorder (OCD), and major depressive disorder (MDD) and several modules to provide further clinical information or to determine ineligibility (suicidality, manic/hypomanic episode, and psychotic disorders).

After completing the MINI and satisfying study criteria, the subjects will complete a wide range of self-assessments that are targeted to probe the positive and negative valence domains, cognitive systems and interoceptive systems. Subjects included in the study will return for a behavioral testing session (session 2) and neuroimaging and biomarker testing sessions (sessions 3-5). During the behavioral session participants will complete a battery of neuropsychological assessments, a set of cognitive tasks which have been selected based on underlying computational models, a modified dot probe detection task, an approach/avoidance conflict task, and an emotional reactivity task in which they view blocks of emotional images. Interoception will be probed using a series of heartbeat detection tasks, an inspiratory breathhold experiment, and a cold pressor test. State affect and physiology will be assessed throughout the behavioral session procedures. The biomarker session will include a blood draw, microbiome collection, physical measurements including height, weight, body

composition assessment, hip/waist ratio, and vital signs (pulse, blood pressure). The structural MRI, functional MRI and EEG session will include high resolution anatomical brain scans, a resting state functional scan and task-based functional scans targeting neural systems associated with reward, attention, inhibition, interoception and fear conditioning.

The details of each session are listed in Table 1: the first column indicates which construct will be examined, the second column lists the name of the test. All self-report assessment measures will be administered electronically through REDCap [123].

Study Sessions

Detailed descriptions of the clinical, demographic, self-report, behavioral, neuropsychological and functional neuroimaging measures listed below are provided in the supplementary materials.

The Baseline Session

Clinical interview, demographics, and questionnaires detailed in Table 1 will be administered by masters or nurse level assistants who are supervised by licensed clinical psychologists and board certified psychiatrists. Session 1 is expected to take approximately 4.5 hours to complete and can be split into two or more sessions.

Table 1. Baseline Session 1: Clinical Interview, Demographics and Questionnaires

Domain	Assessment
Clinical Rating Scales and Demographics	
Diagnosis	MINI 6.0 [124]
Demographics	Demographics and Psychosocial Form
History	Assessment of Medical and Medication History
History	Life chart interview
Substance Use	Customary Drinking and Drug Use Record (CDDR) [125]
Handedness	Edinburgh Handedness Inventory [126]
Compliance	Medication Compliance
Compliance	Therapy Compliance
Traumatic Head Injury	Tulsa Head Injury Screen
Family Psychiatric History	Family History Screen (FHS) [127]
Suicidal Ideation	Columbia-Suicide Severity Rating Scale (C-SSRS) [128, 129]
Pain	Wong-Baker FACES Pain Rating Scale [130]
Self-Report Scales	
Negative Valence	State Trait Anxiety Inventory (STAI) [131]
Negative Valence/Interoception	Anxiety Sensitivity Index (ASI-3) [132]

Negative Valence	Ruminative Responses Scale (RRS) [133]
Depression	Quick Inventory of Depressive Symptomatology [134]
Trauma	Traumatic Events Questionnaire (TEQ) [135]
Trauma	Child Trauma Questionnaire (CTQ) [136]
Positive/Negative Valence	Positive and Negative Affect Schedule-Expanded Form (PANAS-X) [182]
Positive/Negative Valence	Behavioral Inhibition System/Behavioral Approach Scale (BIS/BAS) [137]
Positive Valence	TEPS anticipation/consumption/pleasure [138]
Positive Valence	UPPS Impulsive Behavior Scale[139]
Empathy-like	Interpersonal Reactivity Index (IRI) [140, 141]
Personality	Big Five Inventory (BFI) [142]
Arousal/Interoception	Toronto Alexithymia Scale (TAS) [143, 144]
Arousal/Interoception	Multidimensional Assessment of Interoceptive Awareness (MAIA) [82]
Eating Behaviors	Three Factor Eating Questionnaire (TFEQ) [145-147]
Eating Behaviors	Eating Disorders Diagnostic Scale (EDDS) [148]
Eating Behaviors	Simplified Nutritional Appetite Questionnaire (SNAQ) [149]
Physical Activity	International Physical Activity Questionnaire (IPAQ) [150]
Disability	World Health Organization (WHO) Disability Assessment Schedule [151]
Absenteeism/Presenteeism	WHO Health & Work Performance Questionnaire (WHOHPQ) [152]

PROMIS Measures **[153, 154]**

Negative Valence	PROMIS Anxiety
Negative Valence	PROMIS Depression
Negative Valence	PROMIS Anger
Positive Valence	PROMIS/Neuro-QOL Positive Affect and Well-being
Cognitive	PROMIS Cognitive Abilities
Cognitive	PROMIS Cognitive General
Fatigue	PROMIS Fatigue
Sleep	PROMIS Sleep Disturbance
Sleep	PROMIS Sleep-related impairment
Alcohol	PROMIS Alcohol Use
Alcohol	PROMIS Alcohol: Negative Consequences
Alcohol	PROMIS Alcohol: Positive Consequences
Alcohol	PROMIS Alcohol: Negative Expectancies
Alcohol	PROMIS Alcohol: Positive Expectancies
Social	PROMIS Social Satisfaction DSA
Social	PROMIS Social Satisfaction Role
Social	PROMIS Ability to Participate Social
Social	PROMIS Emotional Support
Social	PROMIS Information Support

Social	PROMIS Instrument Support
Social	PROMIS Satisfaction Roles Activities
Social	PROMIS Social Isolation
Physical	PROMIS Physical Function
Pain	PROMIS Pain Interference
Pain	PROMIS PAIN Behavior
Sex	PROMIS Global Satisfaction with Sex Life
Sex	PROMIS Interest in Sex Activity
Nicotine	Nicotine Dependence
Nicotine	Coping Expectancies
Nicotine	Emotional and Sensory Expectancies
Nicotine	Health Expectancies
Nicotine	Psychosocial Expectancies
Nicotine	Social Motivations

Baseline Behavioral Session

Behavioral tests will be administered via computer interfaces, with the exception of neuropsychological testing which will be conducted face to face by an assessor. The neuropsychological assessments will be administered by trained clinical assistants, directly supervised by licensed clinical psychologists and board certified psychiatrists. Behavioral assessments will be conducted by trained research assistants. The behavioral session is expected to take about 4 hours to complete and can be split into 2 or more sessions (Table 2).

Table 2. Behavioral and Neuropsychological Tasks

Domain	**Task**
Computational- Cognitive	Change Point Detection Task [155] Three Arm Bandit Task [156] Start/Stop Task [157]
Positive/Negative Valence	Implicit Approach/Avoidance Task [158] Attentional Bias/Dot Probe Task [159] Emotional Reactivity Task [160] Approach Avoidance Conflict Task [161]
Arousal/Interoception	Breath Hold Heartbeat Counting Task Cold Pressor [162, 163]
Neuropsychology	WRAT Reading [193] DKEFS [164] Color-Word Inhibition DKEFS verbal fluency WAIS-IV digit span [165] Finger Tapping Test WAIS-IV Digit Symbol Coding

	California Verbal Learning Test [166]

Baseline Biomarkers

Table 3 summarizes the proposed biomarkers and biological specimens that will be obtained from blood samples and microbial samples of the subjects. It is expected to take approximately 30-45 minutes to complete sample collection. A trained phlebotomist or nurse will collect the blood and microbial samples will be collected by the subject.

Table 3. Examples of immune-related measurements

Immunophenotype	**Reported Abnormality in Depression**	**References**
Cytokines	Elevations in pro-inflammatory cytokines	[167-169]
PBMC Gene Expression	Increased mRNA expression of pro-inflammatory mediators	[170-173]
Kynurenine pathway	Increased neurotoxic kynurenine metabolites	[174-176]
T-cells	Altered T-cell function and numbers	[177, 178]
Natural Killer Cells (NKC)	Reduced NKC function	[179, 180]
Pathogens	Increased seropositivity for *T. gondii* and herpesviridae	[181, 182]

Baseline Neuroimaging

The session will consist of one 60 and one 120 minute scan in the MRI machine. One of the neuroimaging sessions will focus on structural differences in the brain and a second session will focus on functional differences. The neuroimaging sessions are expected to take approximately 4 hours total to complete and are split into two sessions (Table 4).

Table 4. Baseline Neuroimaging Sessions

32 Channel Imaging: Structural & Perfusion
Participant Last Use Summary (PLUS)
3-plane localizer, asset calibration
T2-W flair
T2 FRSE
T1-W Clinical MPRAGE
T1-W MPRAGE

T2-W Propeller
Arterial Spin labeling
Diffusion Tensor Imaging

8 Channel Imaging: Functional & EEG

Task Training and Practice
Karolinska Sleepiness Scale: Pre-scan (KSS)
Participant Last Use Summary (PLUS)
EEG Cap Setup
FSPGR Anatomical (T1)
Monetary Incentive Delay (MID) [183, 184]
Stop Signal Task [185]
Resting State
Interoceptive Attention Task [186]
Fear Conditioning/Extinction Task [187]
Karolinska Sleepiness Scale: Post-scan (KSS)

Quarterly Follow-up Session

These sessions will examine the course of outcomes in individuals with dysregulated mood and/or anxiety, substance use, or problematic eating behavior. These assessments will be brief in-person visits. The quarterly follow-up assessments will take approximately 1 hour every 3 months during the 12-month follow-up time period (Supplementary Table 1).

One-year Follow-up Session

This session will examine the course of outcomes 1 year after baseline. For neuropsychological assessment, alternative forms will be used as available. Assessments will be administered during in-person sessions that take approximately 7.5 hours to complete over 2 to 3 appointments (Supplementary Table 2).

Biomarker measures

We will investigate neuroendocrine, metabolic, inflammatory, and cardiovascular biomarkers associated with positive and negative valence domains, cognitive systems and arousal/interoceptive systems. These measures help to extend our multi-level analysis of NIMH RDoC constructs into the cellular and molecular units of analysis. Biochemical assays will be performed on biological samples collected at baseline and during the 1-year follow-up to quantify a range of biomarkers and their relationship with other variables and units of analysis.

Participants will have fasting blood drawn by venipuncture by a trained phlebotomist for the biomarker panels. This will be scheduled to occur the morning of one of the visits, or at a time

convenient for the participant. Resting blood pressure and heart rate will be assessed. Additionally, in order to lay the foundation for future studies, we will also collect and process a small quantity of blood to be banked for potential future endocrine, immune and/or genomic analyses.

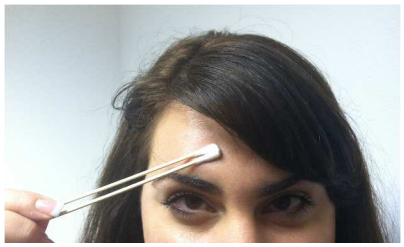
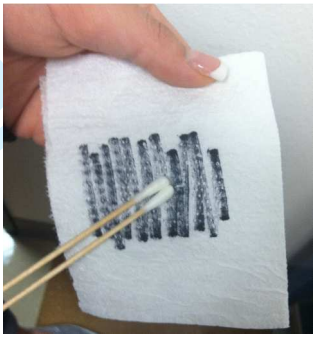
Sample collection, processing distribution and storage procedures

A trained phlebotomist will obtain all blood samples. Less than 150 mL of blood will be collected per subject during each session (baseline and 1-year follow-up), which is well within the safety limit of ~450 mL per blood draw. Blood will not be drawn from subjects with a hematocrit below 30%. Samples for stem cells and genetics will be shipped to Rutgers University laboratory for processing and storage. Blood samples for plasma, serum, and PBMCs will be transported to and processed at the University of Oklahoma Integrative Immunology Center (IIC) Laboratories. Plasma and serum samples will be stored in secure freezers at -80ºC. Freezers will be maintained in a specially equipped room with emergency backup power and an automated telephone alarm system that is programmed to call in case of failure. Additional aliquots of samples will be stored at -80^{o}C should repeat analyses be required at a later date. PBMCs will be stored in liquid nitrogen dewars with liquid level monitors and alarms in a secure room at the University of Oklahoma IIC Laboratories.

Microbiome Collection

Participants will be asked to provide microbial samples during the Biomarker session. All participants will be asked to provide forehead, mouth and stool samples.

Figure 2. Microbiome Collection Sites

Forehead	Mouth	Stool
		

A research assistant will provide the participant with an all-in-one sample collection kit system for collecting, stabilizing, transporting, and purifying samples which includes cotton-swabs, tubes labeled by body area, and step by step instructions, including the pictures in Figure 2. Participants will be asked to perform the sampling themselves.

Compensation

Subjects will receive the following payment for completing the study (Table 5):

Table 5. Compensation

SESSION	TIME	PAYMENT*
Interview and Demographic Information	4.5 hours	$90
Behavioral assessments & Computerized Tasks	4 hours	$80 $10-$20 reward
Biomarkers	30 minutes	$50
Neuroimaging & EEG & Setup	4 hours	$170 $0-$60 reward
3 month Follow up*	1.5 hours	$30
6 month Follow up	1.5 hours	$30
9 month Follow up	1.5 hours	$30
12 month Follow up	7 hours	$200 $10-20 reward
Total	23.5 hours	$700 to $780

DATA ANALYSIS

Behavioral and Psychophysiological Data Analyses

Self-report questionnaires, interviews, neuropsychological assessments, computer-based behavioral assessments, and psychophysiological assessments will be scored according to published methods (as cited in the Tables). These variables will then be used in conjunction with collected biological data in the latent variable approach. The analysis strategy consists of the following steps. First, the characteristics of all measures will be examined for deviation from normality prior to subsequent analyses. For each unit of analysis (self-report, behavior, physiology, circuits, biomarkers), separate principal components analyses (PCA) will be performed and a separate analysis will be conducted for each behavioral task to minimize task-specific factors in subsequent analysis steps. Next, the number of components for each analysis will be determined using a number of different approaches [188]. In particular, if the number of components to be extracted differed across the extraction approaches, both solutions will be explored [189, 190]. Component scores from each unit of analyses will be extracted for each participant and used for the following analyses.

MRI, EEG and fMRI Data Analysis

The basic structural and functional image processing will be done with the Analysis of Functional Neuroimages (AFNI) software package [191].

EEG-fMRI

The EEG data will be acquired simultaneously with the fMRI data and corrected for artifacts related to the gradient switching and cardiac ballistic effect using the template subtraction method [192-194] implemented in BrainVision Analyzer software (Brain Products GmbH, Munich, Germany). Residual ballistocardiac artifacts in the EEG signals will be removed using the independent component analysis method. The de-noised data will be subsequently band-pass filtered from 1 Hz to 70 Hz, downsampled to 250 Hz, and re-referenced to the common average reference. For the EEG signals recorded outside the scanner, data will be similarly band-pass filtered from 1 Hz to 70 Hz, downsampled to 250 Hz, and re-referenced to the common average reference.

During fMRI scans we will simultaneously record EEG using a 31-electrode cap attached to an MRI-compatible BrainAmp MR Plus amplifier. The sintered Ag/AgCl ring electrodes are mounted into a scalp cap according to the standard 10-5 system. All electrodes are referenced to the FCz position, while a ground electrode is located at the AFz position. One additional electrode will be placed on the subjects' back to monitor the electrocardiographic signal. The impedance of all electrodes will be maintained below 10 KΩ throughout the recording. The internal sampling clock of the EEG amplifier will be synchronized with the MRI scanner 10MHz master clock signal using the SyncBox device (Brain Products GmbH, Munich, Germany), in order to prevent variant sampling of imaging artifacts and to facilitate artifact correction [194]. The signals will be recorded at a sampling frequency of 5000 Hz with an analog filter (from 0.016 to 250 Hz) and a resolution of 0.1 μV.

Besides independent EEG measures of brain state, and EEG-informed fMRI data analysis, we will use EEG data to correct the effects of head movements in simultaneously acquired fMRI data on a slice-by-slice basis [195]. This E-REMCOR, and recently developed automated version aE-REMCORE technique, will make it possible to regress out the effects of rapid head movements from unprocessed fMRI data on slice-by-slice basis prior to volume registration [196]. Thus, aE-REMCOR complements both the traditional fMRI volume registration approach, which performs better for slower head motions, and the RETROICOR method for slice-specific correction of fMRI cardiorespiratory artifacts [197]. Other types of EEG-informed fMRI analyses include: EEG band-pass correlation analysis with fMRI data (Fast Fourier transformation will be used to estimate EEG δ (1–3 Hz), θ (4–7 Hz), α (8-13 Hz), and β (13–30 Hz) frequency band spectral power, and its temporal changes during fMRI) [198], EEG microstate analysis in time and spatial domain (EEG temporal independent microstates and their spatial representation correlates with slow hemodynamic activity in brain resting state networks and their spatial maps) [199, 200], EEG-asymmetry analysis, and EEG-coherence analysis (e.g. quantify and correlate changes in EEG alpha band asymmetry and/or EEG

coherence with fMRI data [201]), and behavioral measures [202]. EEG-informed fMRI analysis will allow us to better elucidate and characterize normal and pathological interactions between cerebral function and behavior, cognition or emotion.

fMRI Preprocessing

Standard fMRI data preprocessing will include a slice-timing correction, signal scaling, spatial smoothing, physiological noise suppression [197, 203], and motion correction. For task fMRI analysis, a multivariate regressor approach will be used to relate changes in echo planar imaging (EPI) intensity to differences in task characteristics. The aE-REMCOR motion will be corrected on a slice by slice basis. fMRI data will be co-registered using a 3D-coregistration algorithm. Motion parameters will be obtained across the time series for each subject. Subjects will be excluded if the average in any one of these six parameters exceeds 2 standard deviations from the mean or if mean displacement exceeds the size of the voxel (4 mm). This assures that differences at group-level are not due to differences in movements during scanning. Motion parameters will be used as regressors to adjust EPI intensity changes due to motion artifacts. This has been shown to increase power in detecting task-related activation. All slices of the EPI scans will be temporally aligned following registration to ensure different relationships with the regressors are not due to the acquisition of different slices at different times during the repetition interval.

Task-based fMRI Analysis

First/Subject-Level Analyses

Multiple regression will be used to analyze individual subjects' data, with predictors in the model constructed by convolving each column of the task design matrix with a canonical hemodynamic response function. Regressors of non-interest will be included in all models to account for (1) head motion (6 motion variables), and (2) other sources causing drifts (each run's signal mean, linear, quadratic, and cubic signal trends). The beta weights and corresponding t statistics for image contrasts of interest will be produced for group-level analyses.

Second/Group-Level Analyses

Both region of interest (ROI) and whole-brain analyses start with voxel-wise statistical tests using mixed-effects modeling on aggregations of maps of the subjects' beta-weights and beta-weight standard errors (AFNI's *3dMEMA* or in-house developed R code). This approach has the advantage of taking into account in the group analysis both effect estimates as well as their within- and between-subjects variances. Correction for multiple comparisons will be conducted as follows. Statistical maps will either be corrected using the false-discovery rate (FDR) or cluster level thresholds. For cluster level thresholds, AFNI's *3dClustSim* (with spatial

autocorrelation function [acf] adjustments) will be used to identify the required cluster-size threshold, given a voxel-wise probability of $p < 0.001$, the smoothness of the residuals from the group level test, and the size of the region tested (either whole-brain or an a priori defined ROI).

Resting State fMRI Analysis

Pre-Processing

Data pre-processing will be conducted using afni_proc.py. The first three volumes of the functional scans will be discarded to allow the signal to reach T1 equilibrium, and a de-spiking algorithm will be used to remove any transient signal spikes from the data. Prior to slice time correction, physiological signals of non interest (pulse, respiration) will be removed using RETROICOR. For each subject, the remaining volumes will be corrected for differences in slice acquisition time; head motion will be corrected by rigid body translation and rotation; the third volume of the functional run will be co-registered to the anatomical coordinates of the participant's structural scan by linear warping, then normalized to the Talairach template and resampled to 2x2x2 mm^3 voxels. The six motion parameters from the image registration process will be used to construct a time series reflecting the Euclidean normalized derivatives of the motion, and any time point, plus one prior, where the derivative is greater than 0.2 or where more than 10% of brain voxels are considered as outliers will be censored. Nuisance variables will be regressed out of the normalized data and include the de-meaned motion parameters and their derivatives, the average signal taken from a local eroded local white matter mask, the first 3 principal components of the lateral ventricles, and terms reflecting baseline drift.

First/Subject-Level Analyses

For each participant, the time courses of the residual images from the pre-processing step will be averaged across voxels within each ROI, and Pearson correlation coefficients will be computed between the mean signal time courses of pairs of ROIs. These correlation coefficients will be converted by Fisher *r*-to-*z* transformation, which will be used as predictors of treatment outcomes.

The identified brain activation at ROIs and/or functional connectivity z-scores will be analyzed by PCA, and the extracted principal component scores will be used with scores from other units of analyses.

General Unifying Statistical Approach

The goal of this project is to derive latent variables that adequately quantify the positive and negative valence, cognition, and interoception/arousal domains across different units of analyses collected at baseline. The analysis of the variables that are extracted from each unit

will consist of three steps. First, a principal component analysis will be conducted for each unit of analysis to determine the number of independent degrees of freedom contributing to the variance observed in each unit. We expect to extract at least two independent components. The action units that show the highest correlation with the components will be used for subsequent analyses. Second, we will conduct a confirmatory factor analysis with the variables from each unit of analysis that showed the highest correlation with the principal components of four proposed factors – positive valence system, negative valence system, arousal/interoceptive system, and cognitive system. We will subsequently test the statistical significance of the coefficients contributing to the factors. Finally, we will conduct a latent variable analysis as detailed below to relate one unit directly to another unit of analysis.

Statistical Analysis Plan

Baseline/Cross-sectional analyses

We will relate different units of analyses by regularized generalized canonical correlation analysis (RGCCA) [204]. Classical CCA identifies linear combinations of two sets of variables such that their correlations are maximized. RGCCA extends classical CCA from two sets of variables to multiple sets. When applied to multiple units of analyses, RGCCA identifies linear combinations (canonical variates) of principal component scores within each unit of analyses, such that the sum of correlations or covariance across canonical variates is maximized. The results of RGCCA can be demonstrated as a network that shows which unit of analyses are connected, and which are not. Moreover, the canonical correlations obtained from RGCCA can be used to define biotypes by cluster analysis as described in Drysdale et al. who used two sets of variables (clinical symptoms and resting state functional connectivity) to define biotypes [205]. These dimension-defined biotypes will be linked to the category-defined groups by cross tabulation.

Longitudinal analysis

The self-report outcomes will be measured at baseline and months 3, 6, 9, and 12, and these time trajectories will be compared between groups based on categorical diagnosis (comparison subjects, substance use disorders, mood disorders, and eating disorders) and between dimension-defined biotypes using models for longitudinal data – mixed effects and generalized estimating equations (GEE) models. No functional form will be assumed for the time trajectories and profile models will be used (i.e., time variable is treated as a factor in the model). The biotype/group effect will be measured as a time-by-group interaction. Comparisons between the time profiles of the groups will use appropriate Wald and likelihood ratio tests. In addition, linear time effects will be considered; these will be used if they are preferable to the profile models in model comparison using Akaike information criterion (AIC).

Statistical Power

We will base statistical power on two considerations: (1) power to estimate latent factor models with precisions, and (2) accuracy of prediction of outcomes using baseline variables and latent factors as predictors. Although controversial [206], typically one suggests that there should be at least n=10 subjects for each identified latent variable. In comparison, this study is likely to have n=100 subjects per latent construct. More recent recommendations for power take into account the quality of the indicators for the latent variables and the number of items per factor. For a moderate to low communality (conservative assumption), a sample size of n=300 would give an excellent coefficient of congruence of K=0.97. This allows for fitting latent factor models to each patient subgroup separately with adequate power [207]. We also compute power to predict the year follow-up clinical outcomes: assuming 100 healthy controls (HC), 100 eating disorder (ED), 500 mood/anxiety (MA), and 300 substance use (SU) participants at baseline and a uniform 20% attrition rate for each group at one-year follow-up (i.e., with remaining 80, 80, 400, and 240 participants in the corresponding groups), we will have 80% power to detect effect sizes (Cohen's D for between-group differences in changes from baseline to 1-year follow-up) of 0.57 (ED vs. HC), 0.43 (MA vs. HC or ED), 0.45 (SU vs. HC or ED), 0.29 (MA vs. SU) at two-sided Type I error rate 0.05/6 = 0.008 (Bonferroni correction) in t-test for post hoc comparisons.

ETHICS and DISSEMINATION

Gender/minority/pediatric inclusion for research

Women and minorities will be included in the study without prejudice and represented according to the study population. Participants will be recruited from the greater metropolitan areas of Tulsa, Oklahoma and efforts will be made to ensure the subject population is representative of the gender, ethnicity and racial demographics of the region according to the US Census Bureau data.

Exclusion Criteria

The following exclusion criteria will apply: (1) inability to provide informed consent, (2) no telephone or easy access to telephone, (3) history of unstable liver or renal insufficiency; glaucoma; significant and unstable cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, rheumatologic, or metabolic disturbance; or any other condition that, in the opinion of the investigator, would make participation not be in the best interest (e.g., compromise the well-being) of the subject or that could prevent, limit, or confound the protocol-specified assessments, (4) a positive test for drugs of abuse, including alcohol (breath test), cocaine, marijuana, opiates, amphetamines, methamphetamines, phencyclidine,

benzodiazepines, barbiturates, methadone, and oxycodone, (5) has any of the following DSM-V disorders: schizophrenia spectrum and other psychotic disorders, bipolar and related disorders, obsessive-compulsive and related disorders, (6) moderate to severe traumatic brain injury or other neurocognitive disorder with evidence of neurological deficits, neurological disorders, or severe or unstable medical conditions that might be compromised by participation in the study (to be determined by primary care provider), (7) active suicidal ideation with intent or plan, (8) change in the dose or prescription of a medication within the 6 weeks before enrolling in the study that could affect brain functioning, e.g., anxiolytics, antipsychotics, antidepressants, or mood stabilizers. However, we expect there to be changes in the dosing and prescription of medications during the course of the study protocol. This will be acceptable for the study and participants will be asked to inform the investigators of any treatments they undergo during their time in the study, (9) prescription of a medication outside of the accepted range, as determined by the best clinical practices and current research, (10) taking drugs that affect the fMRI hemodynamic response (e.g., methylphenidate, acetazolamide, excessive caffeine intake > 1000 mg/day), (11) MRI contraindications including: cardiac pacemaker, metal fragments in eyes/skin/body (shrapnel), aortic/aneurysm clips, prosthesis, by-pass surgery/coronary artery clips, hearing aid, heart valve replacement, shunt (ventricular or spinal), electrodes, metal plates/pins/screws/wires, or neuro/bio-stimulators (TENS unit), (12) persons who have ever been a professional metal worker/welder, history of eye surgery/eyes washed out because of metal, vision problems uncorrectable with lenses, (13) inability to lie still on one's back for 60-120 minutes; (14) prior neurosurgery, (15) tattoos or cosmetic makeup with metal dyes, (16) unwillingness to remove body piercings, (17) pregnancy, (18) unwillingness or inability to complete any of the major aspects of the study protocol, including magnetic resonance imaging (i.e., due to claustrophobia), biopsy, blood draws, or behavioral assessment. However, failing to complete some individual aspects of these assessment sessions will be acceptable (i.e., being unwilling to answer individual items on some questionnaires or being unwilling to complete a behavioral task), (19) non-correctable vision or hearing problems.

Specimens, records, data collection

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study. Study consent records will be stored in the locked records room at the Laureate Institute for Brain Research. Only approved study personnel will have access to study records that contain any identifying information. Study data records and blood/urine/biological samples will be assigned code numbers and will not be individually identifiable. Code numbers are a combination of numbers and letters. The electronic data will be kept in a firewalled and password protected database on a secure server managed by LIBR. Vanderbilt University, with collaboration from a consortium of institutional partners, has developed a software toolset and workflow

methodology for electronic collection and management of research and clinical trial data REDCap (Research Electronic Data Capture) [123] data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team with planning assistance from the information technology staff. The iterative development and testing process results in a well-planned data collection strategy for individual studies. REDCap servers are housed in a local data center at Laureate Institute for Brain Research and all web-based information transmission is encrypted. REDCap was developed specifically around HIPAA-Security guidelines and is recommended to LIBR researchers by both our Privacy Office and the Western Institutional Review Board (WIRB). REDCap has been disseminated for use locally at other institutions and currently supports 240+ academic/non-profit consortium partners on six continents and over 26,000 research end-users (www.project-redcap.org).

Records of the subject's participation in this study will be held confidential except as disclosure is required by law or as described in the informed consent document (under "Confidentiality"). The study doctor, the sponsor or persons working on behalf of the sponsor, and under certain circumstances, the United States Food and Drug Administration (FDA) and WIRB will be able to inspect and copy confidential study-related records which identify the subject by name. Therefore, absolute confidentiality cannot be guaranteed. If the results of this study are published or presented at meetings, the subject will not be identified. Paper copies of consents, screening forms, the Research Privacy Form, and any other forms, testing results or papers containing Personally Identifiable Information (PII) will be stored in a secured medical records room with access granted only to authorized personnel.

Recruitment and consent procedure

Recruitment into the T-1000 study at the Laureate Institute for Brain Research will be ongoing for 4 years from January 2015 through December 2018. The study will be completed by December 2019 after the completion of the 1-year follow-ups from 2018. Study participants will be recruited through the clinical services of the Laureate Psychiatric Clinic and Hospital (LPCH), local service providers for behavioral health, mental health, and addiction and recovery (e.g. Family and Children's Services, 12&12, local psychiatrist and physician offices), and through online, newspaper, flyer, radio or other media advertisements in the Tulsa metropolitan area. Participants will also be recruited through a pre-approved LIBR Screening protocol (WIRB #20101611) and through the Laureate Institute for Brain Research REDCap database. Informed Consent will be obtained by members of the research team that have received training from the PI to obtain consent for this study. All participant interactions including consenting will be conducted in private interview/exam rooms. These exam rooms at LIBR are secured from public areas via combination locked doors that are only accessible to authorized personnel.

Dissemination of results

Results from the study will be submitted to relevant journals for peer-reviewed publication and presented at national and/or international biomedical conferences.

Registration

In accordance with the recommendations of the International Committee of Medical Journal Editors, the proposed study is registered in a public registry (http://www.clinicaltrials.gov/, Trial Registration Number: NCT02450240).

Collaborators

University of Oklahoma

University of California-San Diego

Rutgers University

Contributors

All authors made a significant contribution to the conception and design of the study protocol. The protocol was written by MPP and TAV and critically reviewed by SK, JB, JF, RA, HY and WKS. All authors gave permission and approval for publication.

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Competing Interests

None

Patient consent

Obtained

Ethics Approval

The study protocol is approved by the Western Institutional Review Board, Puyallup, Washington (WIRB, protocol number 194919).

Provenance and peer review

Not commissioned; externally peer reviewed.

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SUPPLEMENTARY MATERIALS

Baseline Diagnostic and Demographic Assessment Measures

Patient Health Questionnaire (PHQ-9): The Patient Health Questionnaire (PHQ) is a self-administered diagnostic instrument for common mental disorders. The PHQ-9 is the depression module, which scores each of the 9 DSM-IV criteria as "0" (not at all) to "3" (nearly every day). Scores of 1-4 are considered minimal depression, 5-9 mild depression, 10-14 moderate depression, 15-19 moderately severe depression and 20-27 severe depression [1].

Overall Anxiety Severity and Impairment Scale (OASIS): The OASIS is a brief questionnaire (5 Items) that can be used as a continuous measure of anxiety-related severity and impairment across anxiety disorders. Each item is rated on a 5-point scale and the ratings are summed to obtain a total score. A cut-score of 8 has been shown to correctly classified 87% of individuals as having an anxiety diagnosis or not [2]. The OASIS has demonstrated excellent 1-month test–retest reliability, and convergent and divergent validity [3].

Drug Abuse Screening Test (DAST-10): The DAST-10 [4] is a brief version of the 28-item DAST designed to identify drug-use related problems in the previous year. It has demonstrated good internal consistency and temporal stability in psychiatric samples; the DAST-10 discriminates between psychiatric outpatient with or without drug use disorders (with scores between 2-4; [5]). This measure consists of 10 yes/no questions. Responding yes to score > 2 of the questions is considered an indicator that the individual should seek further evaluation for problematic drug use behaviors.

Eating Disorder Screen (SCOFF): The SCOFF was developed by British researchers as a screening tool for eating problems in a primary care setting [6]. It consists of 5 yes/no questions that inquire about eating behaviors and beliefs or obsessions with eating. Responding yes to ≥ 2 of the five items is considered an indicator that the participant should seek further evaluation for eating concerns.

Life chart interview: This interview was adapted from published methodologies for obtaining life histories of important life events relevant to mental health [7]. The purpose of this interview will be to obtain qualitative information regarding the temporal sequence of

important events throughout the participant's life, which will be used to inform the structured diagnostic interview (MINI) and provide a more thorough and holistic understanding of the factors that have contributed to the individual's mental health. The Life Chart will ask questions pertaining to what important events happened during specific intervals of the person's life, including: (1) birth (2) childhood to the start of elementary school, (3) elementary school, (4) middle school to leaving/finishing high school (5) after high school to age 25 (6) ages 25-35 (7) ages 35-45 (8) ages 45-55. For each interval, subjects will be asked questions about potentially important events in their life, such as whether they moved, had any births or deaths in their family, sought mental health treatment, etc. From this comprehensive list, the 0-3 most significantly life events will be selected from each time interval and the participant will be asked to rate their mood level (on a scale of 1-5) for those events as well as on average for that time interval. Participants may be asked to be audio recorded during the life chart interview. The recordings will be strictly optional and refusal will not impact participants' inclusion in the study. The recorded interviews will be used to develop reliability ratings among clinicians at LIBR and development of an event timeline. A visual timeline displaying the most significant events identified throughout their lifetime and their mood ratings throughout this time will be constructed and provided to the participant upon request.

Mini International Neuropsychiatric Interview (MINI Version 6.0): This is a widely used structured interview that assesses diagnostic criteria related to psychotic disorders, mood disorders, substance use disorders, and anxiety disorders. This interview will be used to assess symptoms and diagnostic criteria related to Axis I disorders. The MINI has been validated with the Structured Clinical Interview for DSM Axis I Diagnoses (SCID) with an average Kappa statistic of 0.67 across all 22 diagnoses measured on the MINI, and an average inter-rater reliability of 0.97 across diagnoses [8].

Demographics and Psychosocial Form: This form will ask participants to indicate their age, date of birth, contact information, ethnicity, race, gender, marital status and family makeup, language use, average income, education level, occupational and/or student status, and health insurance.

Assessment of Medical and Medication History: This form was created specifically for the purposes of this study and will ask questions related to medical and mental health diagnoses the participants has received currently or in the lifetime. This will involve a review of systems (e.g., constitutional, cardiovascular, respiratory) to inquire about previous or current problems, questions concerning in inpatient stays/treatments, surgeries, medications, and psychotherapies. For each mental health treatment, they will be asked to rate their compliance with that treatment. At the follow-up session, this interview will be repeated, but only in reference to the year of the study.

Diagnostic Review and Verification of Clinical Information: After completing the Assessment and Medication History, Lifecharting, and MINI structured interview, each participant's information will be presented to a board certified psychiatrist for review, verification, and potential revision. This includes a targeted review of medical and psychiatric history and current medications for the purpose of identifying and correcting any collection errors. Participants for whom the DSM diagnosis is questionable will be re-evaluated in person by a board certified psychiatrist for independent diagnostic verification.

Edinburgh Handedness Inventory (EHI): The EHI is a self-report laterality scale that estimates the degree of right or left hand dominance during everyday activities [9].

Customary Drinking and Drug Use Record (CDDR [10] with Michigan Negative Reinforcement Questionnaire (MNRQ [11]): The CDDR provides current (past 3 months) and lifetime measures of 4 alcohol and other drug-related domains, including level of involvement, withdrawal characteristics, psychological/behavioral dependence symptoms, and negative consequences. The measure has been found to have good internal consistency, test-retest reliability, and construct validity [10]. The MNRQ was originally developed to assess beliefs about positive and negative consequences of smoking specifically and was found to have good reliability and validity in relation to diagnostic measures of nicotine dependence [12]. This measure has subsequently been adapted for use related to other substances of dependence and will be

administered along with the CDDR in the current study to obtain measures of alcohol and drug use as well as participant beliefs concerning the consequences of that drug use.

Tulsa Head Injury Screen (THIS): The THIS is a questionnaire that asks participants about their history of head injuries and loss of consciousness.

Family History Screen (FHS): The FHS is a questionnaire that asks about the psychiatric history of the participant's family members, including biological parents, siblings and children.

Columbia-Suicide Severity Rating Scale (C-SSRS): The C-SSRS is a tool used to determine the presence of suicidal ideation or behavior in a participant [13].

Wong-Baker FACES Pain Rating Scale: This questionnaire is used to assess the current degree of physical pain being experienced by the participant [14].

Self-Report Measures

State-Trait Anxiety Inventory (STAI): This is a widely-used psychometric instrument designed to assess an individual's anxiety proneness. This measure has both a "state" subscale meant to measure temporary anxiety symptoms and a "trait" subscale meant to measure more long-standing anxiety proneness. Each subscale consists of 20 items using 4-point scales ("not at all" to "almost always"). The STAI is a validated measure with good internal consistencies for both subscales and has high test-retest reliability for the trait subscale and low to moderate test-retest reliability for the state measure [15].

Anxiety Sensitive Index (ASI-3): This instrument includes 18 items designed to measure the fear of arousal-related sensations, specifically along the dimensions/subscales of Physical, Cognitive, and Social Concerns. Each item is answered on a scale of 0-4 ("very little" to "very much"). The ASI-3 has been found to have adequate performance on several measures of reliability and validity [16].

Quick Inventory of Depressive Symptomatology (QIDS-SR): The QIDS-SR is a self-report 16 item assessment of the severity of depressive symptoms [17].

Simplified Nutritional Appetite Questionnaire (SNAQ): The SNAQ is a reliable tool with appraisal questions that focus on appetite and evaluating weight loss. [18]

Ruminative Responses Scale (RRS): This instrument is used to measure dispositional tendencies to ruminate in response to negative affect. It consists of 22 questions concerning how they respond to sad mood, which are focused on the self, on one's symptoms, and on the possible causes and consequences of the mood state (i.e., "Think 'why do I have problems other people don't have'?"). Responses are rated on a 4-point scale (e.g., 1 =almost never respond in this way; 4=almost always respond in this way). The RRS has three factor-analytically derived subscales, including depression, brooding, and reflection. The RRS has been found to have good test–retest reliability (.67) and satisfactory convergent and predictive validity [19, 20].

Traumatic Events Questionnaire (TEQ) – Civilian Version: The Traumatic Events Questionnaire (TEQ) [21], assesses 11 specific traumatic events: (1) combat, (2) large fires/explosions, (3) serious industrial/farm accidents, (4) sexual assault, rape (forced unwanted sexual activity), (5) natural disasters, (6) violent crime, (7) adult abusive relationships, (8) physical/sexual child abuse, (9) witnessing someone being mutilated, seriously injured, or violently killed, (10) other life threatening situations, and (11) violent or unexpected death of a loved one. Two nonspecific questions, "other event" and "can't tell," complete the scale. Individuals are asked to indicate the frequency, severity (on a 7-point scale), and age at the time of the event. The scale has been found to have very high reliability (.91) and has been found to relate to PTSD, anxiety, and depressive symptoms [21].

Childhood Trauma Questionnaire, Short Form (CTQ-SF): This instrument is used to screen adolescents and adults for a history of child abuse and neglect. The CTQ has five subscales: (1) Physical abuse, (2) Sexual abuse, (3) Emotional abuse, (4) Physical neglect, and (5) Emotional neglect. The CTQ will be used to identify traumatic childhood conditions characteristic of the negative valence domain. The CTQ consists of 28 items which are rated on a 5 point scale (1=never true; 5=very often true). The full CTQ has been found to have good reliability and validity and the CTQ –SF was found to have good validity in reference to the full version [22].

Positive and Negative Affective Schedule- State/Trait (PANAS) [23] [145] [156]: The PANAS is a widely used measure comprising 20-items assessing activated forms of PA and NA using 5-point scales (1 = very slightly/not at all, 5 = extremely). To assess trait PA and NA, participants will be asked to respond according to how they have felt "during the past week". State PA and NA will be asked by asking participants to rate how they feel “right now (that is, at the present moment)”. The PANAS has high internal consistency and temporal stability (trait version). Correlational data support its convergent and discriminant validity. Confirmatory factor analyses support the construct validity of the PANAS [132].

Behavioral Inhibition and Activation Scales (BIS/BAS): The behavioral inhibition and activation scales (BIS/BAS) include 20-items assessing dispositional BIS and BAS sensitivities (i.e. avoidance and approach motives), which are hypothesized to reflect the negative and positive valence systems, respectively. Items are rated on four-point scales (1 = strongly disagree; 4 = strongly agree). The BAS has three subscales (Drive, Reward Responsiveness, and Fun Seeking); however, factor analyses support a single higher-order factor. The BIS/BAS has good test-retest reliability. Correlational data support the relative orthogonality and convergent, discriminant, and predictive validity of the subscales [24].

Temporal Experience of Pleasure Scale (TEPS): The TEPS is a recently developed measure of anticipatory pleasure and consummatory pleasure. It has 18 items, each of which are rated on a 6 point scale (e.g., 1=very false for me; 6=very true for me). Initial investigations with this measure indicate good validity and independence of the two subscales (anticipatory and consummatory; [25]).

UPPS Impulsive Behavior Scale (UPPS): The UPPS [26] was designed to measure impulsivity across dimensions of the Five Factor Model of personality. The scale has 45 items that use a 4-point scale, e.g., 1=; 4=) and has 4 subscales, including Premeditation (lack of), Urgency, Sensation Seeking, and Perseverance (lack of). The subscales have been shown to have good internal consistencies (.82-.91; [26]) and the measures has been shown to distinguish between subgroups of psychopathology compared to control groups [27].

Snaith-Hamilton Pleasure Scale (SHAPS): This instrument is used to measure hedonic capacity. It consists of 14 items, rated on a 4-point scale (1=Definitely Agree; 4=Strongly Disagree). This instrument has been found to have excellent internal consistency and adequate convergent and discriminant validity [28].

Interpersonal Reactivity Index (IRI): The IRI was developed to measure empathy, defined as the "reactions of one individual to the observed experiences of another". This is a 28-item measure, each rated on a 5-point Likert scale (1="Does not describe me well"; 5="Describes me very well"). The measure has 4 subscales, each made up of 7 different items. These subscales include Perspective Taking, Fantasy, Empathic Concern, and Personal Distress. Good internal consistency. The scale has also been shown to have good construct validity with related measures [29, 30].

Big Five Inventory (BFI): The BFI measures an individual on the Big Five Factors (dimensions) of personality [152], which include (1) extraversion versus introversion, (2) agreeableness versus antagonism, (3) Conscientiousness vs. lack of direction, (4) neuroticism vs. emotional stability, (5) openness vs. closedness to experience. This measure has 44-items, each of which are rated on a 5-point scale (1=disagree strongly, 5= agree strongly). This measure has been shown to have high internal consistency, test-retest reliability, and good convergent and divergent validity with other Big Five measures [31].

Toronto Alexithymia Scale (TAS-20): The TAS is one of the most commonly used measures of alexithymia, or the difficulty identifying and describing emotions. This is a 20-item measure, with each rated on a 5-point scale (1=strongly disagree, 5=strongly agree). There are three subscales, including (1) Difficulty Describing Feelings, (2) Difficulty Identifying Feeling, and (3) Externally-Oriented Thinking. The TAS-20 has been shown to have good internal consistency (.81), test-retest reliability (.77), and adequate convergent and concurrent validity [32, 33].

Multidimensional Assessment of Interoceptive Awareness (MAIA): This measure was recently developed to measure trait interoceptive body awareness. It consists of 32 items, each rated on a 6-point scale (0=never, 6=always). There are 8 subscales, including: (1) Noticing, (2) Not-distracting, (3) Not-worrying, (4) Attention Regulation, (5) Emotional Awareness, (6) Self-

regulation, (7) Body listening and (8) Trusting. The measure was found to have good measures of internal consistency on each subscale and showed adequate construct validity with other, related measures of emotional processing anxiety, and body awareness [34].

Three Factor Eating Questionnaire (TFEQ): The TFEQ was developed to measure three dimensions of human eating behavior: cognitive restraint of eating, disinhibition, and hunger. This is a 51-item measure, including 36 items with yes/no responses, 14 items on a 4-point scale (1=unlikely; 4=very likely), and one item of restraint on a 6-point scale (0="eat whatever you want, whenever you want"; 5="constantly limit food intake, never give in"). A subscale score is calculated for each of the three dimensions of human eating behavior. Cognitive Restraint is designed to measure control over food intake. Disinhibition measures loss of control over eating. The Hunger scale concerns subjective feelings of hunger and food cravings. The TFEQ has been found to have high test-retest reliability and internal consistency, and adequate construct validity [35-37].

Eating Disorders Diagnostic Scale (EDDS): The EDDS [38] measures the presence of anorexia nervosa, bulimia nervosa and binge eating disorder. It was developed as a self-report measures based on the Eating Disorder Examination (EDE) and the eating disorder module of the Structured Clinical Interview for DSM-IV. The EDDS provides both full and subthreshold diagnoses as well as a continuous symptom composite score. It consists of 22 items, 4 of which are on a 6-point scale (1=not at all; 6=extremely), 9 of which are yes/no questions, 6 items that ask for frequency of events (e.g., episodes of uncontrolled eating) over the week or month; and 3 remaining questions asking for height, weight, and number of missed periods over the past 3 months. The EDDS was shown to have good test-retest reliability, internal consistency, and convergent validity with other eating-pathology scales [38]. Research has shown it to be sensitive as a screening measure in detecting change with eating disorder treatment and is predictive of the development of eating disorder symptoms and depression [39].

International Physical Activity Questionnaires (IPAQ): The IPAQ is used to obtain internationally comparable data on health-related physical activity. Extensive reliability and validity testing has been undertaken in 12 countries (14 sites) across 6 continents since 2000. The short, self-

administered format, for use with young and middle-aged adults, will be utilized – which has been shown to have adequate validity and reliability [40].

World Health Organization Disability Assessment Schedule (WHODAS): The WHODAS (12-item version) is a generic assessment instrument for health and disability, and covers 6 domains: (1) Cognition (understanding & communicating), (2) Mobility (moving & getting around), (3) Self-care (hygiene, dressing, eating & staying alone), (4) Getting along (interacting with other people), (5) Life activities (domestic responsibilities, leisure, work & school), and (6) Participation (joining in community activities). The WHODAS produces standardized disability levels and profiles, is applicable across cultures in adult populations, and has a direct conceptual link to the International Classification of Functioning, Disability and Health (ICF) [41].

World Health Organization Health and Work Performance Questionnaire (HPQ): The WHO HPQ is a 9-item questionnaire to evaluate absenteeism and presenteeism in the workplace as indirect costs of illness. The instrument includes questions regarding days (full or in part) of work missed due to personal physical or mental health, days of work missed for other reasons, arriving early or late to work or working on a day off, hours worked in the past 4 weeks and self-evaluations of job performance recently, over the past year, and in comparison to other employees [42] [43].

PROMIS® (Patient Reported Outcome Measurement Information System) Measures (http://www.nihpromis.org; [44, 45]: PROMIS is a U.S.-based cooperative group of research sites and centers of excellence, funded by NIH, and convened to develop and standardize patient outcome measures across studies and settings. The PROMIS measures were developed using item response theory and calibrated on a sample of 21,133 people, with the aim of providing highly reliable, precise measures of patient–reported health status for physical, mental, and social well–being. Most question banks utilize a 7-day recall period and five response options (e.g., 1=Not at all, 5=very much). All instruments developed to be used with computer adaptive testing (CAT) to reduce patient burden. With CAT, the specific construct item that best distinguished between individuals in their test populations is administered first. Based on the individual's response to this item, the computer picks what question will be administered next, and so on, until a reliable estimate of their total score on that construct can

be determined. With this method, an average of 5 items is administered for each PROMIS construct listed, thus taking an estimate 1 minute or less to complete. The instruments have been reported to have good reliability and validity [44, 45].

Behavioral Tasks

Bandit Task*:* This task is included to apply Bayesian computational approaches that quantify how individuals switch between an "exploration" and "exploitation" strategy. Subjects have to sample from different choice options with unknown probabilities of success/failure with the goal of maximizing success. The optimal strategy is to start by trying all available options (exploration) to gauge the rate of success of each option, and to switch relatively early to only selecting the option with the highest likelihood of success (exploitation). Participants will perform a total of 20 three-armed bandit games with a known number of trials (i.e., token) per game. For each game, participants will have 16 tokens (stacked in the middle of the screen) and will have to assign each token to one of three lotteries of their choice (white panels on left, right and middle of the screen). After placing each token, they will earn 1 point if the token turns green or zero points if the token turns red. Each token decision will last about 2 sec. After the button press, the chosen lottery is highlighted for 250ms, after which the token turns green or red to reveal the decision outcome. Participants will be instructed to find the most rewarding lottery and maximize the points earned in each game. Participants are paid an additional $5 or $10 based on the performance on this task.

Change Point Detection Task: For each trial, subjects will attempt to locate a target stimulus in one of three possible locations. The target stimulus consists of a patch of dots, which are predominantly moving in one direction. The other two locations have distractors with dots moving in the opposite direction. However, at the beginning of the trial, the patches of dots are hidden by white circles, which initially appear in the three locations. The subject first selects a location in which to see a patch of dots; a button press indicates the location of choice. The subject is then shown the patch of dots at the selected location, and asked to determine whether it is the target or the distractor. If the subject indicates that the patch is the target, the trial ends. If the subject believes the patch is a distractor, the subject can then indicate a second location to view, and be shown the patch of dots corresponding to the new

location. The trial continues in this manner until the subject chooses the patch of dots which is believed to represent the target location. The position of the target location on each trial is determined by a probability distribution, such that one location is most likely to contain the target. It is therefore possible for the subject to learn over several trials which location is most likely to contain the target. However, at random intervals, the probability distribution will change, and a new location will become most likely to contain the target. The subject will then have to update their beliefs about the most likely location in which to locate the target. The experiment consists of 3 blocks with 60 trials per block. Prior to the experimental blocks, the subject will complete practice blocks until accuracy exceeds a certain threshold. Additionally, there is one block of 20 trials where all locations have equal probability that is used as a baseline measure for response time. Response time and learning rate over time with each target location are the main variables of interest. Participants are paid an additional $5 or $10 based on the performance on this task.

Move-Go and Speed-Stop Task: Driving, as a common real-time motor task, is determined by both motivational factors (safety, time, etc.), and perceptual-motor limits (perceptual delay, motor delay, etc.). It has been shown that people with emotional disorders have impaired driving performance. For example, there have been growing evidence show that depression increases the odds ratio for car accidents and reduces driving performance in a driving simulator. It also has been shown that mood (influenced by music) can impact driving behavior in healthy population. Thus we propose to use a simulated driving task to collect behavioral data. The driving task has two separate components. The Move-Go component is used to measure perceptual and motor speed. In it, subjects are asked to attend to a car presented at the bottom of the screen. As soon as they perceive that the car has started to move, subjects are to move the joy stick all the way forward as quickly as possible. In the Speed-Stop component, subjects are instructed to drive a virtual car on a computer screen from an initial position to a stop sign as quickly as possible and stop as close to the stop-sign as possible without crossing the stop-sign, by pushing or pulling a joystick to control the velocity of the car. Each trial has a fixed time-window of 10 seconds. The car has a linear dynamic system, in which velocity is controlled by joystick position (dXt = *AXtdt* + *BUtdt,* in which Xt = [car position, car velocity], Ut = control action (car

velocity based on joystick position), A = [0 1; 0 -.35], B = [0; 0.5]). This task will be used to estimate each individual's motivational component (goal state, accuracy/effort ratio) using computational models.

Implicit Approach Avoidance Task (AAT): Purpose: This task is designed to assess automatic action tendencies to approach or avoid positive, negative, and neutral stimuli [46]. Description: In this task, participants are asked to respond to a series of cues conveying positive, negative, or neutral emotional information (e.g., happy, angry, disgusted, neutral faces) by either pulling (approach) or pushing (avoidance) a joystick towards or away from themselves. Participants will see a picture in the center of the screen framed by either a blue or a yellow border. They will be instructed to pull the joystick towards themselves when the border is one color and to push the joystick away when the border is the other (counterbalanced across subjects). Pushing the joystick results in the picture zooming out and pulling the joystick results in the picture zooming in, thereby creating the visual impression that the pictures are coming closer or moving away. Reaction times are calculated based on the duration from the time the picture appeared on the screen to the time it disappeared. An approach bias score is computed by subtracting each participant's mean response latency in the pull condition for a given stimulus type from their mean response latency in the corresponding push condition (e.g., positive faces-push minus positive faces-pull). The AAT is a well-established measure of implicit approach/avoidance behavioral tendencies [47].

Approach-avoidance conflict task (AAC): This computer-based task is designed to examine decision-making in the context of affective risk. For this task, the participant is presented with a series of decisions between two different outcomes. Each outcome is associated with either a positive or negative valenced image/sound pair (IAPS and IADS), and some amount of point or gains. The participant is not able to select with certainty one outcome over the other. Instead, only the probability of the two outcomes is chosen, in the range from 10-90%, depending on the subject's stated preference for the two outcomes on a 9 point scale. The standardized IAPS and IADS stimulus sets have been used extensively in emotion research and are reliable elicitors of affective arousal [48, 49]. Conflict trials are those in which a negative affective image is combined with point rewards, while the positive affective image is combined with no point

rewards. There are three levels of conflict (2-point, 4-point, and 6-point). The main outcome variables of the task are: (1) mean approach behavioral for the different condition types (conflict, approach-only, and avoid-only). Before and after the task, participants rate their mood in terms of pleasantness, unpleasantness, and overall intensity on a visual analogue scale (VAS). After the task, participants complete a 14-item questionnaire asking questions about their experience of the task (i.e., "Overall, this task was enjoyable"), rating each item on a 1-7 Likert scale. This measure was originally developed by Dr. Aupperle [50]. This task takes approximately 20 minutes to administer.

Modified Probe Detection Task (MPDT): Attentional bias for positive and negative information will be measured using a version of the modified probe detection task [51]). Each trial consists of the identification of a cue location, brief presentation of a cue at that location (a small line oriented either horizontally or vertically), presentation of a pair of images (one representational, one non-representational), and presentation of a target, which is another line in either of two locations and is either horizontal or vertical. This target is presented until the participant responds, indicating whether the target is of the same or different orientation from the cue. Representational [51] stimuli will comprise IAPS images taken from positive, negative, or neutral valence sets. Each representational image is paired with one non-representational image, taken from a set of images of abstract art. Participants are presented with a total of 192 trials: 64 from each of positive, negative, and neutral images. The following traits are balanced across trials: representational image location, cue location, cue orientation, target location, target orientation, image duration (500 or 1000ms). The main outcome measures are the positive and negative engagement and disengagement biases [52].

Emotional Reactivity: This task consists of the presentation of 8 positive, 10 neutral, and 8 negative images. Each trial begins with a 20-26s fixation period, followed by presentation of one image for 6s. After each image, the participant makes valence and arousal ratings on a 7 point scale. During image presentation and sometimes during fixation, participants receive a ~95DB 50ms white noise sound meant to elicit a startle response [53]. The main purpose of this paradigm is to provide a reliable and validated assessment of psychophysiological

responses to emotional stimuli and startle-eliciting stimuli [54]. The collection of psychophysiological recordings will therefore be integral to this task specifically.

Heartbeat Counting: This task will contain four 1 minute trials, during which the participant has their eyes closed and is tapping a vmeter device [55].

Cold Pressor Challenge: This task will have each participant immerse their left hand in a circulating pool of water cooled to 6 degrees Celsius. Participants will be asked to keep their hand in the water for as long as they can tolerate, providing a brief measure of pain/stress tolerance and emotional reactivity/regulation. During each immersion participants will provide real-time ratings of their degree of pain unpleasantness/discomfort using the vmeter. The Cold Pressor paradigm is the gold standard which has been repeatedly used over the past century to safely induce transient states of intense pain [56, 57]. Maximum trial length will be 2 minutes.

Breath Hold Challenge: This task will have participants undergo 2 expiratory breath holds, providing a brief measure of interoceptive distress tolerance and carbon dioxide sensitivity. The maximum trial length is 1 minute, and there will be a 2-minute rest between trials. Participants are instructed to hold their breath for as long as they can tolerate following a normal (not forced) exhalation. The duration of each breath hold will be calculated starting from the moment when they begin exhaling and ending the moment they start inhaling again. All participants will need to wear a nose clip to ensure they are not inhaling any air.

Psychophysiological Recordings: Heart rate (ECG), respiration (RSP), skin conductance (SCR), and eye blink electromyogram (EMG) will be recorded continuously during each the behavioral tasks described above, using BIOPAC instrumentation (Lehigh, Pennsylvania). These physiological indices will also be measured during a 5-minute passive viewing task where subjects are presented with a slideshow of images of different flowers. The images are not expected to affect the physiological recordings, so data from this task are used as a physiological baseline to compare to the behavioral tasks (also described below). Measuring these indices during the behavioral tasks listed above will not add any time to the tasks themselves, but should take approximately 10-15 minutes for setup (i.e., to attach all electrodes, respiration belt, etc.).

BIOPAC Systems provides both hardware for collection of these measures (BioPac MP150 system) and software (AcqKnowledge software) for analyzing these measures. All of these measures are commonly used in emotional processing research and are relatively non-invasive. The use of all of these measures concurrently allows for a more thorough understanding of sympathetic and parasympathetic nervous system influences on physiological responses to negatively and positively-valenced stimuli, interoceptive stimuli, cognitive processing and decision-making. Descriptions of how these measures are obtained and the purposes of each are described below.

Facial Expressions: Advances in computer vision and machine learning over the past 15 years have led to the emergence of technology for automatic analysis of affective behavior [58]. During this time, the Machine Perception Laboratory at UCSD (MPLab) has focused on development of systems for automatic analysis of facial behavior, including audio-visual speech recognition [59-61] and recognition of facial expressions [60-64]. The output of the face detector is scaled to 90x90 and fed directly to the facial expression analysis system. First the face image is passed through a bank of Gabor filters at 8 orientations and 9 scales (2-32 pixels/cycle at 0.5 octave steps). The filterbank representations are then channeled to a classifier to code the image in terms of a set of expression dimensions. Research at the MPLab has demonstrated that performing feature selection on the Gabor filters prior to classification enhances both speed and accuracy. This approach combines feature selection based on Adaboost with feature integration using support vector machine. *Automatic Facial Expression Analysis*: A video camera will record each participant during the behavioral tasks described above in order to permit coding of facial expressions. Automatic facial expression analysis will be conducted by the EMOTIENT [65], software developed and validated by our collaborators at the Machine Perception Laboratory at UCSD (MPLab). EMOTIENT analysis corresponds to the well-validated Facial Action Coding System (FACS [66, 67]), a comprehensive method to objectively code facial expressions. EMOTIENT automatically codes the intensity of 26 component facial movements referred to as action units (Aus).

Neuropsychological Tasks

Wide Range Achievement Test (WRAT-4 reading): The WRAT-4 is an individually administered test of reading designed to measure general academic competence. The main variable of interest will be the total words pronounces correctly [193].

Delis-Kaplan Executive Function System (D-KEFS) Color-Word Inhibition Test: The D-KEFS Color-Word Inhibition Test is designed to assess verbal response inhibition and attentional switching. Participants are asked to name patches of colored ink (Color Naming subtest), read color-related words (Word Reading subtest), or to name the ink that color-related words are written in (Inhibition subtest). The speed at which participants complete the task and the number of mistakes made during completion are recorded. The main variables of interest for this study are the total time to complete the word reading, color naming, inhibition, and inhibition/switching subtests [68].

Delis-Kaplan Executive Function System (DKEFS) Verbal Fluency: This test is meant to measure information retrieval that is under conscious cognitive control and presumably an aspect of executive functions. On each of six one-minute trials, the examinee is asked to say as many distinct words as possible that meet a certain criterion. For the first three trials, the words must begin with a particular letter, for the next two trials, the words must belong to a particular semantic category, and for the last trial, words must alternate between two semantic categories. The main variable of interest is the total number of words correctly identified for the letter subtests and the semantic category subtests [68].

Wechsler Adult Intelligence Scale (WAIS-IV) Digit Span: This sub-test of the WAIS-IV is used to assess attention and working memory and requires participants to repeat a series of numbers in forwards and backwards order (Digit Span). The accuracy of their responses is recorded. The main variables of interest are the total score forward and backward [69].

Finger Tapping Test (FTT): The FTT is a neuropsychological test that examines motor functioning, specifically, motor speed and has also been shown as a sensitive measure of testing effort [70]. The main variables of interest are the average number of taps with the index finger per 10 seconds for dominant and non-dominant hands.

WAIS-IV Digit Symbol Coding [69] The Digit Symbol is a neuropsychological test of visuomotor speed and working memory. The test requires individuals to match a symbol to a number according to a key at the top of the page. The main variable of interest will be the number of symbols matched in the time limit (90 seconds).

California Verbal Learning Test (CVLT-II): The CVLT-II is used to evaluate verbal learning and memory. The CVLT consists of a list of 16 words from four semantic categories that is presented orally for five immediate recall trials (List A). Subsequent to the five learning trials of List A, a second 16-item word list (List B) is presented once. Free- and category-cued-recall trials of List A follow the immediate free-recall of List B. After a 20-min delay, free recall, cued recall, and a recognition trial of List A occur. The recognition trial contains the 16 target items from the first list along with 28 distractor items. During the recognition trial, the examiner presents each of the 44 items orally to the participant, who indicates whether or not the item was from the first word list. The main variables of interests for this study are the immediate recall from Trials 1-5 List A, Immediate and Delayed free recall and cued recall of List A. In addition, as most patients (even those with neurological disorders) are expected to score above chance on Recognition, this test will also be used to assess whether participants are putting in sufficient effort towards testing [196].

Functional MRI Tasks

Reward Processing Task: To measure behavioral and neural responses to rewards and losses, participants will complete the monetary incentive delay task (MID), a well-established measure of reward processing [71, 72]. This task dissociates anticipatory and consummatory phases of reward processing and has been shown to reliably activate brain regions implicated in regulating approach-related response tendencies and reward sensitivity (e.g., ventral striatum). On each trial, participants are given a cue indicating potential reward (circle), loss (square), or no reward/loss (circle or square). In order to receive a specified reward or avoid a loss, participants are required to press a button within a certain duration of time (adapted for individual participant reaction times) following presentation of a white square (target cue). Task difficulty, based on reaction times collected during a practice session, is set such that each

participant should succeed on ~66% of trials. The degree of potential reward or loss is varied on three levels indicated by the number of horizontal lines in a cue, i.e., one line indicates the lowest reward value (no reward), two lines an intermediate reward, and three lines the highest reward. For the MID task, participants can gain or lose points and earn an average of $30. The primary outcomes of interest will be: (1) anticipation of reward vs. no-reward, (2) receipt of reward outcomes vs. no-reward outcomes; (3) anticipation of loss vs. no-loss, and (4) receipt of loss outcomes vs. no-loss outcomes. The Monetary Incentive Delay Task will take about 18 minutes to complete.

Fear Conditioning Task: The fear conditioning task is based closely on the task successfully used by [73] to uncover neural bases of fear conditioning associated with trait anxiety [73]. The stimuli will consist of two neutral, non-social, abstract images as conditioned stimuli (CS), presented for 2 seconds at a time. Which image is the CS+ (paired with the unconditioned stimulus (US) during fear acquisition) and which is the CS- (never paired with the US) will be counter-balanced across participants. The US will be a 1s scream beginning 500ms after image onset. In the 9-15 seconds between CS image presentations, participants will be engaged in a continuous performance task requiring a right or left button press in response to right or left facing arrows. This serves to increase engagement and attention in the inter-trial interval. The task will consist of three components: a brief familiarization period, fear acquisition, and fear extinction. First, the *familiarization phase* (2.5 minutes) involves five presentations of each CS with no instances of the US to provide a baseline and allow familiarization to the scanner environment. Next, the *acquisition phase* will be broken into two runs of 8 minutes each. Each run will consist of 15 presentations of the CS- and 20 presentations of the CS+: five with (CS+ paired) and 15 without (CS+ unpaired) the US. This follows Sehlmeyer et al. [74] and allows for an equal number of trials to be included in the analysis (the CS+ paired trials will be excluded from analysis so as to not confound processing of the CS+ with reactivity to the US). Finally, the *extinction phase* will involve 25 presentations of each CS with no instances of the US. Participants will rate their valence, arousal and anxiety level to each CS at four times during the task: after familiarization, halfway through acquisition, after acquisition, and after extinction.

Trials will be presented in a fixed, pseudo-randomized order, constrained so that no more than two identical trials occur in a row.

Stop Signal (Inhibition) Task: At the onset of each trial, either an 'X' or an 'O' appears on a black background back-projected to the magnetic resonance imaging room. Participants are instructed to press, as quickly as possible, the left button when an 'X' appeared, and the right button when an 'O' appeared. They are also instructed not to press either button whenever they hear a tone during a trial (stop trials). Each trial lasts 1300 ms and each trial is separated by 200-ms inter-stimulus intervals (blank screen; see [75]). Individual response latency is used to denote the period of inhibitory processing and provide a subject-dependent jittered reference function. Participants perform six blocks of the task, each containing a total of 48 trials (12 stop and 36 nonstop trials in each block). Trial order is pseudo-randomized throughout the task and counterbalanced. Prior to scanning, participants perform the stop task in a behavioral testing session in order to determine their mean reaction time (RT) from 'X' and 'O' stimuli onset. Such individual measures are used to determine the stop signal delay (SSD) for the six different stop trial types. Specifically, stop signals are delivered at 0 (RT-0), 100 (RT-100), 200 (RT-200), 300 (RT-300), 400 (RT-400), or 500 (RT-500) ms less than the mean RT after the beginning of the trial, thus providing a range of difficulty level.

Interoceptive Attention Task: During this task, subjects alternate between two conditions: the interoception condition and the exteroception condition. During the interoception condition, the word "HEART" or "STOMACH" is presented on the screen and subjects are instructed to focus their attention on interoceptive sensations from that organ. For example, upon seeing the word "HEART", subjects focus on how intensely they can feel the sensation of their heart beating. During the exteroception control condition, the word "TARGET" is presented in the middle of the screen and the color of the word alternates from black to a lighter shade of gray every second. The subjects are instructed to focus their attention on the intensity of these color changes. Each task condition is presented in 10-second blocks, and half of the blocks are followed immediately by a 5-second response period during which the subject uses a visual scale (1-to-7) to rate the intensity of interoceptive sensations or exteroceptive color changes experienced during the preceding trial. Blocks are often separated by a variable inter-stimulus

interval, during which subjects look at a fixation mark. Each run of the task begins with a 10-sec initial fixation period and ends with a 10-sec final fixation period. Subjects will perform 2 scanning runs, each lasting 360 seconds (including initial and final fixation periods).

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Supplementary Table 1. Quarterly Follow-up Assessments

QUARTERLY FOLLOW-UP ASSESSMENTS	
Domain	Description
STANDARD SCALES	
Demographics	Demographics and Psychosocial Form (update)
History	Assessment of Medical and Medication History (update)
History	Life chart interview (update)
Substance Use	Customary Drinking and Drug Use Record (CDDR)
Depression	Quick Inventory of Depressive Symptomatology (QIDS-SR)
Eating Behavior	Simplified Nutritional Appetite Questionnaire (SNAQ)
Compliance	Medication Compliance
Compliance	Therapy Compliance
Disability	World Health Organization Disability Assessment Schedule
Presenteeism/Absenteeism	(WHODAS)
Suicidal Ideation	WHO Health and Work Performance Questionnaire (WHO HPQ)
Pain	Columbia-Suicide Severity Rating Scale (C-SSRS)
	Wong-Baker FACES Pain Rating Scale
PROMIS MEASURES	
Negative Valence	PROMIS Anxiety
Negative Valence	PROMIS Depression
Negative Valence	PROMIS Anger
Positive Valence	PROMIS/Neuro-QOL Positive Affect and Well-being
Cognitive	PROMIS Cognitive Abilities
Cognitive	PROMIS Cognitive General
Fatigue	PROMIS Fatigue
Sleep	PROMIS Sleep Disturbance
Sleep	PROMIS Sleep-related Impairment
Alcohol	PROMIS Alcohol Use
Alcohol	PROMIS Alcohol: Negative Consequences
Alcohol	PROMIS Alcohol: Positive Consequences
Alcohol	PROMIS Alcohol: Negative Expectancies
Alcohol	PROMIS Alcohol: Positive Expectancies
Nicotine	Nicotine Dependence
Nicotine	Coping Expectancies
Nicotine	Emotional and Sensory Expectancies
Nicotine	Health Expectancies
Nicotine	Psychosocial Expectancies
Nicotine	Social Motivations
Social	PROMIS Social Satisfaction DSA
Social	PROMIS Social Satisfaction Role
Social	PROMIS Ability to Participate Social

Social	PROMIS Emotional Support
Social	PROMIS Information Support
Social	PROMIS Instrumental Support
Social	PROMIS Satisfaction Roles Activities
Social	PROMIS Social Isolation
Physical	PROMIS Physical Function
Pain	PROMIS Pain Interference
Pain	PROMIS PAIN Behavior
Sex	PROMIS Global Satisfaction with Sex Life
Sex	PROMIS Interest in Sex Activity

Supplementary Table 2. One-Year Follow-up Session

ONE-YEAR FOLLOW-UP SESSION	
Domain	Description
DIAGNOSTIC AND DEMOGRAPHIC ASSESSMENT	
Diagnosis	MINI 6.0
Demographics	Demographics and Psychosocial Form (update)
History	Assessment of Medical and Medication History (update)
History	Life chart interview (update)
Substance Use	Customary Drinking and Drug Use Record (CDDR)
Compliance	Medication Compliance
Compliance	Therapy Compliance
Suicidal Ideation	Columbia-Suicide Severity Rating Scale (C-SSRS)
Pain	Wong-Baker FACES Pain Rating Scale
STANDARD SELF-REPORT SCALES	
Negative Valence/Interoception	Anxiety Sensitive Index (ASI-3)
Negative Valence	Ruminative Responses Scale (RRS)
Positive / Negative Valence	Positive and Negative Affect Schedule-Expanded Form (PANAS)
Depression	Quick Inventory of Depressive Symptomatology (QIDS-SR)
Positive Valence	TEPS anticipation/consumption/ pleasure
Arousal / Interoception	Multidimensional Assessment of Interoceptive Awareness
Eating Behaviors	Eating Disorders Diagnostic Scale
Eating Behaviors	Simplified Nutritional Appetite Questionnaire (SNAQ)
Physical Activity	International Physical Activity Questionnaire (IPAQ)
Disability	World Health Organization Disability Assessment Schedule (WHODAS)
Trauma	Traumatic Events Questionnaire (TEQ)
Absenteeism/Presenteeism	WHO Health and Work Performance Questionnaire
PROMIS MEASURES	
Negative Valence	PROMIS Anxiety
Negative Valence	PROMIS Depression
Negative Valence	PROMIS Anger
Positive Valence	PROMIS/Neuro-QOL Positive Affect and Well-being
Cognitive	PROMIS Cog Abilities
Cognitive	PROMIS Cog General
Fatigue	PROMIS Fatigue
Sleep	PROMIS Sleep Disturbance
Sleep	PROMIS Sleep-related Impairment
Alcohol	PROMIS Alcohol Use
Alcohol	PROMIS Alcohol: Negative Consequences
Alcohol	PROMIS Alcohol: Positive Consequences

Alcohol	PROMIS Alcohol: Negative Expectancies
Alcohol	PROMIS Alcohol: Positive Expectancies
Nicotine	Nicotine Dependence
Nicotine	Coping Expectancies
Nicotine	Emotional and Sensory Expectancies
Nicotine	Health Expectancies
Nicotine	Psychosocial Expectancies
Nicotine	Social Motivations
Social	PROMIS Social Satisfaction DSA
Social	PROMIS Social Satisfaction Role
Social	PROMIS Ability to Participate Social
Social	PROMIS Emotional Support
Social	PROMIS Information Support
Social	PROMIS Instrumental Support
Social	PROMIS Satisfaction Roles Activities
Social	PROMIS Social Isolation
Physical	PROMIS Physical Function
Pain	PROMIS Pain Interference
Pain	PROMIS PAIN Behavior
Sex	PROMIS Global Satisfaction with Sex Life
Sex	PROMIS Interest in Sex Activity
	Physio Setup
Computational - cognitive	Change Point Detection Task
	Regular Bandit Task
	Start / Stop Task (Driving)
Positive / Negative Valence	Implicit Approach / Avoidance Task
	Attentional Bias / Dot Probe Task
	Emotional Reactivity Task
	Baseline Task
	Approach Avoidance Conflict Task
Arousal / Interoception	Breath hold
	Heartbeat Counting Task
	Cold Pressor
Neuropsychology	WRAT reading
	DKEFS Color-Word Inhibition
	DKEFS verbal fluency
	WAIS-IV digit span
	Finger Tapping Test
	WAIS-IV Digit Symbol Coding
	California Verbal Learning Test
Biomarker and Microbiome	Repeat baseline measures, except for stem cells and genetics

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract **Pages 1-2**	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale **Pages 3-10**	2	Explain the scientific background and rationale for the investigation being reported
Objectives **Pages 10-11**	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design **Page 12**	4	Present key elements of study design early in the paper
Setting **Pages 13, 27**	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants **Pages 11, 13, 25-26**	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables **Pages 10-13**	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement **Pages 13-19, supplementary materials**	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias **Pages 26-27**	9	Describe any efforts to address potential sources of bias
Study size **Page 25**	10	Explain how the study size was arrived at
Quantitative variables **Pages 20-25**	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods **Pages 20-25**	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants N/A	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data N/A	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data N/A	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results N/A	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses N/A	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results N/A	18	Summarise key results with reference to study objectives
Limitations **Page 3**	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation N/A	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability **Page 3**	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding **Page 28**	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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The Tulsa 1000: A naturalistic study protocol for multi-level assessment and outcome prediction in a large psychiatric sample

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The Tulsa 1000: A naturalistic study protocol for multi-level assessment and outcome prediction in a large psychiatric sample

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ABSTRACT

Introduction: Although neuroscience has made tremendous progress toward understanding the basic neural circuitry underlying important processes such as attention, memory, and emotion, little progress has been made in applying these insights to psychiatric populations to make clinically meaningful treatment predictions. The overall aim of the Tulsa 1000 (T-1000) study is to use the NIMH Research Domain Criteria (RDoc) framework to establish a robust and reliable dimensional set of variables that quantifies the positive and negative valence, cognition, and arousal domains, including interoception, to generate clinically useful treatment predictions.

Methods and Analysis: The Tulsa 1000 is a naturalistic study that will recruit, assess, and longitudinally follow 1,000 participants, including healthy controls and treatment-seeking individuals with mood, anxiety, substance use, and eating disorders. Each participant will undergo interivew, behavioral, biomarker and neuroimaging assessments over the course of one year. The study goal is to determine how disorders of affect, substance use, and eating behavior organize across different levels of analysis (genes, molecules, cells, neural circuits, physiology, behavior, and self-report) to predict long-term prognosis, symptom severity, and treatment outcome. The data will be used to generate computational models based on Bayesian statistics. The final end-point of this multi-level latent variable analysis will be standardized assessments that can be developed into a clinical tool to help clinicians predict outcome and select the best intervention for an individual patient, thereby reducing the burden of mental disorders, and taking psychiatry a step closer toward personalized medicine.

Ethics and Dissemination: Ethical approval was obtained from Western Institutional Review Board (WIRB) screening protocol #20101611. The dissemination plan includes informing health professionals of results for clinical practice, submitting results to journals for peer-reviewed publication, presenting results at national and international conferences, and making the dataset available to researchers and mental health professionals.

Trial registration number: NCT02450240

STRENGTHS AND LIMITATIONS

Strengths

- The study uses multiple units of analysis for phenotyping.
- The study explores dimensional psychopathology that is representative of clinical populations.
- The study includes a clear and cohesive statistical analysis plan for a large and complex dataset.

Limitations

- The study does not include controlled treatment interventions.
- The study is a longitudinal observational study.
- The study is representative of a local Midwestern community that may not generalize to populations in different parts of the country or world.

INTRODUCTION

Mood [1] and anxiety [2] disorders are the most common form of mental illness and represent one of the biggest health issues worldwide, accounting for approximately $16 trillion in lost productivity or 25% of the global gross domestic product over the next 20 years [3]. Epidemiological data estimate the lifetime prevalence of Major Depressive Disorder (MDD) at about 18% and the 12-month prevalence at 7% [4]. Both MDD and anxiety disorders are associated with significant medical comorbidities [5] including substance use and eating disorders, which further exacerbate the cost and suffering associated with these disorders. The lifetime prevalence of eating disorders is comparatively lower at less than 3.5% [6], however, individuals exhibit extreme changes in body physique together with some of the highest mortality rates of all psychiatric disorders [7, 8]. Furthermore, most patients fail to remit or recover following treatment and up to 20% remain chronically ill [9-12]. Similarly, substance use disorders are among the most disabling conditions worldwide [13, 14]. Recovery includes abstinence [15, 16] and remission [17] but may not be adequately captured as an all-or-nothing process [18]. Recovery rates can differ across the primary drug of choice [19] and are highly nonlinear such that as many as 50% of treatment-seeking individuals relapse within a month of last use. The neural basis and behavioral changes associated with recovery are poorly understood because very few sufficiently powered, neurobiologically-based prospective, longitudinal studies have been conducted [20-25]. The heterogeneity of psychiatric disorders and the limited ability to identify broadly efficacious interventions have provided an impetus to utilize dimensional approaches to help delineate distinct syndromes that better reflect the underlying neurobiology [26].

Although neuroscience has made tremendous progress in understanding the basic neural circuitry that underlies important processes such as attention, memory, and basic emotion processing, little progress has been made in applying these insights to psychiatric populations in order to make clinically meaningful predictions. This may be because the current diagnostic system for mental disorders is based on statistically aggregated categories relying solely on verbal report and clinically observable behaviors [27]. Unfortunately, the connection between psychiatric disorders and their underlying neurobiology has been difficult to establish. The NIMH Research Domain Criteria (RDoC) framework was developed as a heuristic approach to better integrate pathophysiology with psychopathology [26]. The RDoC initiative highlights

two important goals for this objective: (1) psychiatric studies should transcend traditional diagnostic groups in order to adequately capture the inherent heterogeneity of symptomatology, and (2) clinical neuroscience and advanced statistical approaches should be used to determine the relationship between different units of analyses (self-report, behavior, physiology, neural circuitry, genetics, and clinically relevant psychopathology). The Tulsa 1000 aims to address these needs by determining how biological and objective behavioral measures can contribute to improving assessment and treatment of mental illness.

We use the RDoC framework as a heuristic to recruit, assess, and follow up a group of treatment-seeking individuals with mood and anxiety, substance use and eating disorders. Within these groups we aim to determine how affective, addictive, and feeding abnormalities organize across different levels of analysis and subsequently identify whether these latent factors can be used to generate clinically useful predictions. We aim to establish a robust and reliable dimensional set of variables that quantify the positive and negative valence, cognition, and arousal/interoception RDoC domains based on a latent variable approach [28-30]. These variables will be used to determine whether (a) measures of each domain (across different units of analyses) consistently relate to one another, (b) they predict the progression of symptoms over time (including natural recovery or worsening of symptoms), (c) they predict response to independently-sought pharmacological or behavioral treatments, and (d) they can be used in subsequent computational models of mental health to gain a more fundamental understanding of the pathology and predict illness course and recovery.

Overview of RDoC domains

Positive and Negative Valence Systems

Affect, or the tendency to experience a given emotion, is often subdivided into two domains [31]. Positive affect is the experience of positive emotions, such as happiness, excitement, elation, and enthusiasm. Negative affect is the experience of negative emotions, such as anger, resentment, sadness, anxiety, and fear. Positive affect and negative affect systems represent dimensions of psychopathology identified by the RDoC work groups [32, 33]. For example, high negative affect is common to anxiety and depression [34-36] and comorbid anxiety and depression is associated with more negative affect than each disorder alone [37]. Low positive affect is relatively specific to depression, with some evidence of low positive affect in social anxiety as well [34, 38]. In addition, psychophysiological and neurobiological data indicate that the negative affect system is closely tied to threat sensitivity whereas the positive affect system is closely tied to reward sensitivity. More detailed information on specific constructs of the positive valence system, including approach motivation, reward seeking and reward sensitivity and constructs of the negative valence system, including acute threat, potential harm are described in the Supplementary Materials.

Cognitive System

The major constructs that were considered by the RDoC committee on cognitive systems include: (1) *attention,* i.e. a set of processes that regulate access to capacity-limited systems, such as awareness, higher perceptual processes, and motor action; (2) *perception*, i.e. process(es) that perform computations on sensory data to construct and transform representations of the external environment to make predictions and guide action; (3) *declarative memory*, i.e. the acquisition or encoding, storage, consolidation, and retrieval of facts and events; (4) *language*, i.e. a system of shared symbolic representations of the world, the self and abstract concepts that supports thought and communication; (5) *cognitive control*, i.e. a system that modulates the operation of other cognitive and emotional systems, in the service of goal-directed behavior, when prepotent modes of responding are not adequate to meet the demands of the current context; (6) *working memory*, i.e. the active maintenance and flexible updating of goal/task relevant information (items, goals, strategies, etc.) in a form that has limited capacity and resists interference.

The T-1000 will focuses primarily on two constructs within the cognitive system (a) *cognitive control* and (b) *attention*. Inhibitory control, the ability to withhold a prepotent action, is an important cognitive control process, and is hypothesized to be dysfunctional in individuals with substance use problems [39]. However, it is unclear how dysfunctional cognitive control is associated with continuing substance use, and how this affects relapse following a period of recovery from substance use. For example, prior investigations have shown inhibitory control deficits in stimulant dependent individuals and moderate correlations with drug use indices [40-45].

In this study protocol, we will combine Bayesian ideal observer model-based analysis with fast, event-related functional magnetic resonance imaging (fMRI) data, to investigate subtle behavioral and neural differences among the target populations. Bayesian ideal observer models have been applied widely to the study of choice in uncertain environments, and to identify potential neural markers of the iterative processes of belief update underlying such models [46, 47]. Subsequent modeling studies have shown that such a framework is readily adapted to various aspects of executive function, including attentional and inhibitory control [48-51].

Arousal/Interoceptive System

Arousal is defined as a continuum of sensitivity of the organism to stimuli, both external and internal. Interoception refers to how the brain receives, processes, and integrates internal signals from the body to affect motivated behavior [52-54]. One important aspect of the arousal domain is the link to homeostatic drives and interoception. Different conceptualizations of interoception have included its definition as the state of the individual at a particular point in time [55], or as the sensing of body-related information in terms of awareness [56], or as the

accuracy of the sensing process [57], or as a trait phenomenon [58]. It is therefore a multifaceted process operating across numerous physiological and neural organ systems [59, 60]. Interoception provides an anatomical framework for identifying pathways focused on modulating the internal state of the individual. The anterior insula is predominately activated by effortful cognitive processing, whereas the posterior region is mostly activated by interoceptive sensory signals [61]. The insula is thought to be the central nervous system hub for interoceptive processing. There is an emerging generalized view that the anterior cingulate cortex (ACC), among other functions, orchestrates approach or avoidance behaviors in response to particular internal body states that involve homeostatic perturbations [62]. This function of the ACC is supported by the strong functional [63] and anatomical [64] connections between the anterior insula and the ACC. Taken together, the insula and ACC receive information about the individual's current body state and use this information to predict future body states and select actions that will help maintain bodily homeostasis.

Based on the RDoC criteria described above, the primary units of analyses for the Tulsa 1000 study are (a) symptoms, (b) paradigms / behavior, (c) physiology, (d) circuits, and (e) molecules that will be assessed via clinical and self-report interviews of past and current psychiatric symptoms, computational tasks of behavior and neuropsychology, biomarkers for genetics inflammation and microbiome, and structural and functional neuroimaging . There are several new emerging areas that either provide opportunities to examine how individual domains are affected by biological influences other than the individual or have the potential to yield cellular models of diseases. Next, these other units of analysis are described further.

Microbiome

The human body can be considered a super-organism composed of 10 times more microbial cells than our body cells. A meta-genomic study of the human microbiome has shown that microbial cells contain 150 times more genes than our own genome and make up an extraordinarily diverse set of over 1000 bacterial species [65]. Our understanding of the vast collection of microbes that live on and inside us (*microbiota*) and their collective genes (*microbiome*) has been revolutionized by culture-independent 'metagenomic' techniques and DNA sequencing technologies. Gut microbiota play an important role in health and disease and can be considered a 'microbial organ' [66]. Each individual's microbiota shows significant variability across body habitats and time, which may provide clues as to how microbiome changes cause or prevent disease [67].

The interaction between microbiota and human organs has been extended recently to brain-gut interactions [68]. The brain can influence enteric microbiota indirectly, via changes in gastrointestinal motility and secretion, and intestinal permeability, or directly, via signaling molecules released into the gut lumen from cells in the lamina propria [69]. There is emerging preclinical evidence that variations in the composition of gut microbes may be associated with

changes in the normal functioning of the nervous system [70]. Explorations of the microbiome thus offer new insight into our neurodevelopment, behavioral phenotypes, and perhaps disorders affecting complex processes, such as cognition, personality, mood, sleep and eating.

Human induced pluripotent stem (hiPS) cells

The molecular mechanisms responsible for dysregulated mood and anxiety, substance use, and eating behaviors are not well understood and few defining characteristics of diseased neurons have been identified. We intend to address this by generating dopamine cells (or neurons) that have been derived from a subset of individuals with extreme phenotypes of depression and/or anxiety, substance use, or eating behaviors. We aim to create cell-based human models for psychiatric disorders by directly reprogramming blood cells into human induced pluripotent stem (hiPS) cells in both healthy individuals and those with clinically-significant complaints related to affect, substance use, or eating [71-73]. We aim to identify specific neuronal defects associated with dopamine neurons *in vitro* and demonstrate the reversibility of the disease phenotype in human neurons, with the expectation to ultimately screen chemical libraries to identify novel therapeutic targets. The goal of these experiments is to identify key molecular events involved in the dysregulation of these target populations and to exploit these as possible points of intervention.

Genetics and Epigenetics

In humans, there is considerable evidence that anxiety and depression are moderately heritable and influenced by multiple genes. Most experts now believe that it is highly unlikely that there are "genes for psychiatric disorders". Rather, genes involved in susceptibility to psychiatric disorders can best be understood at the level of more basic biological processes (e.g., neuronal cell migrations during development) and/or mental function in the context of particular life experiences that are requisite for the expression of psychopathology.

Data from twin and adoption studies indicate that major depressive disorder (MDD), addiction disorders, and eating disorders (anorexia nervosa and bulimia) are moderately heritable - in the region of 40% to 60% - suggestive of a significant genetic contribution [74-76]. Clearly identifying the genetic variants that are associated with risk for developing these disorders would be helpful for predicting who is at risk of becoming ill and increasing our understanding of the pathophysiological basis of these disorders. Unfortunately, given the heterogeneity and complexity of MDD and anorexia nervosa, even well-powered genome-wide association study (GWAS) datasets of ~10,000 cases and ~10,000 controls and ~5,500 cases and ~20,000 controls, respectively, have failed to identify alleles that achieve genome-wide significance [77, 78].

A more tractable approach than the traditional case-control association study is offered by large scale longitudinal designs such as the Tulsa 1000. Here the proposed within-subject genetic analyses will emphasize the prediction of naturalistic clinical outcomes such as response to pharmacological and/or non-pharmacological treatment. Further, the genetic data collected will be stored for future testing and combined with multiple phenotypes (e.g. neuroimaging, clinical, cognitive assessments, and other bioassays) to provide an integrated theoretical perspective on the genetic basis for disorders of mood, anxiety, eating and addiction [79-81].

Immunophenotyping

Data from several different fields of study suggest that at least a subset of individuals with depression and other psychiatric illnesses show immunological dysregulation characterized by activation of the innate immune system together with suppression of elements of the adaptive immune response (reviewed in [82-85]). However, progress has been limited by a disproportionate focus on a static and narrow aspect of innate immunity, i.e. single time-point measurements of CRP or cytokines to the exclusion of other potentially informative markers of innate and adaptive immune function. Here, we will leverage the T-1000 design to obtain a wide-range of immunophenotypes both at baseline and post-treatment. Further, the range of tasks embedded within the T-1000 will provide a rich opportunity to examine the effect of experimental manipulations on immune function. The data obtained will not only further our understanding of the nature of immune dysfunction in psychiatric illness but may lead to the identification of prognostic and/or predictive biomarkers that possess clinical utility.

METHODS

Aims and Objective

This is a multi-level, longitudinal observational study of healthy controls and treatment-seeking individuals with mental health problems in Tulsa and the surrounding regions of Oklahoma. The overall aim is to obtain a comprehensive assessment based on RDoC principles, in order to:

(1) Determine relationships among variables assessing positive/negative valence, cognition, and arousal/interoception domains in order to derive latent variables that describe psychopathology across units of analysis and diagnostic groups.

(2) Investigate whether latent factors can be used to generate clinically meaningful outcome predictions across different domains and diagnostic groups.

Thus, this study has the potential to substantially improve our understanding of how disorders of mood, anxiety, substance use, and eating behavior are organized across different units of analysis (genes, molecules, cells, neural circuits, physiology, behavior, and self-report) and

different domains of functioning (positive and negative valence, cognition, and arousal/interoception). Upon completion, we will have robust and reliable dimensional measures that quantify these relationships among different units of analysis and different domains of functioning. The latent constructs will be the main outcome variables of this protocol. The baseline assessments will be used with individual-based prediction methods (e.g., random forests or support vector machines) to develop predictors. These predictors will be evaluated with test-specific statistics such as positive and negative likelihood ratios and standard measures such as area under the Receiver Operation Characteristic curve and area under Precision-Recall curve to determine which baseline measure or combination of measures best predicts clinical outcomes. Ultimately, the aim is to develop a set of assessments that can be used as a clinical tool to enhance outcome prediction for the clinician. These measures may also serve as an aid to determine who would likely benefit from different interventions.

Participants

We propose to collect complete datasets on a total of 1000 participants with approximately 500 mood and/or anxiety, 300 substance use, 100 eating disorder and 100 mentally and physically healthy control participants. In order to obtain 1000 participants who complete the year-long study, we plan to enroll up to 1400 participants between January 2015 and December 2018. Subjects will be between 18 and 55 years of age and have a body mass index between 17-38kg/m^2. Subjects will be referred from local treatment facilities or seeking treatment for anxiety and/or depressive symptoms, problems related to substance use, or problems related to eating behavior. As part of the inclusion criteria, mood/anxiety, substance, and eating disorder participants must also screen positive for these conditions as indicated by a score on the Patient Health Questionnaire (PHQ-9) ≥ 10 and/or Overall Anxiety Severity and Impairment Scale (OASIS) ≥ 8, (DAST-10) score > 2 or Sick, Control, One, Fat, Food Questionnaire eating disorder screen (SCOFF) score ≥ 2. Participants who meet criteria for one primary domain may also screen positive for one of the other study domains. Healthy control participants will screen negative for these inclusion measures.

Exclusion Criteria

The following exclusion criteria will apply: (1) inability to provide informed consent, (2) no telephone or easy access to telephone, (3) history of unstable liver or renal insufficiency; glaucoma; significant and unstable cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, rheumatologic, or metabolic disturbance; or any other condition that, in the opinion of the investigator, would make participation not be in the best interest (e.g., compromise the well-being) of the subject or that could prevent, limit, or confound the protocol-specified assessments, (4) a positive test for drugs of abuse, including alcohol (breath test), cocaine, marijuana, opiates, amphetamines, methamphetamines, phencyclidine,

benzodiazepines, barbiturates, methadone, and oxycodone, (5) has any of the following DSM-5 disorders: schizophrenia spectrum and other psychotic disorders, bipolar and related disorders, obsessive-compulsive and related disorders, (6) moderate to severe traumatic brain injury or other neurocognitive disorder with evidence of neurological deficits, neurological disorders, or severe or unstable medical conditions that might be compromised by participation in the study (to be determined by primary care provider), (7) active suicidal ideation with intent or plan, (8) change in the dose or prescription of a medication within the 6 weeks before enrolling in the study that could affect brain functioning, e.g., anxiolytics, antipsychotics, antidepressants, or mood stabilizers. However, we expect there to be changes in the dosing and prescription of medications during the course of the study protocol. This will be acceptable for the study and participants will be asked to inform the investigators of any treatments they undergo during their time in the study, (9) prescription of a medication outside of the accepted range, as determined by the best clinical practices and current research, (10) taking drugs that affect the fMRI hemodynamic response (e.g., methylphenidate, acetazolamide, excessive caffeine intake > 1000 mg/day), (11) MRI contraindications including: cardiac pacemaker, metal fragments in eyes/skin/body (shrapnel), aortic/aneurysm clips, prosthesis, by-pass surgery/coronary artery clips, hearing aid, heart valve replacement, shunt (ventricular or spinal), electrodes, metal plates/pins/screws/wires, or neuro/bio-stimulators, (12) persons who have ever been a professional metal worker/welder, history of eye surgery/eyes washed out because of metal, vision problems uncorrectable with lenses, (13) inability to lie still on one's back for 60-120 minutes; (14) prior neurosurgery, (15) tattoos or cosmetic makeup with metal dyes, (16) unwillingness to remove body piercings, (17) pregnancy, (18) unwillingness or inability to complete any of the major aspects of the study protocol, including magnetic resonance imaging (i.e., due to claustrophobia), biopsy, blood draws, or behavioral assessment. However, failing to complete some individual aspects of these assessment sessions will be acceptable (i.e., being unwilling to answer individual items on some questionnaires or being unwilling to complete a behavioral task), (19) non-correctable vision or hearing problems.

Study design

The study's dependent variables will focus on the *positive and negative valence systems, cognition, and arousal/interoception domains* proposed by the RDoC [32, 33]. Using self-report, behavior, physiology, neural circuit, cell, molecule, and gene unit of analysis measures, we will apply these constructs to a clinical population of individuals with dysregulation of affect, substance use, and eating behavior recruited from treatment providers across different sites in the community. Through the application of latent variable analysis, we will derive latent constructs of positive and negative valence, cognition, and arousal/interoception system functioning that cut across units of analyses and diagnostic groups. Subjects will undergo a multi-level assessment based on the RDoC approach that consists of (a) a standardized

diagnostic assessment , (b) self-report questionnaires assessing the positive and negative valence domains as well as interoception, (c) behavioral tasks assessing positive and negative valence, cognition, and interoception, (d) physiological measurements consisting of skin conductance, facial emotion expression monitoring, heart rate, respiration and eye-blink startle response, (e) functional magnetic resonance imaging focusing on reward-related processing, fear conditioning and extinction, cognitive control and inhibition, and interoceptive processing, (f) biomarker assessment, (g) microbiome assessment, (h) blood to derive induced pluripotent stem cells (IPS), (i) and genetic as well as epigenetic assessments. Subsequently, these individuals will be followed up quarterly and for one year. At months 3, 6, and 9, only self-report assessments will be collected, and the participants and will be re-assessed using a multi-domain assessment of functioning, which will include: (a) symptom severity and duration, (b) subjective well-being, (c) psychosocial function, (c) occupational function, (d) physical health, (e) utilization of mental health resources (treatment), and (f) adherence to treatment.

The workflow schematic in Figure 1 describes the overall outline of the T-1000 study and the measures obtained at different points in time.

Potential subjects will be screened by phone or in-person using the Western Institutional Review Board (WIRB) screening protocol 20101611. Once an individual has been identified as a potential subject in the T-1000, he or she will complete two to six in-person sessions within a two-week time period. However, completion of these sessions may be broken into more or less visits depending on what works best for the participant's schedule. The order of the baseline assessments may also be modified to ensure timely and efficient completion, given individual differences in completion times for the various measures (e.g., variability in how long individuals may take to complete self-report measures).

Although entry into the study is not based on meeting diagnostic criteria for a particular mood, anxiety, substance use, or eating disorder, it will be important to characterize how our findings map onto the Diagnostic and Statistical Manual of Mental Disorders (DSM) (using DSM-5 criteria)[86]. Accordingly, patients will complete a diagnostic interview with study personnel, using an abbreviated version of the Mini International Neuropsychiatric Interview (MINI Version 6.0) [87]. The MINI was chosen over other diagnostic interviews because of its relative brevity, good inter-rater reliability, and suitability for use by an interviewer with limited training. We will include sections on panic disorder (PD), social anxiety disorder (SAD), posttraumatic stress disorder (PTSD), generalized anxiety disorder (GAD), eating disorders (ED), obsessive-compulsive disorder (OCD), and major depressive disorder (MDD) and several modules to provide further clinical information or to determine ineligibility (suicidality, manic/hypomanic episode, and psychotic disorders).

After completing the MINI and satisfying study criteria, the subjects will complete a wide range of self-assessments that are targeted to probe the positive and negative valence domains, cognitive systems and interoceptive systems. Subjects included in the study will return for a behavioral testing session (session 2) and neuroimaging and biomarker testing sessions (sessions 3-5). During the behavioral session participants will complete a battery of neuropsychological assessments, a set of cognitive tasks which have been selected based on underlying computational models, a modified dot probe detection task, an approach/avoidance conflict task, and an emotional reactivity task in which they view blocks of emotional images. Interoception will be probed using a series of heartbeat detection tasks, an inspiratory breathhold experiment, and a cold pressor test. State affect and physiology will be assessed throughout the behavioral session procedures. The biomarker session will include a blood draw, microbiome collection, physical measurements including height, weight, body composition assessment, hip/waist ratio, and vital signs (pulse, blood pressure). The structural MRI, functional MRI and EEG session will include high resolution anatomical brain scans, a resting state functional scan and task-based functional scans targeting neural systems associated with reward, attention, inhibition, interoception and fear conditioning.

The details of each session are listed in Table 1: the first column indicates which construct will be examined, the second column lists the name of the test. All self-report assessment measures will be administered electronically through REDCap [88].

Study Sessions

Detailed descriptions of the clinical, demographic, self-report, behavioral, neuropsychological and functional neuroimaging measures listed below are provided in the Supplementary Materials.

The Baseline Session

Clinical interview, demographics, and questionnaires detailed in Table 1 will be administered by masters or nurse level assistants who are supervised by licensed clinical psychologists and board certified psychiatrists. The clinical portion of the baseline assessements is expected to take approximately 4.5 hours to complete and can be split into two or more visits.

Table 1. Baseline Session: Clinical Interview, Demographics and Questionnaires

Domain	Assessment
Clinical Rating Scales and Demographics	
Diagnosis	MINI 6.0 [89]
Demographics	Demographics and Psychosocial Form
History	Assessment of Medical and Medication History

History	Life chart interview
Substance Use	Customary Drinking and Drug Use Record (CDDR) [90]
Handedness	Edinburgh Handedness Inventory [91]
Compliance	Medication Compliance
Compliance	Therapy Compliance
Traumatic Head Injury	Tulsa Head Injury Screen
Family Psychiatric History	Family History Screen (FHS) [92]
Suicidal Ideation	Columbia-Suicide Severity Rating Scale (C-SSRS) [93, 94]
Pain	Wong-Baker FACES Pain Rating Scale [95]

Self-Report Scales

Negative Valence	State Trait Anxiety Inventory (STAI) [96]
Negative Valence/Interoception	Anxiety Sensitivity Index (ASI-3) [97]
Negative Valence	Ruminative Responses Scale (RRS) [98]
Depression	Quick Inventory of Depressive Symptomatology [99]
Trauma	Traumatic Events Questionnaire (TEQ) [100]
Trauma	Child Trauma Questionnaire (CTQ) [101]
Positive/Negative Valence	Positive and Negative Affect Schedule-Expanded Form (PANAS-X) [102]
Positive/Negative Valence	Behavioral Inhibition System/Behavioral Approach Scale (BIS/BAS) [103]
Positive Valence	TEPS anticipation/consumption/pleasure [104]
Positive Valence	UPPS Impulsive Behavior Scale[105]
Empathy-like	Interpersonal Reactivity Index (IRI) [106, 107]
Personality	Big Five Inventory (BFI) [108]
Arousal/Interoception	Toronto Alexithymia Scale (TAS) [109, 110]
Arousal/Interoception	Multidimensional Assessment of Interoceptive Awareness (MAIA) [58]
Eating Behaviors	Three Factor Eating Questionnaire (TFEQ) [111-113]
Eating Behaviors	Eating Disorders Diagnostic Scale (EDDS) [114]
Eating Behaviors	Simplified Nutritional Appetite Questionnaire (SNAQ) [115]
Physical Activity	International Physical Activity Questionnaire (IPAQ) [116]
Disability	World Health Organization (WHO) Disability Assessment Schedule [117]
Absenteeism/Presenteeism	WHO Health & Work Performance Questionnaire (WHOHPQ) [118]

Patient Reported Outcome Measurement Information System (PROMIS) Measures [119, 120]

Negative Valence	PROMIS Anxiety
Negative Valence	PROMIS Depression
Negative Valence	PROMIS Anger
Positive Valence	PROMIS/Neuro-QOL Positive Affect and Well-being

Cognitive	PROMIS Cognitive Abilities
Cognitive	PROMIS Cognitive General
Fatigue	PROMIS Fatigue
Sleep	PROMIS Sleep Disturbance
Sleep	PROMIS Sleep-related impairment
Alcohol	PROMIS Alcohol Use
Alcohol	PROMIS Alcohol: Negative Consequences
Alcohol	PROMIS Alcohol: Positive Consequences
Alcohol	PROMIS Alcohol: Negative Expectancies
Alcohol	PROMIS Alcohol: Positive Expectancies
Social	PROMIS Social Satisfaction DSA
Social	PROMIS Social Satisfaction Role
Social	PROMIS Ability to Participate Social
Social	PROMIS Emotional Support
Social	PROMIS Information Support
Social	PROMIS Instrument Support
Social	PROMIS Satisfaction Roles Activities
Social	PROMIS Social Isolation
Physical	PROMIS Physical Function
Pain	PROMIS Pain Interference
Pain	PROMIS PAIN Behavior
Sex	PROMIS Global Satisfaction with Sex Life
Sex	PROMIS Interest in Sex Activity
Nicotine	Nicotine Dependence
Nicotine	Coping Expectancies
Nicotine	Emotional and Sensory Expectancies
Nicotine	Health Expectancies
Nicotine	Psychosocial Expectancies
Nicotine	Social Motivations

Baseline Behavioral Session

Behavioral tests will be administered via computer interfaces, with the exception of neuropsychological testing which will be conducted face to face by an assessor. The neuropsychological assessments will be administered by trained clinical assistants, directly supervised by licensed clinical psychologists and board certified psychiatrists. Behavioral assessments will be conducted by trained research assistants. The behavioral session is expected to take about 4 hours to complete and can be split into 2 or more visits (Table 2).

Table 2. Behavioral and Neuropsychological Tasks

Domain	Task
Computational- Cognitive	Change Point Detection Task [121]

	Three Arm Bandit Task [122] Start/Stop Task [123]
Positive/Negative Valence	Implicit Approach/Avoidance Task [124] Attentional Bias/Dot Probe Task [125] Emotional Reactivity Task [126] Approach Avoidance Conflict Task [127]
Arousal/Interoception	Breath Hold Heartbeat Counting Task Cold Pressor [128, 129]
Neuropsychology	WRAT Reading [130] DKEFS Color-Word Inhibition [131] DKEFS verbal fluency [131] WAIS-IV digit span [132] Finger Tapping Test WAIS-IV Digit Symbol Coding [132] California Verbal Learning Test [133]

Baseline Biomarkers

Table 3 summarizes the proposed biomarkers and biological specimens that will be obtained from blood samples and microbial samples of the subjects. It is expected to take approximately 30-45 minutes to complete sample collection.

Table 3. Examples of immune-related measurements

Immunophenotype	**Reported Abnormality in Depression**	**References**
Cytokines	Elevations in pro-inflammatory cytokines	[134-136]
PBMC Gene Expression	Increased mRNA expression of pro-inflammatory mediators	[137-140]
Kynurenine Pathway	Increased neurotoxic kynurenine metabolites	[141-143]
T-cells	Altered T-cell function and numbers	[144, 145]
Natural Killer Cells (NKC)	Reduced NKC function	[146, 147]
Pathogens	Increased seropositivity for *T. gondii* and herpesviridae	[148, 149]

Baseline Neuroimaging

The session will consist of one 60 and one 120 minute scan in the MRI machine. One of the neuroimaging sessions will focus on structural differences in the brain and a second session will

focus on functional differences. The neuroimaging sessions are expected to take approximately 4 hours total to complete and are split into two visits (Table 4).

Table 4. Baseline Neuroimaging Sessions

32 Channel Head Coil MRI Imaging: Structural & Perfusion
Participant Last Use Summary (PLUS)
3-plane localizer, asset calibration
T2-W Clinical Flair
T2-W Clinical FSE
T1-W Clinical MPRAGE
T1-W MPRAGE HI-RES
T2-W Propeller FSE HI-RES
Arterial Spin labeling
Diffusion Tensor Imaging
8 Channel Head Coil MRI, and fMRI with concurrent EEG
Task Training and Practice
Karolinska Sleepiness Scale: Pre-scan (KSS)
Participant Last Use Summary (PLUS)
EEG Cap Setup
MRI Anatomical scan (T1-W)
fMRI Monetary Incentive Delay Task (MID) [150, 151]
fMRI Stop Signal Task [152]
fMRI Resting State with eyes open
fMRI Interoceptive Attention Task [153]
fMRI Fear Conditioning/Extinction Task [154]
Karolinska Sleepiness Scale: Post-scan (KSS)

Quarterly Follow-up Session

These sessions will examine the course of outcomes in individuals with dysregulated mood and/or anxiety, substance use, or problematic eating behavior. These assessments will be brief in-person visits. The quarterly follow-up assessments will take approximately 1.5 hours every 3 months during the 12-month follow-up time period (Supplementary Table 1).

One-year Follow-up Session

This session will examine the course of outcomes 1 year after baseline. For neuropsychological assessment, alternative forms will be used as available. Assessments will be administered during in-person sessions that take approximately 7 hours to complete over 1 to 3 visits

(Supplementary Table 2).

Biomarker measures

Blood Collection

We will investigate neuroendocrine, metabolic, inflammatory, and cardiovascular biomarkers associated with positive and negative valence domains, cognitive systems and arousal/interoceptive systems. These measures help to extend our multi-level analysis of NIMH RDoC constructs into the cellular and molecular units of analysis. Biochemical assays will be performed on biological samples collected at baseline and during the 1-year follow-up to quantify a range of biomarkers and their relationship with other variables and units of analysis.

Participants will have fasting blood drawn by venipuncture by a trained phlebotomist for the biomarker panels. This will be scheduled to occur the morning of one of the visits, or at a time convenient for the participant. Resting blood pressure and heart rate will be assessed. Additionally, in order to lay the foundation for future studies, we will also collect and process a small quantity of blood to be banked for potential future endocrine, immune and/or genomic analyses.

Sample collection, processing distribution and storage procedures

A trained phlebotomist will obtain all blood samples. Less than 150 mL of blood will be collected per subject during each session (baseline and 1-year follow-up), which is well within the safety limit of ~450 mL per blood draw. Samples for stem cells and genetics will be shipped to Rutgers University laboratory for processing and storage. Blood samples for plasma, serum, and peripheral blood mononuclear cells (PBMCs) will be transported to and processed at the University of Oklahoma Integrative Immunology Center (IIC) Laboratories. Plasma and serum samples will be stored in secure freezers at -80^{o}C. Freezers will be maintained in a specially equipped room with emergency backup power and an automated telephone alarm system that is programmed to call in case of failure. Additional aliquots of samples will be stored at -80^{o}C should repeat analyses be required at a later date. PBMCs will be stored in liquid nitrogen dewars with liquid level monitors and alarms in a secure room at the University of Oklahoma IIC Laboratories.

Microbiome Collection

Participants will be asked to provide microbial samples during the biomarker session. All participants will be asked to provide forehead, mouth and stool samples.

A research assistant will provide the participant with an all-in-one sample collection kit system for collecting, stabilizing, transporting, and purifying samples which includes cotton-swabs, tubes

labeled by body area, and step by step instructions.. Participants will be asked to perform the sampling themselves. Samples will be stored at the University of Oklahoma IIC Laboratories after initial processing until they are shipped to The University of San Diego-California for final processing and sample analysis.

Compensation

Subjects will receive the following payment for completing the study (Table 5):

Table 5. Compensation

SESSION	TIME	PAYMENT*
Interview and Demographic Information	4.5 hours	$90
Behavioral assessments & Computerized Tasks	4 hours	$80 $10-$20 reward
Biomarkers	30 minutes	$50
Neuroimaging & EEG & Setup	4 hours	$170 $0-$60 reward
3 month Follow up*	1.5 hours	$30
6 month Follow up	1.5 hours	$30
9 month Follow up	1.5 hours	$30
12 month Follow up	7 hours	$200 $10-20 reward
Total	23.5 hours	$700 to $780

DATA ANALYSIS

Behavioral and Psychophysiological Data Analyses

Self-report questionnaires, interviews, neuropsychological assessments, computer-based behavioral assessments, and psychophysiological assessments will be scored according to published methods (as cited in the Tables). These variables will then be used in conjunction with collected biological data in the latent variable approach. The analysis strategy consists of the following steps. First, the characteristics of all measures will be examined for deviation from normality prior to subsequent analyses. For each unit of analysis (self-report, behavior, physiology, circuits, biomarkers), separate principal components analyses (PCA) will be performed and a separate analysis will be conducted for each behavioral task to minimize task-specific factors in subsequent analysis steps. Next, the number of components for each analysis will be determined using a number of different approaches [155]. In particular, if the number of components to be extracted differed across the extraction approaches, both solutions will be explored [156, 157]. Component scores from each unit of analyses will be extracted for each

participant and used for the following analyses.

MRI, EEG and fMRI Data Analysis

The basic structural and functional image processing will be done with the Analysis of Functional Neuroimages (AFNI) software package [158].

EEG-fMRI

The EEG data will be acquired simultaneously with the fMRI data and corrected for artifacts related to the gradient switching and cardiac ballistic effect using the template subtraction method [159-161] implemented in BrainVision Analyzer software (Brain Products GmbH, Munich, Germany).

During fMRI scans we will simultaneously record EEG using a 31-electrode cap attached to an MRI-compatible BrainAmp MR Plus amplifier. The sintered Ag/AgCl ring electrodes are mounted into a scalp cap according to the standard 10-5 system. All electrodes are referenced to the FCz position, while a ground electrode is located at the AFz position. One additional electrode will be placed on the subjects' back to monitor the electrocardiographic signal. The impedance of all electrodes will be maintained below 10 KΩ throughout the recording. The internal sampling clock of the EEG amplifier will be synchronized with the MRI scanner 10MHz master clock signal using the SyncBox device (Brain Products GmbH, Munich, Germany), in order to prevent variant sampling of imaging artifacts and to facilitate artifact correction [161]. The signals will be recorded at a sampling frequency of 5000 Hz with an analog filter (from 0.016 to 250 Hz) and a resolution of 0.1 µV.

Besides independent EEG measures of brain state, and EEG-informed fMRI data analysis, we will use EEG data to correct the effects of head movements in simultaneously acquired fMRI data on a slice-by-slice basis [162]. This E-REMCOR, and recently developed automated version aE-REMCORE technique, will make it possible to regress out the effects of rapid head movements from unprocessed fMRI data on slice-by-slice basis prior to volume registration [163]. Thus, aE-REMCOR complements both the traditional fMRI volume registration approach, which performs better for slower head motions, and the RETROICOR method for slice-specific correction of fMRI cardiorespiratory artifacts [164]. EEG-informed fMRI analysis will allow us to better elucidate and characterize normal and pathological interactions between cerebral function and behavior, cognition or emotion.

fMRI Pre-Processing

Standard fMRI data pre-processing will include a slice-timing correction, signal scaling, spatial smoothing, physiological noise suppression [164, 165], and motion correction.

Task-based fMRI Analysis

First/Subject-Level Analyses

Multiple regression will be used to analyze individual subjects' data, with predictors in the model constructed by convolving each column of the task design matrix with a canonical hemodynamic response function. Regressors of non-interest will be included in all models to account for (1) head motion (6 motion variables), and (2) other sources causing drifts (each run's signal mean, linear, quadratic, and cubic signal trends). The beta weights and corresponding t-statistics for image contrasts of interest will be produced for group-level analyses.

Second/Group-Level Analyses

Both region of interest (ROI) and whole-brain analyses start with voxel-wise statistical tests using mixed-effects modeling on aggregations of maps of the subjects' beta-weights and beta-weight standard errors (AFNI's *3dMEMA* or in-house developed R code). This approach has the advantage of taking into account in the group analysis both effect estimates as well as their within- and between-subjects variances. Correction for multiple comparisons will be conducted as follows. Statistical maps will either be corrected using the false-discovery rate (FDR) or cluster level thresholds. For cluster level thresholds, AFNI's *3dClustSim* (with spatial autocorrelation function [acf] adjustments) will be used to identify the required cluster-size threshold, given a voxel-wise probability of $p < 0.001$, the smoothness of the residuals from the group level test, and the size of the region tested (either whole-brain or an a priori defined ROI).

Resting State fMRI Analysis

Pre-Processing

Data pre-processing will be conducted using afni_proc.py. The first three volumes of the functional scans will be discarded to allow the signal to reach T1 equilibrium, and a de-spiking algorithm will be used to remove any transient signal spikes from the data. Prior to slice time correction, physiological signals of non interest (pulse, respiration) will be removed using RETROICOR. For each subject, the remaining volumes will be corrected for differences in slice acquisition time; head motion will be corrected by rigid body translation and rotation; the third volume of the functional run will be co-registered to the anatomical coordinates of the participant's structural scan by linear warping, then normalized to the Talairach template and resampled to 2x2x2 mm^3 voxels.

First/Subject-Level Analyses

For each participant, the time courses of the residual images from the pre-processing step will

be averaged across voxels within each ROI, and Pearson correlation coefficients will be computed between the mean signal time courses of pairs of ROIs. These correlation coefficients will be converted by Fisher *r*-to-*z* transformation, which will be used as predictors of treatment outcomes.

The identified brain activation at ROIs and/or functional connectivity z-scores will be analyzed by PCA, and the extracted principal component scores will be used with scores from other units of analyses.

General Unifying Statistical Approach

The goal of this project is to derive latent variables that adequately quantify the positive and negative valence, cognition, and interoception/arousal domains across different units of analyses collected at baseline. The analysis of the variables that are extracted from each unit will consist of three steps. First, a PCA will be conducted for each unit of analysis to determine the number of independent degrees of freedom contributing to the variance observed in each unit. We expect to extract at least two independent components. The action units that show the highest correlation with the components will be used for subsequent analyses. Second, we will conduct a confirmatory factor analysis with the variables from each unit of analysis that showed the highest correlation with the principal components of four proposed factors – positive valence system, negative valence system, arousal/interoceptive system, and cognitive system. We will subsequently test the statistical significance of the coefficients contributing to the factors. Finally, we will conduct a latent variable analysis as detailed below to relate one unit directly to another unit of analysis.

Statistical Analysis Plan

Baseline/Cross-sectional analyses

We will relate different units of analyses by regularized generalized canonical correlation analysis (RGCCA) [166]. Classical CCA identifies linear combinations of two sets of variables such that their correlations are maximized. RGCCA extends classical CCA from two sets of variables to multiple sets. When applied to multiple units of analyses, RGCCA identifies linear combinations (canonical variates) of principal component scores within each unit of analyses, such that the sum of correlations or covariance across canonical variates is maximized. The results of RGCCA can be demonstrated as a network that shows which unit of analyses are connected, and which are not. Moreover, the canonical correlations obtained from RGCCA can be used to define biotypes by cluster analysis from two sets of variables (clinical symptoms and resting state functional connectivity) to define biotypes [167]. These dimension-defined biotypes will be linked to the category-defined groups by cross tabulation.

Longitudinal analysis

The self-report outcomes will be measured at baseline and months 3, 6, 9, and 12, and these time trajectories will be compared between groups based on categorical diagnosis (comparison subjects, substance use disorders, mood disorders, and eating disorders) and between dimensionally-defined biotypes using models for longitudinal data – mixed effects and generalized estimating equations (GEE) models. No functional form will be assumed for the time trajectories and profile models will be used (i.e., time variable is treated as a factor in the model). The biotype/group effect will be measured as a time-by-group interaction. Comparisons between the time profiles of the groups will use appropriate Wald and likelihood ratio tests. In addition, linear time effects will be considered; these will be used if they are preferable to the profile models in model comparison using Akaike information criterion (AIC).

Statistical Power

We will base statistical power on two considerations: (1) power to estimate latent factor models with precisions, and (2) accuracy of prediction of outcomes using baseline variables and latent factors as predictors. Although controversial [168], typically one suggests that there should be at least n=10 subjects for each identified latent variable. In comparison, this study is likely to have up to n=100 subjects per latent construct. More recent recommendations for power take into account the quality of the indicators for the latent variables and the number of items per factor. For a moderate to low communality (conservative assumption), a sample size of n=300 would give an excellent coefficient of congruence of K=0.97. This allows for fitting latent factor models to each patient subgroup separately with adequate power [169]. We also compute power to predict the year follow-up clinical outcomes: assuming 100 healthy controls (HC), 100 eating disorder (ED), 500 mood/anxiety (MA), and 300 substance use (SU) participants at baseline and a uniform 20% attrition rate for each group at one-year follow-up (i.e., with remaining 80, 80, 400, and 240 participants in the corresponding groups), we will have 80% power to detect effect sizes (Cohen's D for between-group differences in changes from baseline to 1-year follow-up) of 0.57 (ED vs. HC), 0.43 (MA vs. HC or ED), 0.45 (SU vs. HC or ED), 0.29 (MA vs. SU) at two-sided Type I error rate 0.05/6 = 0.008 (Bonferroni correction) in t-test for post hoc comparisons.

ETHICS and DISSEMINATION

Gender/minority/pediatric inclusion for research

Women and minorities will be included in the study without prejudice and represented according to the study population. Participants will be recruited from the greater metropolitan areas of Tulsa, Oklahoma and efforts will be made to ensure the subject population is

representative of the gender, ethnicity and racial demographics of the region according to the US Census Bureau data. No participants under the age of 18 will be enrolled in the study.

Specimens, records, data collection

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study. Study consent records will be stored in the locked records room at the Laureate Institute for Brain Research. Only approved study personnel will have access to study records that contain any identifying information. Study data records and blood/urine/biological samples will be assigned code numbers and will not be individually identifiable. Code numbers are a combination of numbers and letters. The electronic data will be kept in a firewalled and password protected database on a secure server managed by LIBR. Vanderbilt University, with collaboration from a consortium of institutional partners, has developed a software toolset and workflow methodology for electronic collection and management of research and clinical trial data REDCap (Research Electronic Data Capture) [88] data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team with planning assistance from the information technology staff. The iterative development and testing process results in a well-planned data collection strategy for individual studies. REDCap servers are housed in a local data center at Laureate Institute for Brain Research and all web-based information transmission is encrypted. REDCap was developed specifically around HIPAA-Security guidelines and is recommended to LIBR researchers by both our Privacy Office and the Western Institutional Review Board (WIRB). REDCap has been disseminated for use locally at other institutions and currently supports 240+ academic/non-profit consortium partners on six continents and over 26,000 research end-users (www.project-redcap.org).

Records of the subject's participation in this study will be held confidential except as disclosure is required by law or as described in the informed consent document (under "Confidentiality"). The study doctor, the sponsor or persons working on behalf of the sponsor, and under certain circumstances, the United States Food and Drug Administration (FDA) and WIRB will be able to inspect and copy confidential study-related records which identify the subject by name. Therefore, absolute confidentiality cannot be guaranteed. If the results of this study are published or presented at meetings, the subject will not be identified. Paper copies of consents, screening forms, the Research Privacy Form, and any other forms, testing results or papers containing Personally Identifiable Information (PII) will be stored in a secured medical records room with access granted only to authorized personnel.

Recruitment and consent procedure

Recruitment into the T-1000 study at the Laureate Institute for Brain Research will be ongoing

for 4 years from January 2015 through December 2018. The study will be completed by December 2019 after the completion of the 1-year follow-ups from 2018. Study participants will be recruited through the clinical services of the Laureate Psychiatric Clinic and Hospital (LPCH), local service providers for behavioral health, mental health, and addiction and recovery (e.g. Family and Children's Services, 12&12 Inc., local psychiatrist and physician offices), and through online, newspaper, flyer, radio or other media advertisements in the Tulsa metropolitan area. Participants will also be recruited through a pre-approved LIBR Screening protocol (WIRB #20101611) and through the Laureate Institute for Brain Research REDCap database. Informed Consent will be obtained by members of the research team that have received training from the PI to obtain consent for this study. All participant interactions including consenting will be conducted in private interview/exam rooms. These exam rooms at LIBR are secured from public areas via combination locked doors that are only accessible to authorized personnel.

Expected outcomes

The final end-point of this multi-level latent variable analysis will be a set of standardized assessments that can be developed into a clinical tool to help clinicians predict outcomes for an individual patient with a mood, anxiety, eating, or substance use disorder following implementation of standard treatment interventions. These variables will be used to determine whether (a) measures of each domain (across different units of analyses) consistently relate to one another, (b) they predict the progression of symptoms over time (including natural recovery or worsening of symptoms), (c) they predict response to independently-sought pharmacological or behavioral treatments, and (d) they can be used in subsequent computational models of mental health to gain a more fundamental understanding of the pathology and predict illness course and recovery. By establishing a robust and reliable dimensional set of variables that quantify the positive and negative valence, cognition, and arousal/interoception RDoC domains based on a latent variable approach, this project will take psychiatry a step closer towards personalized and biologically based medicine [28-30].

Dissemination of results

Results from the study will be submitted to relevant journals for peer-reviewed publication and presented at national and/or international biomedical conferences.

Registration

In accordance with the recommendations of the International Committee of Medical Journal Editors, the proposed study is registered in a public registry (http://www.clinicaltrials.gov/, Trial Registration Number: NCT02450240).

Collaborators

University of Oklahoma

University of California-San Diego

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Contributors

All authors made a significant contribution to the conception and design of the study protocol. The protocol was written by MPP and TAV and critically reviewed by SK, JB, JF, RA, HY and WKS. All authors gave permission and approval for publication.

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None

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Figure 1. T1000 Workflow Schematic

Abbreviations (in alphabetical order): BOLD: Blood-Oxygen-Level-Dependent; DAST: Drug Abuse Screening Test; DTI: Diffusion Tensor Imaging; EEG: Electroencephalogram; MINI: Mini International Neuropsychiatric Interview; MRI: Magnetic Resonance Imaging; OASIS: Overall Anxiety Severity and Impairment Scale; PHQ-9: Patient Health Questionnaire; PROMIS: Patient Reported Outcome Measurement Information System; SCOFF: Sick, Control, One, Fat, Food Questionnaire; T1/T2: T1- weighted (longitudinal relaxation time) and T2-weighted (transverse relaxation time)

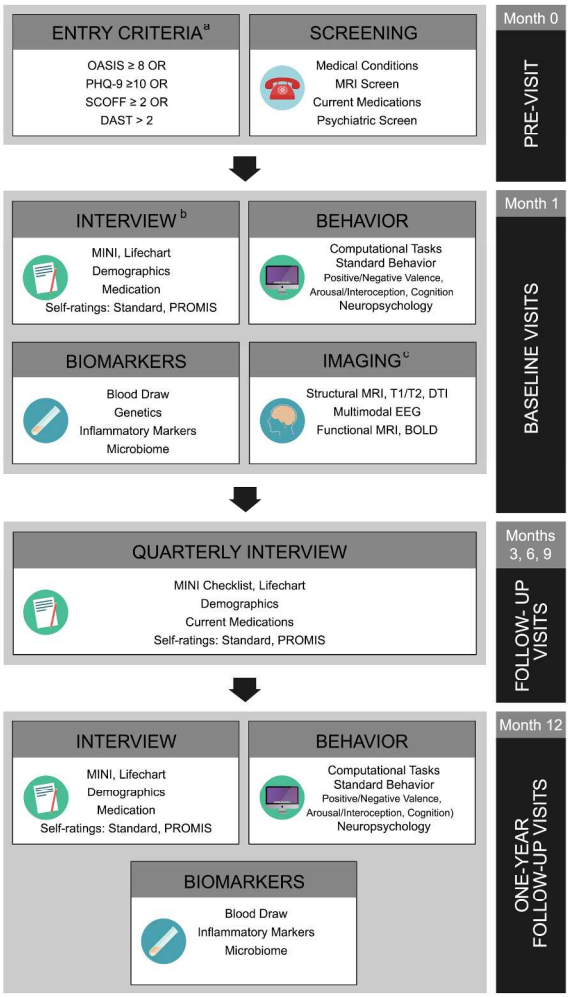

Figure 1. T1000 Workflow Schematic

215x279mm (300 x 300 DPI)

SUPPLEMENTARY MATERIALS

Positive and Negative Valence Domains

Positive Valence System

A central construct of the positive valence system is *approach motivation*, which can be defined as processes that regulate the direction and maintenance of approach behavior. The constructs of *reward seeking* and *reward sensitivity* are components of approach motivation. Reward sensitivity refers to the anticipation and receipt of positive stimuli. The primary neural mechanisms of reward sensitivity involve the ventral striatum (VS) and orbitofrontal cortex (OFC). These structures are involved in the processing of primary rewards, such as pleasant tastes [1], smells [2] or sights [3], as well as secondary (monetary) rewards [3-5]. The VS plays an important role in the anticipation of reward [6, 7] as well as the receipt of reward [4, 8]. The VS is part of a larger fronto-striatal circuit subserving reward-related processing that also includes the OFC, a subregion of the prefrontal cortex [9]. An important functional coupling exists between the VS and OFC [10]. Reward-processing also involves other neural regions, including the amygdala [11-13], dorsal anterior cingulate cortex (ACC) [14] and the hippocampus [15].

Relationship between reward sensitivity and the positive valence system: Extant evidence shows that individuals have deficits in positive affect (i.e., individuals with depressive disorders) show deficits in reward processing, at both the behavioral [16] and the neural levels [17]. At the behavioral level, individuals with major depression are less responsive to reward-relevant stimuli than non-depressed individuals and deficits in reward responding are associated with deficits in positive affect or the ability to experience pleasure [16, 18]. At the neural level, depression is associated with reduced activation in fronto-striatal circuits, namely the VS and caudate, during reward processing compared with healthy controls [17]. Anhedonia [19, 20] (or, the inability to experience pleasure) and reward-related processing [21] have been considered critical factors in the development of depression. Reward sensitivity in anxiety disorders has been less well studied. Similar to depression, evidence of reduced striatal activation during reward processing has been found in individuals diagnosed with

posttraumatic stress disorder (PTSD) compared with healthy controls [22, 23], particularly in relation to anhedonic features of PTSD (e.g., emotional numbing). Other studies, however, find evidence of heightened striatal activation during reward anticipation in some anxiety disorders [24]. This heterogeneity underscores the potential value of moving towards a dimensional understanding of reward sensitivity and positive valence system functioning in anxiety, mood, substance and eating disorders.

Negative Valence System

Responses to *acute threat* (fear) and *potential harm* (anxiety) were considered by the RDoC workshop committee to be central constructs within the negative valence system. One approach to measuring response to threat is via fear conditioning, which involves excitatory learning of conditioned stimulus vs. unconditioned stimulus (CS-US) associations [25, 26]. Research on fear learning uniquely adapts to translational neuroscience contexts because we understand with great precision the relevant neural processes in many species, including humans. The brain regions that have most consistently been associated with fear conditioning are the amygdala [27-31] and insular cortex [32]. In healthy adults, increased activity in the amygdala and insula is typically observed in response to the CS during conditioning. Response to loss was cited by the RDoC committee as another critical component process of the negative valence system, and may be particularly related to depression. Reward paradigms that include loss or punishment trials (e.g., losing money for incorrect responses [33-35]) can be used to measure behavioral and neural responses to loss anticipation and outcome. Research in healthy adults suggests that the ventral and dorsal striatum (caudate) are associated with anticipation and receipt of loss or punishment using these paradigms [33, 34].

Baseline Diagnostic and Demographic Assessment Measures

Patient Health Questionnaire (PHQ-9): The Patient Health Questionnaire (PHQ) is a self-administered diagnostic instrument for common mental disorders. The PHQ-9 is the depression module, which scores each of the 9 DSM-IV criteria as “0” (not at all) to “3” (nearly every day). Scores of 1-4 are considered minimal depression, 5-9 mild depression, 10-14 moderate depression, 15-19 moderately severe depression and 20-27 severe depression [36].

Overall Anxiety Severity and Impairment Scale (OASIS): The OASIS is a brief questionnaire (5 Items) that can be used as a continuous measure of anxiety-related severity and impairment across anxiety disorders. Each item is rated on a 5-point scale and the ratings are summed to obtain a total score. A cut-score of 8 has been shown to correctly classified 87% of individuals as having an anxiety diagnosis or not [37]. The OASIS has demonstrated excellent 1-month test–retest reliability, and convergent and divergent validity [38].

Drug Abuse Screening Test (DAST-10): The DAST-10 [39] is a brief version of the 28-item DAST designed to identify drug-use related problems in the previous year. It has demonstrated good internal consistency and temporal stability in psychiatric samples; the DAST-10 discriminates between psychiatric outpatient with or without drug use disorders (with scores between 2-4; [40]). This measure consists of 10 yes/no questions. Responding yes to score > 2 of the questions is considered an indicator that the individual should seek further evaluation for problematic drug use behaviors.

Sick, Control, One, Fat, Food Questionnaire (SCOFF): The SCOFF eating disorder screen was developed by British researchers as a screening tool for eating problems in a primary care setting [41]. It consists of 5 yes/no questions that inquire about eating behaviors and beliefs or obsessions with eating. Responding yes to ≥ 2 of the five items is considered an indicator that the participant should seek further evaluation for eating concerns.

Life chart interview: This interview was adapted from published methodologies for obtaining life histories of important life events relevant to mental health [42]. The purpose of this interview will be to obtain qualitative information regarding the temporal sequence of important events throughout the participant's life, which will be used to inform the structured diagnostic interview (MINI) and provide a more thorough and holistic understanding of the factors that have contributed to the individual's mental health. The Life Chart will ask questions pertaining to what important events happened during specific intervals of the person's life, including: (1) birth (2) childhood to the start of elementary school, (3) elementary school, (4) middle school to leaving/finishing high school (5) after high school to age 25 (6) ages 25-35 (7) ages 35-45 (8) ages 45-55. For each interval, subjects will be asked questions about potentially important events in their life, such as whether they moved, had any births or deaths in their

family, sought mental health treatment, etc. From this comprehensive list, the 0-3 most significantly life events will be selected from each time interval and the participant will be asked to rate their mood level (on a scale of 1-5) for those events as well as on average for that time interval. Participants may be asked to be audio recorded during the life chart interview. The recordings will be strictly optional and refusal will not impact participants' inclusion in the study. The recorded interviews will be used to develop reliability ratings among clinicians at LIBR and development of an event timeline. A visual timeline displaying the most significant events identified throughout their lifetime and their mood ratings throughout this time will be constructed and provided to the participant upon request.

Mini International Neuropsychiatric Interview (MINI Version 6.0): This is a widely used structured interview that assesses diagnostic criteria related to psychotic disorders, mood disorders, substance use disorders, and anxiety disorders. This interview will be used to assess symptoms and diagnostic criteria related to Axis I disorders. The MINI has been validated with the Structured Clinical Interview for DSM Axis I Diagnoses (SCID) with an average Kappa statistic of 0.67 across all 22 diagnoses measured on the MINI, and an average inter-rater reliability of 0.97 across diagnoses [43].

Demographics and Psychosocial Form: This form will ask participants to indicate their age, date of birth, contact information, ethnicity, race, gender, marital status and family makeup, language use, average income, education level, occupational and/or student status, and health insurance.

Assessment of Medical and Medication History: This form was created specifically for the purposes of this study and will ask questions related to medical and mental health diagnoses the participants has received currently or in the lifetime. This will involve a review of systems (e.g., constitutional, cardiovascular, respiratory) to inquire about previous or current problems, questions concerning in inpatient stays/treatments, surgeries, medications, and psychotherapies. For each mental health treatment, they will be asked to rate their compliance with that treatment. At the follow-up session, this interview will be repeated, but only in reference to the year of the study.

Diagnostic Review and Verification of Clinical Information: After completing the Assessment and Medication History, Life Charting, and MINI structured interview, each participant's information will be presented to a board certified psychiatrist for review, verification, and potential revision. This includes a targeted review of medical and psychiatric history and current medications for the purpose of identifying and correcting any collection errors. Participants for whom the DSM diagnosis is questionable will be re-evaluated in person by a board certified psychiatrist for independent diagnostic verification.

Edinburgh Handedness Inventory (EHI): The EHI is a self-report laterality scale that estimates the degree of right or left hand dominance during everyday activities [44].

Customary Drinking and Drug Use Record (CDDR [45] with Michigan Negative Reinforcement Questionnaire (MNRQ [46]): The CDDR provides current (past 3 months) and lifetime measures of 4 alcohol and other drug-related domains, including level of involvement, withdrawal characteristics, psychological/behavioral dependence symptoms, and negative consequences. The measure has been found to have good internal consistency, test-retest reliability, and construct validity [45]. The MNRQ was originally developed to assess beliefs about positive and negative consequences of smoking specifically and was found to have good reliability and validity in relation to diagnostic measures of nicotine dependence [47]. This measure has subsequently been adapted for use related to other substances of dependence and will be administered along with the CDDR in the current study to obtain measures of alcohol and drug use as well as participant beliefs concerning the consequences of that drug use.

Tulsa Head Injury Screen (THIS): The THIS is a questionnaire that asks participants about their history of head injuries and loss of consciousness.

Family History Screen (FHS): The FHS is a questionnaire that asks about the psychiatric history of the participant's family members, including biological parents, siblings and children.

Columbia-Suicide Severity Rating Scale (C-SSRS): The C-SSRS is a tool used to determine the presence of suicidal ideation or behavior in a participant [48].

Wong-Baker FACES Pain Rating Scale: This questionnaire is used to assess the current degree of physical pain being experienced by the participant [49].

Self-Report Measures

State-Trait Anxiety Inventory (STAI): This is a widely-used psychometric instrument designed to assess an individual's anxiety proneness. This measure has both a "state" subscale meant to measure temporary anxiety symptoms and a "trait" subscale meant to measure more long-standing anxiety proneness. Each subscale consists of 20 items using 4-point scales ("not at all" to "almost always"). The STAI is a validated measure with good internal consistencies for both subscales and has high test-retest reliability for the trait subscale and low to moderate test-retest reliability for the state measure [50].

Anxiety Sensitive Index (ASI-3): This instrument includes 18 items designed to measure the fear of arousal-related sensations, specifically along the dimensions/subscales of Physical, Cognitive, and Social Concerns. Each item is answered on a scale of 0-4 ("very little" to "very much"). The ASI-3 has been found to have adequate performance on several measures of reliability and validity [51].

Quick Inventory of Depressive Symptomatology (QIDS-SR): The QIDS-SR is a self-report 16 item assessment of the severity of depressive symptoms [52].

Simplified Nutritional Appetite Questionnaire (SNAQ): The SNAQ is a reliable tool with appraisal questions that focus on appetite and evaluating weight loss. [53]

Ruminative Responses Scale (RRS): This instrument is used to measure dispositional tendencies to ruminate in response to negative affect. It consists of 22 questions concerning how they respond to sad mood, which are focused on the self, on one's symptoms, and on the possible causes and consequences of the mood state (i.e., "Think 'why do I have problems other people don't have'?"). Responses are rated on a 4-point scale (e.g., 1 =almost never respond in this way; 4=almost always respond in this way). The RRS has three factor-analytically derived

subscales, including depression, brooding, and reflection. The RRS has been found to have good test–retest reliability (.67) and satisfactory convergent and predictive validity [54, 55].

Traumatic Events Questionnaire (TEQ) – Civilian Version: The Traumatic Events Questionnaire (TEQ) [56], assesses 11 specific traumatic events: (1) combat, (2) large fires/explosions, (3) serious industrial/farm accidents, (4) sexual assault, rape (forced unwanted sexual activity), (5) natural disasters, (6) violent crime, (7) adult abusive relationships, (8) physical/sexual child abuse, (9) witnessing someone being mutilated, seriously injured, or violently killed, (10) other life threatening situations, and (11) violent or unexpected death of a loved one. Two nonspecific questions, "other event" and "can't tell," complete the scale. Individuals are asked to indicate the frequency, severity (on a 7-point scale), and age at the time of the event. The scale has been found to have very high reliability (.91) and has been found to relate to PTSD, anxiety, and depressive symptoms [56].

Childhood Trauma Questionnaire, Short Form (CTQ-SF): This instrument is used to screen adolescents and adults for a history of child abuse and neglect. The CTQ has five subscales: (1) Physical abuse, (2) Sexual abuse, (3) Emotional abuse, (4) Physical neglect, and (5) Emotional neglect. The CTQ will be used to identify traumatic childhood conditions characteristic of the negative valence domain. The CTQ consists of 28 items which are rated on a 5 point scale (1=never true; 5=very often true). The full CTQ has been found to have good reliability and validity and the CTQ –SF was found to have good validity in reference to the full version [57].

Positive and Negative Affective Schedule- State/Trait (PANAS) [58]: The PANAS is a widely used measure comprising 20-items assessing activated forms of PA and NA using 5-point scales (1 = very slightly/not at all, 5 = extremely). To assess trait PA and NA, participants will be asked to respond according to how they have felt "during the past week". State PA and NA will be asked by asking participants to rate how they feel “right now (that is, at the present moment)”. The PANAS has high internal consistency and temporal stability (trait version). Correlational data support its convergent and discriminant validity. Confirmatory factor analyses support the construct validity of the PANAS.

Behavioral Inhibition and Activation Scales (BIS/BAS): The behavioral inhibition and activation scales (BIS/BAS) include 20-items assessing dispositional BIS and BAS sensitivities (i.e. avoidance and approach motives), which are hypothesized to reflect the negative and positive valence systems, respectively. Items are rated on four-point scales (1 = strongly disagree; 4 = strongly agree). The BAS has three subscales (Drive, Reward Responsiveness, and Fun Seeking); however, factor analyses support a single higher-order factor. The BIS/BAS has good test-retest reliability. Correlational data support the relative orthogonality and convergent, discriminant, and predictive validity of the subscales [59].

Temporal Experience of Pleasure Scale (TEPS): The TEPS is a recently developed measure of anticipatory pleasure and consummatory pleasure. It has 18 items, each of which are rated on a 6 point scale (e.g., 1=very false for me; 6=very true for me). Initial investigations with this measure indicate good validity and independence of the two subscales (anticipatory and consummatory; [60]).

UPPS Impulsive Behavior Scale (UPPS): The UPPS [61] was designed to measure impulsivity across dimensions of the Five Factor Model of personality. The scale has 45 items that use a 4-point scale, e.g., 1=; 4=) and has 4 subscales, including Premeditation (lack of), Urgency, Sensation Seeking, and Perseverance (lack of). The subscales have been shown to have good internal consistencies (.82-.91; [61]) and the measures has been shown to distinguish between subgroups of psychopathology compared to control groups [62].

Snaith-Hamilton Pleasure Scale (SHAPS): This instrument is used to measure hedonic capacity. It consists of 14 items, rated on a 4-point scale (1=Definitely Agree; 4=Strongly Disagree). This instrument has been found to have excellent internal consistency and adequate convergent and discriminant validity [63].

Interpersonal Reactivity Index (IRI): The IRI was developed to measure empathy, defined as the "reactions of one individual to the observed experiences of another". This is a 28-item measure, each rated on a 5-point Likert scale (1="Does not describe me well"; 5="Describes me very well"). The measure has 4 subscales, each made up of 7 different items. These subscales include Perspective Taking, Fantasy, Empathic Concern, and Personal Distress. Good internal

consistency. The scale has also been shown to have good construct validity with related measures [64, 65].

Big Five Inventory (BFI): The BFI measures an individual on the Big Five Factors (dimensions) of personality [152], which include (1) extraversion versus introversion, (2) agreeableness versus antagonism, (3) Conscientiousness vs. lack of direction, (4) neuroticism vs. emotional stability, (5) openness vs. closedness to experience. This measure has 44-items, each of which are rated on a 5-point scale (1=disagree strongly, 5= agree strongly). This measure has been shown to have high internal consistency, test-retest reliability, and good convergent and divergent validity with other Big Five measures [66].

Toronto Alexithymia Scale (TAS-20): The TAS is one of the most commonly used measures of alexithymia, or the difficulty identifying and describing emotions. This is a 20-item measure, with each rated on a 5-point scale (1=strongly disagree, 5=strongly agree). There are three subscales, including (1) Difficulty Describing Feelings, (2) Difficulty Identifying Feeling, and (3) Externally-Oriented Thinking. The TAS-20 has been shown to have good internal consistency (.81), test-retest reliability (.77), and adequate convergent and concurrent validity [67, 68].

Multidimensional Assessment of Interoceptive Awareness (MAIA): This measure was recently developed to measure trait interoceptive body awareness. It consists of 32 items, each rated on a 6-point scale (0=never, 6=always). There are 8 subscales, including: (1) Noticing, (2) Not-distracting, (3) Not-worrying, (4) Attention Regulation, (5) Emotional Awareness, (6) Self-regulation, (7) Body listening and (8) Trusting. The measure was found to have good measures of internal consistency on each subscale and showed adequate construct validity with other, related measures of emotional processing anxiety, and body awareness [69].

Three Factor Eating Questionnaire (TFEQ): The TFEQ was developed to measure three dimensions of human eating behavior: cognitive restraint of eating, disinhibition, and hunger. This is a 51-item measure, including 36 items with yes/no responses, 14 items on a 4-point scale (1=unlikely; 4=very likely), and one item of restraint on a 6-point scale (0="eat whatever you want, whenever you want"; 5="constantly limit food intake, never give in"). A subscale score is calculated for each of the three dimensions of human eating behavior. Cognitive Restraint is

designed to measure control over food intake. Disinhibition measures loss of control over eating. The Hunger scale concerns subjective feelings of hunger and food cravings. The TFEQ has been found to have high test-retest reliability and internal consistency, and adequate construct validity [70-72].

Eating Disorders Diagnostic Scale (EDDS): The EDDS [73] measures the presence of anorexia nervosa, bulimia nervosa and binge eating disorder. It was developed as a self-report measures based on the Eating Disorder Examination (EDE) and the eating disorder module of the Structured Clinical Interview for DSM-IV. The EDDS provides both full and subthreshold diagnoses as well as a continuous symptom composite score. It consists of 22 items, 4 of which are on a 6-point scale (1=not at all; 6=extremely), 9 of which are yes/no questions, 6 items that ask for frequency of events (e.g., episodes of uncontrolled eating) over the week or month; and 3 remaining questions asking for height, weight, and number of missed periods over the past 3 months. The EDDS was shown to have good test-retest reliability, internal consistency, and convergent validity with other eating-pathology scales [73]. Research has shown it to be sensitive as a screening measure in detecting change with eating disorder treatment and is predictive of the development of eating disorder symptoms and depression [74].

International Physical Activity Questionnaires (IPAQ): The IPAQ is used to obtain internationally comparable data on health-related physical activity. Extensive reliability and validity testing has been undertaken in 12 countries (14 sites) across 6 continents since 2000. The short, self-administered format, for use with young and middle-aged adults, will be utilized – which has been shown to have adequate validity and reliability [75].

World Health Organization Disability Assessment Schedule (WHODAS): The WHODAS (12-item version) is a generic assessment instrument for health and disability, and covers 6 domains: (1) Cognition (understanding & communicating), (2) Mobility (moving & getting around), (3) Self-care (hygiene, dressing, eating & staying alone), (4) Getting along (interacting with other people), (5) Life activities (domestic responsibilities, leisure, work & school), and (6) Participation (joining in community activities). The WHODAS produces standardized disability levels and profiles, is applicable across cultures in adult populations, and has a direct conceptual link to the International Classification of Functioning, Disability and Health (ICF) [76].

World Health Organization Health and Work Performance Questionnaire (HPQ): The WHO HPQ is a 9-item questionnaire to evaluate absenteeism and presenteeism in the workplace as indirect costs of illness. The instrument includes questions regarding days (full or in part) of work missed due to personal physical or mental health, days of work missed for other reasons, arriving early or late to work or working on a day off, hours worked in the past 4 weeks and self-evaluations of job performance recently, over the past year, and in comparison to other employees [77] [78].

PROMIS® (Patient Reported Outcome Measurement Information System) Measures (http://www.nihpromis.org; [79, 80]): PROMIS is a U.S.-based cooperative group of research sites and centers of excellence, funded by NIH, and convened to develop and standardize patient outcome measures across studies and settings. The PROMIS measures were developed using item response theory and calibrated on a sample of 21,133 people, with the aim of providing highly reliable, precise measures of patient–reported health status for physical, mental, and social well–being. Most question banks utilize a 7-day recall period and five response options (e.g., 1=Not at all, 5=very much). All instruments developed to be used with computer adaptive testing (CAT) to reduce patient burden. With CAT, the specific construct item that best distinguished between individuals in their test populations is administered first. Based on the individual's response to this item, the computer picks what question will be administered next, and so on, until a reliable estimate of their total score on that construct can be determined. With this method, an average of 5 items is administered for each PROMIS construct listed, thus taking an estimate 1 minute or less to complete. The instruments have been reported to have good reliability and validity [79, 80].

Behavioral Tasks

Bandit Task*:* This task is included to apply Bayesian computational approaches that quantify how individuals switch between an "exploration" and "exploitation" strategy. Subjects have to sample from different choice options with unknown probabilities of success/failure with the goal of maximizing success. The optimal strategy is to start by trying all available options (exploration) to gauge the rate of success of each option, and to switch relatively early to only selecting the option with the highest likelihood of success (exploitation). Participants will

perform a total of 20 three-armed bandit games with a known number of trials (i.e., token) per game. For each game, participants will have 16 tokens (stacked in the middle of the screen) and will have to assign each token to one of three lotteries of their choice (white panels on left, right and middle of the screen). After placing each token, they will earn 1 point if the token turns green or zero points if the token turns red. Each token decision will last about 2 sec. After the button press, the chosen lottery is highlighted for 250ms, after which the token turns green or red to reveal the decision outcome. Participants will be instructed to find the most rewarding lottery and maximize the points earned in each game. Participants are paid an additional $5 or $10 based on the performance on this task.

Change Point Detection Task: For each trial, subjects will attempt to locate a target stimulus in one of three possible locations. The target stimulus consists of a patch of dots, which are predominantly moving in one direction. The other two locations have distractors with dots moving in the opposite direction. However, at the beginning of the trial, the patches of dots are hidden by white circles, which initially appear in the three locations. The subject first selects a location in which to see a patch of dots; a button press indicates the location of choice. The subject is then shown the patch of dots at the selected location, and asked to determine whether it is the target or the distractor. If the subject indicates that the patch is the target, the trial ends. If the subject believes the patch is a distractor, the subject can then indicate a second location to view, and be shown the patch of dots corresponding to the new location. The trial continues in this manner until the subject chooses the patch of dots which is believed to represent the target location. The position of the target location on each trial is determined by a probability distribution, such that one location is most likely to contain the target. It is therefore possible for the subject to learn over several trials which location is most likely to contain the target. However, at random intervals, the probability distribution will change, and a new location will become most likely to contain the target. The subject will then have to update their beliefs about the most likely location in which to locate the target. The experiment consists of 3 blocks with 60 trials per block. Prior to the experimental blocks, the subject will complete practice blocks until accuracy exceeds a certain threshold. Additionally, there is one block of 20 trials where all locations have equal probability that is used as a

baseline measure for response time. Response time and learning rate over time with each target location are the main variables of interest. Participants are paid an additional $5 or $10 based on the performance on this task.

Move-Go and Speed-Stop Task: Driving, as a common real-time motor task, is determined by both motivational factors (safety, time, etc.), and perceptual-motor limits (perceptual delay, motor delay, etc.). It has been shown that people with emotional disorders have impaired driving performance. For example, there have been growing evidence show that depression increases the odds ratio for car accidents and reduces driving performance in a driving simulator. It also has been shown that mood (influenced by music) can impact driving behavior in healthy population. Thus we propose to use a simulated driving task to collect behavioral data. The driving task has two separate components. The Move-Go component is used to measure perceptual and motor speed. In it, subjects are asked to attend to a car presented at the bottom of the screen. As soon as they perceive that the car has started to move, subjects are to move the joy stick all the way forward as quickly as possible. In the Speed-Stop component, subjects are instructed to drive a virtual car on a computer screen from an initial position to a stop sign as quickly as possible and stop as close to the stop-sign as possible without crossing the stop-sign, by pushing or pulling a joystick to control the velocity of the car. Each trial has a fixed time-window of 10 seconds. The car has a linear dynamic system, in which velocity is controlled by joystick position ($dXt = AXtdt + BUtdt$, in which Xt = [car position, car velocity], Ut = control action (car velocity based on joystick position), A = [0 1; 0 -.35], B = [0; 0.5]). This task will be used to estimate each individual's motivational component (goal state, accuracy/effort ratio) using computational models.

Implicit Approach Avoidance Task (AAT): Purpose: This task is designed to assess automatic action tendencies to approach or avoid positive, negative, and neutral stimuli [81]. Description: In this task, participants are asked to respond to a series of cues conveying positive, negative, or neutral emotional information (e.g., happy, angry, disgusted, neutral faces) by either pulling (approach) or pushing (avoidance) a joystick towards or away from themselves. Participants will see a picture in the center of the screen framed by either a blue or a yellow border. They will be instructed to pull the joystick towards themselves when the border is one color and to

push the joystick away when the border is the other (counterbalanced across subjects). Pushing the joystick results in the picture zooming out and pulling the joystick results in the picture zooming in, thereby creating the visual impression that the pictures are coming closer or moving away. Reaction times are calculated based on the duration from the time the picture appeared on the screen to the time it disappeared. An approach bias score is computed by subtracting each participant's mean response latency in the pull condition for a given stimulus type from their mean response latency in the corresponding push condition (e.g., positive faces-push minus positive faces-pull). The AAT is a well-established measure of implicit approach/avoidance behavioral tendencies [82].

Approach-avoidance conflict task (AAC): This computer-based task is designed to examine decision-making in the context of affective risk. For this task, the participant is presented with a series of decisions between two different outcomes. Each outcome is associated with either a positive or negative valenced image/sound pair (IAPS and IADS), and some amount of point or gains. The participant is not able to select with certainty one outcome over the other. Instead, only the probability of the two outcomes is chosen, in the range from 10-90%, depending on the subject's stated preference for the two outcomes on a 9 point scale. The standardized IAPS and IADS stimulus sets have been used extensively in emotion research and are reliable elicitors of affective arousal [83, 84]. Conflict trials are those in which a negative affective image is combined with point rewards, while the positive affective image is combined with no point rewards. There are three levels of conflict (2-point, 4-point, and 6-point). The main outcome variables of the task are: (1) mean approach behavioral for the different condition types (conflict, approach-only, and avoid-only). Before and after the task, participants rate their mood in terms of pleasantness, unpleasantness, and overall intensity on a visual analogue scale (VAS). After the task, participants complete a 14-item questionnaire asking questions about their experience of the task (i.e., "Overall, this task was enjoyable"), rating each item on a 1-7 Likert scale. This measure was originally developed by Dr. Robin Aupperle [85]. This task takes approximately 20 minutes to administer.

Modified Probe Detection Task (MPDT): Attentional bias for positive and negative information will be measured using a version of the modified probe detection task [86]). Each trial consists

of the identification of a cue location, brief presentation of a cue at that location (a small line oriented either horizontally or vertically), presentation of a pair of images (one representational, one non-representational), and presentation of a target, which is another line in either of two locations and is either horizontal or vertical. This target is presented until the participant responds, indicating whether the target is of the same or different orientation from the cue. Representational [86] stimuli will comprise IAPS images taken from positive, negative, or neutral valence sets. Each representational image is paired with one non-representational image, taken from a set of images of abstract art. Participants are presented with a total of 192 trials: 64 from each of positive, negative, and neutral images. The following traits are balanced across trials: representational image location, cue location, cue orientation, target location, target orientation, image duration (500 or 1000ms). The main outcome measures are the positive and negative engagement and disengagement biases [87].

Emotional Reactivity: This task consists of the presentation of 8 positive, 10 neutral, and 8 negative images. Each trial begins with a 20-26s fixation period, followed by presentation of one image for 6s. After each image, the participant makes valence and arousal ratings on a 7 point scale. During image presentation and sometimes during fixation, participants receive a ~95DB 50ms white noise sound meant to elicit a startle response [88]. The main purpose of this paradigm is to provide a reliable and validated assessment of psychophysiological responses to emotional stimuli and startle-eliciting stimuli [89]. The collection of psychophysiological recordings will therefore be integral to this task specifically.

Heartbeat Counting: This task will contain four 1 minute trials, during which the participant has their eyes closed and is tapping a vmeter device [90].

Cold Pressor Challenge: This task will have each participant immerse their left hand in a circulating pool of water cooled to 6 degrees Celsius. Participants will be asked to keep their hand in the water for as long as they can tolerate, providing a brief measure of pain/stress tolerance and emotional reactivity/regulation. During each immersion participants will provide real-time ratings of their degree of pain unpleasantness/discomfort using the vmeter. The Cold

Pressor paradigm is the gold standard which has been repeatedly used over the past century to safely induce transient states of intense pain [91, 92]. Maximum trial length will be 2 minutes.

Breath Hold Challenge: This task will have participants undergo 2 expiratory breath holds, providing a brief measure of interoceptive distress tolerance and carbon dioxide sensitivity. The maximum trial length is 1 minute, and there will be a 2-minute rest between trials. Participants are instructed to hold their breath for as long as they can tolerate following a normal (not forced) exhalation. The duration of each breath hold will be calculated starting from the moment when they begin exhaling and ending the moment they start inhaling again.

Psychophysiological Recordings: Heart rate (ECG), respiration (RSP), skin conductance (SCR), and eye blink electromyogram (EMG) will be recorded continuously during each the behavioral tasks described above, using BIOPAC instrumentation (Lehigh, Pennsylvania). These physiological indices will also be measured during a 5-minute passive viewing task where subjects are presented with a slideshow of images of different flowers. The images are not expected to affect the physiological recordings, so data from this task are used as a physiological baseline to compare to the behavioral tasks. Measuring these indices during the behavioral tasks listed above will not add any time to the tasks themselves, but should take approximately 10-15 minutes for setup (i.e., to attach all electrodes, respiration belt, etc.).

BIOPAC Systems provides both hardware for collection of these measures (BioPac MP150 system) and software (AcqKnowledge software) for analyzing these measures. All of these measures are commonly used in emotional processing research and are relatively non-invasive. The use of all of these measures concurrently allows for a more thorough understanding of sympathetic and parasympathetic nervous system influences on physiological responses to negatively and positively-valenced stimuli, interoceptive stimuli, cognitive processing and decision-making.

Facial Expressions: Advances in computer vision and machine learning over the past 15 years have led to the emergence of technology for automatic analysis of affective behavior [93]. During this time, the Machine Perception Laboratory at UCSD (MPLab) has focused on development of systems for automatic analysis of facial behavior, including audio-visual speech

recognition [94-96] and recognition of facial expressions [95-99]. The output of the face detector is scaled to 90x90 and fed directly to the facial expression analysis system. First the face image is passed through a bank of Gabor filters at 8 orientations and 9 scales (2-32 pixels/cycle at 0.5 octave steps). The filterbank representations are then channeled to a classifier to code the image in terms of a set of expression dimensions. Research at the MPLab has demonstrated that performing feature selection on the Gabor filters prior to classification enhances both speed and accuracy. This approach combines feature selection based on Adaboost with feature integration using support vector machine. *Automatic Facial Expression Analysis*: A video camera will record each participant during the behavioral tasks described above in order to permit coding of facial expressions. Automatic facial expression analysis will be conducted by the EMOTIENT [100], software developed and validated by our collaborators at the Machine Perception Laboratory at UCSD (MPLab). EMOTIENT analysis corresponds to the well-validated Facial Action Coding System (FACS [101, 102]), a comprehensive method to objectively code facial expressions. EMOTIENT automatically codes the intensity of 26 component facial movements referred to as action units (Aus).

Neuropsychological Tasks

Wide Range Achievement Test (WRAT-4 reading): The WRAT-4 is an individually administered test of reading designed to measure general academic competence. The main variable of interest will be the total words pronounces correctly [103].

Delis-Kaplan Executive Function System (D-KEFS) Color-Word Inhibition Test: The D-KEFS Color-Word Inhibition Test is designed to assess verbal response inhibition and attentional switching. Participants are asked to name patches of colored ink (Color Naming subtest), read color-related words (Word Reading subtest), or to name the ink that color-related words are written in (Inhibition subtest). The speed at which participants complete the task and the number of mistakes made during completion are recorded. The main variables of interest for this study are the total time to complete the word reading, color naming, inhibition, and inhibition/switching subtests [104].

Delis-Kaplan Executive Function System (DKEFS) Verbal Fluency: This test is meant to measure information retrieval that is under conscious cognitive control and presumably an aspect of executive functions. On each of six one-minute trials, the examinee is asked to say as many distinct words as possible that meet a certain criterion. For the first three trials, the words must begin with a particular letter, for the next two trials, the words must belong to a particular semantic category, and for the last trial, words must alternate between two semantic categories. The main variable of interest is the total number of words correctly identified for the letter subtests and the semantic category subtests [104].

Wechsler Adult Intelligence Scale (WAIS-IV) Digit Span: This sub-test of the WAIS-IV is used to assess attention and working memory and requires participants to repeat a series of numbers in forwards and backwards order (Digit Span). The accuracy of their responses is recorded. The main variables of interest are the total score forward and backward [105].

Finger Tapping Test (FTT): The FTT is a neuropsychological test that examines motor functioning, specifically, motor speed and has also been shown as a sensitive measure of testing effort [106]. The main variables of interest are the average number of taps with the index finger per 10 seconds for dominant and non-dominant hands.

WAIS-IV Digit Symbol Coding [105] The Digit Symbol is a neuropsychological test of visuomotor speed and working memory. The test requires individuals to match a symbol to a number according to a key at the top of the page. The main variable of interest will be the number of symbols matched in the time limit (90 seconds).

California Verbal Learning Test (CVLT-II): The CVLT-II is used to evaluate verbal learning and memory. The CVLT consists of a list of 16 words from four semantic categories that is presented orally for five immediate recall trials (List A). Subsequent to the five learning trials of List A, a second 16-item word list (List B) is presented once. Free- and category-cued-recall trials of List A follow the immediate free-recall of List B. After a 20-min delay, free recall, cued recall, and a recognition trial of List A occur. The recognition trial contains the 16 target items from the first list along with 28 distractor items. During the recognition trial, the examiner presents each of the 44 items orally to the participant, who indicates whether or not the item was from the first

word list. The main variables of interests for this study are the immediate recall from Trials 1-5 List A, Immediate and Delayed free recall and cued recall of List A. In addition, as most patients (even those with neurological disorders) are expected to score above chance on Recognition, this test will also be used to assess whether participants are putting in sufficient effort towards testing.

Functional MRI Tasks

Reward Processing Task: To measure behavioral and neural responses to rewards and losses, participants will complete the monetary incentive delay task (MID), a well-established measure of reward processing [107, 108]. This task dissociates anticipatory and consummatory phases of reward processing and has been shown to reliably activate brain regions implicated in regulating approach-related response tendencies and reward sensitivity (e.g., ventral striatum). On each trial, participants are given a cue indicating potential reward (circle), loss (square), or no reward/loss (circle or square). In order to receive a specified reward or avoid a loss, participants are required to press a button within a certain duration of time (adapted for individual participant reaction times) following presentation of a white square (target cue). Task difficulty, based on reaction times collected during a practice session, is set such that each participant should succeed on ~66% of trials. The degree of potential reward or loss is varied on three levels indicated by the number of horizontal lines in a cue, i.e., one line indicates the lowest reward value (no reward), two lines an intermediate reward, and three lines the highest reward. For the MID task, participants can gain or lose points and earn an average of $30. The primary outcomes of interest will be: (1) anticipation of reward vs. no-reward, (2) receipt of reward outcomes vs. no-reward outcomes; (3) anticipation of loss vs. no-loss, and (4) receipt of loss outcomes vs. no-loss outcomes. The Monetary Incentive Delay Task will take about 18 minutes to complete.

Fear Conditioning Task: The fear conditioning task is based closely on the task successfully used by [109] to uncover neural bases of fear conditioning associated with trait anxiety [109]. The stimuli will consist of two neutral, non-social, abstract images as conditioned stimuli (CS), presented for 2 seconds at a time. Which image is the CS+ (paired with the unconditioned

stimulus (US) during fear acquisition) and which is the CS- (never paired with the US) will be counter-balanced across participants. The US will be a 1s scream beginning 500ms after image onset. In the 9-15 seconds between CS image presentations, participants will be engaged in a continuous performance task requiring a right or left button press in response to right or left facing arrows. This serves to increase engagement and attention in the inter-trial interval. The task will consist of three components: a brief familiarization period, fear acquisition, and fear extinction. First, the *familiarization phase* (2.5 minutes) involves five presentations of each CS with no instances of the US to provide a baseline and allow familiarization to the scanner environment. Next, the *acquisition phase* will be broken into two runs of 8 minutes each. Each run will consist of 15 presentations of the CS- and 20 presentations of the CS+: five with (CS+ paired) and 15 without (CS+ unpaired) the US. This follows Sehlmeyer et al. [110] and allows for an equal number of trials to be included in the analysis (the CS+ paired trials will be excluded from analysis so as to not confound processing of the CS+ with reactivity to the US). Finally, the *extinction phase* will involve 25 presentations of each CS with no instances of the US. Participants will rate their valence, arousal and anxiety level to each CS at four times during the task: after familiarization, halfway through acquisition, after acquisition, and after extinction. Trials will be presented in a fixed, pseudo-randomized order, constrained so that no more than two identical trials occur in a row.

Stop Signal (Inhibition) Task: At the onset of each trial, either an 'X' or an 'O' appears on a black background back-projected to the magnetic resonance imaging room. Participants are instructed to press, as quickly as possible, the left button when an 'X' appeared, and the right button when an 'O' appeared. They are also instructed not to press either button whenever they hear a tone during a trial (stop trials). Each trial lasts 1300 ms and each trial is separated by 200-ms inter-stimulus intervals (blank screen; see [111]). Individual response latency is used to denote the period of inhibitory processing and provide a subject-dependent jittered reference function. Participants perform six blocks of the task, each containing a total of 48 trials (12 stop and 36 nonstop trials in each block). Trial order is pseudo-randomized throughout the task and counterbalanced. Prior to scanning, participants perform the stop task in a behavioral testing session in order to determine their mean reaction time (RT) from 'X' and

'O' stimuli onset. Such individual measures are used to determine the stop signal delay (SSD) for the six different stop trial types. Specifically, stop signals are delivered at 0 (RT-0), 100 (RT-100), 200 (RT-200), 300 (RT-300), 400 (RT-400), or 500 (RT-500) ms less than the mean RT after the beginning of the trial, thus providing a range of difficulty level.

Interoceptive Attention Task: During this task, subjects alternate between two conditions: the interoception condition and the exteroception condition. During the interoception condition, the word "HEART" or "STOMACH" is presented on the screen and subjects are instructed to focus their attention on interoceptive sensations from that organ. For example, upon seeing the word "HEART", subjects focus on how intensely they can feel the sensation of their heart beating. During the exteroception control condition, the word "TARGET" is presented in the middle of the screen and the color of the word alternates from black to a lighter shade of gray every second. The subjects are instructed to focus their attention on the intensity of these color changes. Each task condition is presented in 10-second blocks, and half of the blocks are followed immediately by a 5-second response period during which the subject uses a visual scale (1-to-7) to rate the intensity of interoceptive sensations or exteroceptive color changes experienced during the preceding trial. Blocks are often separated by a variable inter-stimulus interval, during which subjects look at a fixation mark. Each run of the task begins with a 10-sec initial fixation period and ends with a 10-sec final fixation period. Subjects will perform 2 scanning runs, each lasting 360 seconds (including initial and final fixation periods).

MRI, EEG and fMRI Data Analysis

EEG-fMRI

Residual ballistocardiac artifacts in the EEG signals will be removed using the independent component analysis method. The de-noised data will be subsequently band-pass filtered from 1 Hz to 70 Hz, downsampled to 250 Hz, and re-referenced to the common average reference. For the EEG signals recorded outside the scanner, data will be similarly band-pass filtered from 1 Hz to 70 Hz, downsampled to 250 Hz, and re-referenced to the common average reference.

Other types of EEG-informed fMRI analyses include: EEG band-pass correlation analysis with fMRI data (Fast Fourier transformation will be used to estimate EEG δ (1–3 Hz), θ (4–7 Hz), α (8-13 Hz), and β (13–30 Hz) frequency band spectral power, and its temporal changes during fMRI) [112], EEG microstate analysis in time and spatial domain (EEG temporal independent microstates and their spatial representation correlates with slow hemodynamic activity in brain resting state networks and their spatial maps) [113, 114], EEG-asymmetry analysis, and EEG-coherence analysis (e.g. quantify and correlate changes in EEG alpha band asymmetry and/or EEG coherence with fMRI data [115]), and behavioral measures [116].

fMRI Pre-Processing

For task fMRI analysis, a multivariate regressor approach will be used to relate changes in echo planar imaging (EPI) intensity to differences in task characteristics. The aE-REMCOR motion will be corrected on a slice by slice basis. fMRI data will be co-registered using a 3D-coregistration algorithm. Motion parameters will be obtained across the time series for each subject. Subjects will be excluded if the average in any one of these six parameters exceeds 2 standard deviations from the mean or if mean displacement exceeds the size of the voxel (4 mm). This assures that differences at group-level are not due to differences in movements during scanning. Motion parameters will be used as regressors to adjust EPI intensity changes due to motion artifacts. This has been shown to increase power in detecting task-related activation. All slices of the EPI scans will be temporally aligned following registration to ensure different relationships with the regressors are not due to the acquisition of different slices at different times during the repetition interval.

Resting State Pre-Processing

The six motion parameters from the image registration process will be used to construct a time series reflecting the Euclidean normalized derivatives of the motion, and any time point, plus one prior, where the derivative is greater than 0.2 or where more than 10% of brain voxels are considered as outliers will be censored. Nuisance variables will be regressed out of the normalized data and include the de-meaned motion parameters and their derivatives, the

average signal taken from a local eroded local white matter mask, the first 3 principal components of the lateral ventricles, and terms reflecting baseline drift.

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Supplementary Table 1. Quarterly Follow-up Assessments

QUARTERLY FOLLOW-UP ASSESSMENTS	
Domain	Description
STANDARD SCALES	
Demographics	Demographics and Psychosocial Form (update)
History	Assessment of Medical and Medication History (update)
History	Life chart interview (update)
Substance Use	Customary Drinking and Drug Use Record (CDDR)
Depression	Quick Inventory of Depressive Symptomatology (QIDS-SR)
Eating Behavior	Simplified Nutritional Appetite Questionnaire (SNAQ)
Compliance	Medication Compliance
Compliance	Therapy Compliance
Disability	World Health Organization Disability Assessment Schedule
Presenteeism/Absenteeism	(WHODAS)
Suicidal Ideation	WHO Health and Work Performance Questionnaire (WHO HPQ)
Pain	Columbia-Suicide Severity Rating Scale (C-SSRS)
	Wong-Baker FACES Pain Rating Scale
PROMIS MEASURES	
Negative Valence	PROMIS Anxiety
Negative Valence	PROMIS Depression
Negative Valence	PROMIS Anger
Positive Valence	PROMIS/Neuro-QOL Positive Affect and Well-being
Cognitive	PROMIS Cognitive Abilities
Cognitive	PROMIS Cognitive General
Fatigue	PROMIS Fatigue
Sleep	PROMIS Sleep Disturbance
Sleep	PROMIS Sleep-related Impairment
Alcohol	PROMIS Alcohol Use
Alcohol	PROMIS Alcohol: Negative Consequences
Alcohol	PROMIS Alcohol: Positive Consequences
Alcohol	PROMIS Alcohol: Negative Expectancies
Alcohol	PROMIS Alcohol: Positive Expectancies
Nicotine	Nicotine Dependence
Nicotine	Coping Expectancies
Nicotine	Emotional and Sensory Expectancies
Nicotine	Health Expectancies
Nicotine	Psychosocial Expectancies
Nicotine	Social Motivations
Social	PROMIS Social Satisfaction DSA
Social	PROMIS Social Satisfaction Role
Social	PROMIS Ability to Participate Social

Social	PROMIS Emotional Support
Social	PROMIS Information Support
Social	PROMIS Instrumental Support
Social	PROMIS Satisfaction Roles Activities
Social	PROMIS Social Isolation
Physical	PROMIS Physical Function
Pain	PROMIS Pain Interference
Pain	PROMIS PAIN Behavior
Sex	PROMIS Global Satisfaction with Sex Life
Sex	PROMIS Interest in Sex Activity

Supplementary Table 2. One-Year Follow-up Session

ONE-YEAR FOLLOW-UP SESSION	
Domain	Description
DIAGNOSTIC AND DEMOGRAPHIC ASSESSMENT	
Diagnosis	MINI 6.0
Demographics	Demographics and Psychosocial Form (update)
History	Assessment of Medical and Medication History (update)
History	Life chart interview (update)
Substance Use	Customary Drinking and Drug Use Record (CDDR)
Compliance	Medication Compliance
Compliance	Therapy Compliance
Suicidal Ideation	Columbia-Suicide Severity Rating Scale (C-SSRS)
Pain	Wong-Baker FACES Pain Rating Scale
STANDARD SELF-REPORT SCALES	
Negative Valence/Interoception	Anxiety Sensitive Index (ASI-3)
Negative Valence	Ruminative Responses Scale (RRS)
Positive / Negative Valence	Positive and Negative Affect Schedule-Expanded Form (PANAS)
Depression	Quick Inventory of Depressive Symptomatology (QIDS-SR)
Positive Valence	TEPS anticipation/consumption/ pleasure
Arousal / Interoception	Multidimensional Assessment of Interoceptive Awareness
Eating Behaviors	Eating Disorders Diagnostic Scale
Eating Behaviors	Simplified Nutritional Appetite Questionnaire (SNAQ)
Physical Activity	International Physical Activity Questionnaire (IPAQ)
Disability	World Health Organization Disability Assessment Schedule (WHODAS)
Trauma	Traumatic Events Questionnaire (TEQ)
Absenteeism/Presenteeism	WHO Health and Work Performance Questionnaire
PROMIS MEASURES	
Negative Valence	PROMIS Anxiety
Negative Valence	PROMIS Depression
Negative Valence	PROMIS Anger
Positive Valence	PROMIS/Neuro-QOL Positive Affect and Well-being
Cognitive	PROMIS Cog Abilities
Cognitive	PROMIS Cog General
Fatigue	PROMIS Fatigue
Sleep	PROMIS Sleep Disturbance
Sleep	PROMIS Sleep-related Impairment
Alcohol	PROMIS Alcohol Use
Alcohol	PROMIS Alcohol: Negative Consequences
Alcohol	PROMIS Alcohol: Positive Consequences

Alcohol	PROMIS Alcohol: Negative Expectancies
Alcohol	PROMIS Alcohol: Positive Expectancies
Nicotine	Nicotine Dependence
Nicotine	Coping Expectancies
Nicotine	Emotional and Sensory Expectancies
Nicotine	Health Expectancies
Nicotine	Psychosocial Expectancies
Nicotine	Social Motivations
Social	PROMIS Social Satisfaction DSA
Social	PROMIS Social Satisfaction Role
Social	PROMIS Ability to Participate Social
Social	PROMIS Emotional Support
Social	PROMIS Information Support
Social	PROMIS Instrumental Support
Social	PROMIS Satisfaction Roles Activities
Social	PROMIS Social Isolation
Physical	PROMIS Physical Function
Pain	PROMIS Pain Interference
Pain	PROMIS PAIN Behavior
Sex	PROMIS Global Satisfaction with Sex Life
Sex	PROMIS Interest in Sex Activity
	Physio Setup
Computational - cognitive	Change Point Detection Task
	Regular Bandit Task
	Start / Stop Task (Driving)
Positive / Negative Valence	Implicit Approach / Avoidance Task
	Attentional Bias / Dot Probe Task
	Emotional Reactivity Task
	Baseline Task
	Approach Avoidance Conflict Task
Arousal / Interoception	Breath hold
	Heartbeat Counting Task
	Cold Pressor
Neuropsychology	WRAT reading
	DKEFS Color-Word Inhibition
	DKEFS verbal fluency
	WAIS-IV digit span
	Finger Tapping Test
	WAIS-IV Digit Symbol Coding
	California Verbal Learning Test
Biomarker and Microbiome	Repeat baseline measures, except for stem cells and genetics

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract **Pages 1-2**	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale **Pages 3-10**	2	Explain the scientific background and rationale for the investigation being reported
Objectives **Pages 10-11**	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design **Page 12**	4	Present key elements of study design early in the paper
Setting **Pages 13, 27**	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants **Pages 11, 13, 25-26**	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables **Pages 10-13**	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement **Pages 13-19, supplementary materials**	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias **Pages 26-27**	9	Describe any efforts to address potential sources of bias
Study size **Page 25**	10	Explain how the study size was arrived at
Quantitative variables **Pages 20-25**	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods **Pages 20-25**	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants N/A	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data N/A	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data N/A	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results N/A	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses N/A	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results N/A	18	Summarise key results with reference to study objectives
Limitations **Page 3**	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation N/A	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability **Page 3**	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding **Page 28**	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

The Tulsa 1000: A naturalistic study protocol for multi-level assessment and outcome prediction in a large psychiatric sample

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The Tulsa 1000: A naturalistic study protocol for multi-level assessment and outcome prediction in a large psychiatric sample

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ABSTRACT

Introduction: Although neuroscience has made tremendous progress toward understanding the basic neural circuitry underlying important processes such as attention, memory, and emotion, little progress has been made in applying these insights to psychiatric populations to make clinically meaningful treatment predictions. The overall aim of the Tulsa 1000 (T-1000) study is to use the NIMH Research Domain Criteria (RDoc) framework in order to establish a robust and reliable dimensional set of variables that quantifies the positive and negative valence, cognition, and arousal domains, including interoception, to generate clinically useful treatment predictions.

Methods and Analysis: The Tulsa 1000 is a naturalistic study that will recruit, assess, and longitudinally follow 1,000 participants, including healthy controls and treatment-seeking individuals with mood, anxiety, substance use, and eating disorders. Each participant will undergo interview, behavioral, biomarker and neuroimaging assessments over the course of one year. The study goal is to determine how disorders of affect, substance use, and eating behavior organize across different levels of analysis (molecules, genes, cells, neural circuits, physiology, behavior, and self-report) to predict symptom severity, treatment outcome, and long-term prognosis. The data will be used to generate computational models based on Bayesian statistics. The final end-point of this multi-level latent variable analysis will be standardized assessments that can be developed into clinical tools to help clinicians predict outcomes and select the best intervention foreach individual, thereby reducing the burden of mental disorders, and taking psychiatry a step closer toward personalized medicine.

Ethics and Dissemination: Ethical approval was obtained from Western Institutional Review Board (WIRB) screening protocol #20101611. The dissemination plan includes informing health professionals of results for clinical practice, submitting results to journals for peer-reviewed publication, presenting results at national and international conferences, and making the dataset available to researchers and mental health professionals.

Trial registration number: NCT02450240

STRENGTHS AND LIMITATIONS

Strengths

- The study uses a comprehensive approach across multiple units of analysis for phenotyping.
- The study focuses on a dimensional psychopathology that cuts across traditional psychiatric diagnoses.

- The study utilizes novel statistical approches to identify and replicate latent constructs within a large and complex dataset.

Limitations

- The study does not include controlled treatment interventions.
- The study is a longitudinal observational study.
- The study recruitment aims to generate a representative sample of a local Midwestern community in the United States, including subsamples selected to represent the United States community at large.

INTRODUCTION

Mood [1] and anxiety [2] disorders are the most common form of mental illness and represent one of the biggest health issues worldwide, accounting for approximately $16 trillion in lost productivity or 25% of the global gross domestic product over the next 20 years [3]. Epidemiological data estimate the lifetime prevalence of Major Depressive Disorder (MDD) at about 18% and the 12-month prevalence at 7% [4]. Both MDD and anxiety disorders are associated with significant medical comorbidities [5] including substance use and eating disorders, which further exacerbate the cost and suffering associated with these disorders. The lifetime prevalence of eating disorders is comparatively lower at less than 3.5% [6], however, individuals exhibit extreme changes in body physique together with some of the highest mortality rates of all psychiatric disorders [7, 8]. Furthermore, most patients fail to remit or recover following treatment and up to 20% remain chronically ill [9-12]. Similarly, substance use disorders are among the most disabling conditions worldwide [13, 14]. Recovery includes abstinence [15, 16] and remission [17] but may not be adequately captured as an all-or-nothing process [18]. Recovery rates can differ across the primary drug of choice [19] and are highly nonlinear such that as many as 50% of treatment-seeking individuals relapse within a month of last use. The neural basis and behavioral changes associated with recovery are poorly understood because very few sufficiently powered, neurobiologically-based prospective, longitudinal studies have been conducted [20-25]. The heterogeneity of psychiatric disorders and the limited ability to identify broadly efficacious interventions have provided an impetus to utilize dimensional approaches to help delineate distinct syndromes that better reflect the underlying neurobiology [26].

Although neuroscience has made tremendous progress in understanding the basic neural circuitry that underlies important processes such as attention, memory, and basic emotion processing, little progress has been made in applying these insights to psychiatric populations in order to make clinically meaningful predictions. This may be because the current diagnostic system for mental disorders is based on statistically aggregated categories relying solely on verbal report and clinically observable behaviors [27]. Unfortunately, the connection between

psychiatric disorders and their underlying neurobiology has been difficult to establish. The NIMH Research Domain Criteria (RDoC) framework was developed as a heuristic approach to better integrate pathophysiology with psychopathology [26]. The RDoC initiative highlights two important goals for this objective: (1) psychiatric studies should transcend traditional diagnostic groups in order to adequately capture the inherent heterogeneity of symptomatology, and (2) clinical neuroscience and advanced statistical approaches should be used to determine the relationship between different units of analyses (self-report, behavior, physiology, neural circuitry, genetics, and clinically relevant psychopathology). The Tulsa 1000 aims to address these needs by determining how biological and objective behavioral measures can contribute to improving assessment and treatment of mental illness.

The overarching goal of this study is to utilized a dimensional psychopathological framework focused on mood, anxiety, eating and substance-related dysfunctions to identify latent variables that generalize across units of analyses, i.e. that can connect symptoms with underlying circuit dysfunctions and molecular abnormalities. We aim to establish a robust and reliable dimensional set of variables that quantify the positive and negative valence, cognition, and arousal/interoception RDoC domains based on a latent variable approach [28-30]. Moreover, we aim to make these data sets available for other investigators for novel analytic approaches aimed to delineate the relationship between variation within a particular domain, e.g. severity of mood symptoms and network characteristics of resting state functuional magnetic resonance imaging. These variables will be used to determine whether (a) measures of each domain (across different units of analyses) consistently relate to one another, (b) they predict the progression of symptoms over time (including natural recovery or worsening of symptoms), (c) they predict response to independently-sought pharmacological or behavioral treatments, and (d) they can be used in subsequent computational models of mental health to gain a more fundamental understanding of the pathology and predict illness course and recovery.

Overview of RDoC domains

Positive and Negative Valence Systems

Affect, or the tendency to experience a given emotion, is often subdivided into two domains [31]. Positive affect is the experience of positive emotions, such as happiness, excitement, elation, and enthusiasm. Negative affect is the experience of negative emotions, such as anger, resentment, sadness, anxiety, and fear. Positive affect and negative affect systems represent dimensions of psychopathology identified by the RDoC work groups [32, 33]. For example, high negative affect is common to anxiety and depression, [34-36] and comorbid anxiety and depression is associated with more negative affect than each disorder alone [37]. Low positive affect is relatively specific to depression, although there also is some evidence of low positive affect in social anxiety [34, 38]. In addition, psychophysiological and neurobiological data

indicate that the negative affect system is closely tied to threat sensitivity whereas the positive affect system is closely tied to reward sensitivity. More detailed information on specific constructs of the positive valence system, including approach motivation, reward seeking and reward sensitivity and constructs of the negative valence system, including acute threat, potential harm are described in the Supplementary Materials.

Cognitive System

The major constructs that were considered by the RDoC committee on cognitive systems included: (1) *attention,* i.e. a set of processes that regulate access to capacity-limited systems, such as awareness, higher perceptual processes, and motor action; (2) *perception*, i.e. process(es) that perform computations on sensory data to construct and transform representations of the external environment to make predictions and guide action; (3) *declarative memory*, i.e. the acquisition or encoding, storage, consolidation, and retrieval of facts and events; (4) *language*, i.e. a system of shared symbolic representations of the world, the self and abstract concepts that supports thought and communication; (5) *cognitive control*, i.e. a system that modulates the operation of other cognitive and emotional systems, in the service of goal-directed behavior, when prepotent modes of responding are not adequate to meet the demands of the current context; (6) *working memory*, i.e. the active maintenance and flexible updating of goal/task relevant information (items, goals, strategies, etc.) in a form that has limited capacity and resists interference.

The T-1000 focuses primarily on two constructs within the cognitive system (a) *cognitive control* and (b) *attention*. Inhibitory control, the ability to suppress a prepotent action, is an important cognitive control process, and is hypothesized to be dysfunctional in individuals with substance use problems [39]. However, it is unclear how dysfunctional cognitive control is associated with continuing substance use, and how this affects relapse following a period of recovery from substance use. For example, prior investigations have shown inhibitory control deficits in stimulant dependent individuals and moderate correlations with drug use indices [40-45].

In this study protocol, we will combine Bayesian ideal observer model-based analysis with fast, event-related functional magnetic resonance imaging (fMRI) data, to investigate subtle behavioral and neural differences among the target populations. Bayesian ideal observer models have been widely applied to the study of choice in uncertain environments, and to identify potential neural markers of the iterative processes of belief update underlying such models [46, 47]. Subsequent modeling studies have shown that such a framework is readily adapted to various aspects of executive function, including attentional and inhibitory control [48-51].

Arousal/Interoceptive System

Arousal is defined as a continuum of sensitivity of the organism to stimuli, both external and

internal. Interoception refers to how the brain receives, processes, and integrates internal signals from the body to affect motivated behavior [52-54]. One important aspect of the arousal domain is the link to homeostatic drives and interoception. Different conceptualizations of interoception have included its definition as the state of the individual at a particular point in time [55], or as the sensing of body-related information in terms of awareness [56], or as the accuracy of the sensing process [57], or as a trait phenomenon [58]. It is therefore a multifaceted process operating across numerous physiological and neural organ systems [59, 60]. Interoception provides an anatomical framework for identifying pathways focused on modulating the internal state of the individual. The anterior insula is predominately activated by effortful cognitive processing, whereas the posterior region is mostly activated by interoceptive sensory signals [61]. The insula is thought to be the central nervous system hub for interoceptive processing. There is an emerging generalized view that the anterior cingulate cortex (ACC), among other functions, orchestrates approach or avoidance behaviors in response to particular internal body states that involve homeostatic perturbations [62]. This function of the ACC is supported by the strong functional [63] and anatomical [64] connections between the anterior insula and the ACC. Taken together, the insula and ACC receive information about the individual's current body state and use this information to predict future body states and select actions that will help maintain bodily homeostasis.

Based on the RDoC criteria described above, the primary units of analyses for the Tulsa 1000 study are: (a) symptoms, (b) paradigms / behavior, (c) physiology, (d) circuits, and (e) molecules. These units of analysis will be assessed via clinical and self-report interviews of past and current psychiatric symptoms, computational tasks of behavior and neuropsychology, biomarkers for genetics inflammation and the microbiome, and structural and functional neuroimaging . There are several new emerging areas that either provide opportunities to examine how individual domains are affected by biological influences other than the individual or have the potential to yield cellular models of diseases. Next, these other units of analysis are described further and specific examples are provided for the relationship to at least one of the diagnostic groups in the Tulsa 1000 study.

Microbiome

The human body can be considered a super-organism composed of 10 times more microbial cells than our body cells. A meta-genomic study of the human microbiome has shown that microbial cells contain 150 times more genes than our own genome and make up an extraordinarily diverse set of over 1000 bacterial species [65]. Our understanding of the vast collection of microbes that live on and inside us (*microbiota*) and their collective genes (*microbiome*) has been revolutionized by culture-independent 'metagenomic' techniques and DNA sequencing technologies. Gut microbiota play an important role in health and disease and can be considered a 'microbial organ'

[66]. Each individual's microbiota shows significant variability across body habitats and time, which may provide clues as to how microbiome changes cause or prevent disease [67].

The interaction between microbiota and human organs has been extended recently to brain-gut interactions [68]. The brain can influence enteric microbiota indirectly, via changes in gastrointestinal motility and secretion, and intestinal permeability, or directly, via signaling molecules released into the gut lumen from cells in the lamina propria [69]. There is emerging preclinical evidence that variations in the composition of gut microbes may be associated with changes in the normal functioning of the nervous system [70]. Explorations of the microbiome thus offer new insight into our neurodevelopment, behavioral phenotypes, and perhaps disorders affecting complex processes, such as cognition, personality, mood, sleep and eating.

Human induced pluripotent stem (hiPS) cells

The molecular mechanisms responsible for dysregulated mood and anxiety, substance use, and eating behaviors are not well understood and few defining characteristics of diseased neurons have been identified. We intend to address this by generating dopamine cells (or neurons) that have been derived from a subset of individuals with extreme phenotypes of depression and/or anxiety, substance use, or eating behaviors. We aim to create cell-based human models for psychiatric disorders by directly reprogramming blood cells into human induced pluripotent stem (hiPS) cells in both healthy individuals and those with clinically-significant complaints related to affect, substance use, or eating [71-73]. We aim to identify specific neuronal defects associated with dopamine neurons *in vitro* and demonstrate the reversibility of the disease phenotype in human neurons, with the expectation to ultimately screen chemical libraries to identify novel therapeutic targets. The goal of these experiments is to identify key molecular events involved in the dysregulation of these target populations and to exploit these as possible points of intervention.

Genetics and Epigenetics

In humans, there is considerable evidence that anxiety and depression are moderately heritable and influenced by multiple genes. Most experts now believe that it is highly unlikely that there are "genes for psychiatric disorders". Rather, genes involved in susceptibility to psychiatric disorders can best be understood at the level of more basic biological processes (e.g., neuronal cell migrations during development) and/or mental function in the context of particular life experiences that are requisite for the expression of psychopathology.

Data from twin and adoption studies indicate that major depressive disorder (MDD), addiction disorders, and eating disorders (anorexia nervosa and bulimia) are moderately heritable - in the region of 40% to 60% - suggestive of a significant genetic contribution [74-76]. Clearly identifying the genetic variants that are associated with risk for developing these disorders would be helpful

for predicting who is at risk of becoming ill and increasing our understanding of the pathophysiological basis of these disorders. Unfortunately, given the heterogeneity and complexity of MDD and anorexia nervosa, even well-powered genome-wide association study (GWAS) datasets of ~10,000 cases and ~10,000 controls and ~5,500 cases and ~20,000 controls, respectively, have failed to identify alleles that achieve genome-wide significance [77, 78].

A more tractable approach than the traditional case-control association study is offered by large scale longitudinal designs such as the Tulsa 1000. Here the proposed within-subject genetic analyses will emphasize the prediction of naturalistic clinical outcomes such as response to pharmacological and/or non-pharmacological treatment. Further, the genetic data collected will be stored for future testing and combined with multiple phenotypes (e.g. neuroimaging, clinical, cognitive assessments, and other bioassays) to provide an integrated theoretical perspective on the genetic basis for disorders of mood, anxiety, eating and addiction [79-81].

Immunophenotyping

Data from several different fields of study suggest that at least a subset of individuals with depression and other psychiatric illnesses show immunological dysregulation characterized by activation of the innate immune system together with suppression of elements of the adaptive immune response (reviewed in [82-87]). However, progress has been limited by a disproportionate focus on a static and narrow aspect of innate immunity, i.e. single time-point measurements of CRP or cytokines to the exclusion of other potentially informative markers of innate and adaptive immune function. Here, we will leverage the T-1000 design to obtain a wide-range of immunophenotypes both at baseline and post-treatment. Further, the range of tasks embedded within the T-1000 will provide a rich opportunity to examine the effect of experimental manipulations on immune function. The data obtained will not only further our understanding of the nature of immune dysfunction in psychiatric illness but may lead to the identification of prognostic and/or predictive biomarkers that possess clinical utility.

METHODS

Aims and Objective

This is a multi-level, longitudinal observational study of healthy controls and treatment-seeking individuals with mental health problems in Tulsa and the surrounding regions of Oklahoma. The overall aim is to obtain a comprehensive assessment based on RDoC principles, in order to:

(1) Determine relationships among variables assessing positive/negative valence, cognition, and arousal/interoception domains in order to derive latent variables that describe psychopathology across units of analysis and diagnostic groups.

(2) Investigate whether latent factors can be used to generate clinically meaningful outcome predictions across different domains and diagnostic groups.

Thus, this study has the potential to substantially improve our understanding of how disorders of mood, anxiety, substance use, and eating behavior are organized across different units of analysis (genes, molecules, cells, neural circuits, physiology, behavior, and self-report) and different domains of functioning (positive and negative valence, cognition, and arousal/interoception). Upon completion, we will aim to have robust and reliable dimensional measures that quantify these relationships among different units of analysis and different domains of functioning. The latent constructs will be the main outcome variables of this protocol. The baseline assessments will be used with individual-based prediction methods (e.g., random forests or support vector machines) to develop predictors. These predictors will be evaluated with test-specific statistics such as positive and negative likelihood ratios and standard measures such as area under the Receiver Operation Characteristic curve and area under Precision-Recall curve to determine which baseline measure or combination of measures best predicts clinical outcomes. Ultimately, the aim is to develop a set of assessments that can be used as a clinical tool to enhance outcome prediction for the clinician. These measures may also serve as an aid to determine who would likely benefit from different interventions.

Participants

We propose to collect complete datasets on a total of 1000 participants with approximately 500 mood and/or anxiety, 300 substance use, 100 eating disorder and 100 mentally and physically healthy control participants. In order to obtain 1000 participants who complete the year-long study, we plan to enroll up to 1400 participants between January 2015 and December 2018. Subjects will be between 18 and 55 years of age and have a body mass index between 17-38kg/m^2. Subjects will be referred from local treatment facilities or seeking treatment for anxiety and/or depressive symptoms, problems related to substance use, or problems related to eating behavior. As part of the inclusion criteria, mood/anxiety, substance, and eating disorder participants must also screen positive for these conditions as indicated by a score on the Patient Health Questionnaire (PHQ-9) ≥ 10 and/or Overall Anxiety Severity and Impairment Scale (OASIS) ≥ 8, (DAST-10) score > 2 or Sick, Control, One, Fat, Food Questionnaire eating disorder screen (SCOFF) score ≥ 2. Participants who meet criteria for one primary domain may also screen positive for one of the other study domains. Healthy control participants will screen negative for these inclusion measures.

Exclusion Criteria

The following exclusion criteria will apply: (1) inability to provide informed consent, (2) no telephone or easy access to telephone, (3) history of unstable liver or renal insufficiency; glaucoma; significant and unstable cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, rheumatologic, or metabolic disturbance; or any other condition that, in the opinion of the investigator, would make participation not be in the best interest (e.g., compromise the well-being) of the subject or that could prevent, limit, or confound the protocol-specified assessments, (4) a positive test for drugs of abuse, including alcohol (breath test), cocaine, marijuana, opiates, amphetamines, methamphetamines, phencyclidine, benzodiazepines, barbiturates, methadone, and oxycodone, (5) has any of the following DSM-5 disorders: schizophrenia spectrum and other psychotic disorders, bipolar and related disorders, obsessive-compulsive and related disorders, (6) moderate to severe traumatic brain injury or other neurocognitive disorder with evidence of neurological deficits, neurological disorders, or severe or unstable medical conditions that might be compromised by participation in the study (to be determined by primary care provider), (7) active suicidal ideation with intent or plan, (8) change in the dose or prescription of a medication within the 6 weeks before enrolling in the study that could affect brain functioning, e.g., anxiolytics, antipsychotics, antidepressants, or mood stabilizers. However, we expect there to be changes in the dosing and prescription of medications during the course of the study protocol. This will be acceptable for the study and participants will be asked to inform the investigators of any treatments they undergo during their time in the study, (9) prescription of a medication outside of the accepted range, as determined by the best clinical practices and current research, (10) taking drugs that affect the fMRI hemodynamic response (e.g., methylphenidate, acetazolamide, excessive caffeine intake > 1000 mg/day), (11) MRI contraindications including: cardiac pacemaker, metal fragments in eyes/skin/body (shrapnel), aortic/aneurysm clips, prosthesis, by-pass surgery/coronary artery clips, hearing aid, heart valve replacement, shunt (ventricular or spinal), electrodes, metal plates/pins/screws/wires, or neuro/bio-stimulators, (12) persons who have ever been a professional metal worker/welder, history of eye surgery/eyes washed out because of metal, vision problems uncorrectable with lenses, (13) inability to lie still on one's back for 60-120 minutes; (14) prior neurosurgery, (15) tattoos or cosmetic makeup with metal dyes, (16) unwillingness to remove body piercings, (17) pregnancy, (18) unwillingness or inability to complete any of the major aspects of the study protocol, including magnetic resonance imaging (i.e., due to claustrophobia), biopsy, blood draws, or behavioral assessment. However, failing to complete some individual aspects of these assessment sessions will be acceptable (i.e., being unwilling to answer individual items on some questionnaires or being unwilling to complete a behavioral task), (19) non-correctable vision or hearing problems. Once participants have been enrolled, they will be followed for the study duration even if they fulfill exclusion criteria for initial enrollment, e.g. substance using individuals who were initially abstinent but experienced a relapse. However, subjects will be excluded if the investigators determine that participation

would interfere with the individual's treatment or might negatively affect the outcome of the underlying disorder.

Study design

The study's dependent variables will focus on the *positive and negative valence systems, cognition, and arousal/interoception domains* proposed by the RDoC [32, 33]. Using self-report, behavior, physiology, neural circuit, cell, molecule, and gene unit of analysis measures, we will apply these constructs to a clinical population of individuals with dysregulation of affect, substance use, and eating behavior recruited from treatment providers across different sites in the community. Through the application of latent variable analysis, we will derive latent constructs of positive and negative valence, cognition, and arousal/interoception system functioning that cut across units of analyses and diagnostic groups. Subjects will undergo a multi-level assessment based on the RDoC approach that consists of (a) a standardized diagnostic assessment , (b) self-report questionnaires assessing the positive and negative valence domains as well as interoception, (c) behavioral tasks assessing positive and negative valence, cognition, and interoception, (d) physiological measurements consisting of skin conductance, facial emotion expression monitoring, heart rate, respiration and eye-blink startle response, (e) functional magnetic resonance imaging focusing on reward-related processing, fear conditioning and extinction, cognitive control and inhibition, and interoceptive processing, (f) biomarker assessment, (g) microbiome assessment, (h) blood to derive induced pluripotent stem cells (IPS), (i) and genetic as well as epigenetic assessments. Subsequently, these individuals will be followed up quarterly and for one year. At months 3, 6, and 9, only self-report assessments will be collected, and the participants and will be re-assessed using a multi-domain assessment of functioning, which will include: (a) symptom severity and duration, (b) subjective well-being, (c) psychosocial function, (c) occupational function, (d) physical health, (e) utilization of mental health resources (treatment), and (f) adherence to treatment.

The workflow schematic in Figure 1 describes the overall outline of the T-1000 study and the measures obtained at different points in time.

Potential subjects will be screened by phone or in-person using the Western Institutional Review Board (WIRB) screening protocol 20101611. Once an individual has been identified as a potential subject in the T-1000, he or she will complete two to six in-person sessions within a two-week time period. However, completion of these sessions may be broken into more or less visits depending on what works best for the participant's schedule. The order of the baseline assessments may also be modified to ensure timely and efficient completion, given individual differences in completion times for the various measures (e.g., variability in how long individuals may take to complete self-report measures).

Although entry into the study is not based on meeting diagnostic criteria for a particular mood, anxiety, substance use, or eating disorder, it will be important to characterize how our findings map onto the Diagnostic and Statistical Manual of Mental Disorders (DSM) (using DSM-5 criteria)[88]. Accordingly, patients will complete a diagnostic interview with study personnel, using an abbreviated version of the Mini International Neuropsychiatric Interview (MINI Version 6.0) [89]. The MINI was chosen over other diagnostic interviews because of its relative brevity, good inter-rater reliability, and suitability for use by an interviewer with limited training. We will include sections on panic disorder (PD), social anxiety disorder (SAD), posttraumatic stress disorder (PTSD), generalized anxiety disorder (GAD), eating disorders (ED), obsessive-compulsive disorder (OCD), and major depressive disorder (MDD) and several modules to provide further clinical information or to determine ineligibility (suicidality, manic/hypomanic episode, and psychotic disorders).

After completing the MINI and satisfying study criteria, the subjects will complete a wide range of self-assessments that are targeted to probe the positive and negative valence domains, cognitive systems and interoceptive systems. Subjects included in the study will return for a behavioral testing session (session 2) and neuroimaging and biomarker testing sessions (sessions 3-5). During the behavioral session participants will complete a battery of neuropsychological assessments, a set of cognitive tasks which have been selected based on underlying computational models, a modified dot probe detection task, an approach/avoidance conflict task, and an emotional reactivity task in which they view blocks of emotional images. Interoception will be probed using a series of heartbeat perception tasks, an inspiratory breathhold experiment, and a cold pressor test. State affect and physiology will be assessed throughout the behavioral session procedures. The biomarker session will include a blood draw, microbiome collection, physical measurements including height, weight, body composition assessment, hip/waist ratio, and vital signs (pulse, blood pressure). The structural MRI, functional MRI and EEG session will include high resolution anatomical brain scans, a resting state functional scan and task-based functional scans targeting neural systems associated with reward, attention, inhibition, interoception and fear conditioning.

The details of each session are listed in Table 1: the first column indicates which construct will be examined, the second column lists the name of the test. All self-report assessment measures will be administered electronically through REDCap [90].

Study Sessions

Detailed descriptions of the clinical, demographic, self-report, behavioral, neuropsychological and functional neuroimaging measures listed below are provided in the Supplementary Materials.

The Baseline Session

Clinical interview, demographics, and questionnaires detailed in Table 1 will be administered by masters or nurse level assistants who are supervised by licensed clinical psychologists and board certified psychiatrists. The clinical portion of the baseline assessements is expected to take approximately 4.5 hours to complete and can be split into two or more visits.

Table 1. Baseline Session: Clinical Interview, Demographics and Questionnaires

Domain	Assessment
Clinical Rating Scales and Demographics	
Diagnosis	MINI 6.0 [91]
Demographics	Demographics and Psychosocial Form
History	Assessment of Medical and Medication History
History	Life chart interview
Substance Use	Customary Drinking and Drug Use Record (CDDR) [92]
Handedness	Edinburgh Handedness Inventory [93]
Compliance	Medication Compliance
Compliance	Therapy Compliance
Traumatic Head Injury	Tulsa Head Injury Screen
Family Psychiatric History	Family History Screen (FHS) [94]
Suicidal Ideation	Columbia-Suicide Severity Rating Scale (C-SSRS) [95, 96]
Pain	Wong-Baker FACES Pain Rating Scale [97]
Self-Report Scales	
Negative Valence	State Trait Anxiety Inventory (STAI) [98]
Negative Valence/Interoception	Anxiety Sensitivity Index (ASI-3) [99]
Negative Valence	Ruminative Responses Scale (RRS) [100]
Depression	Quick Inventory of Depressive Symptomatology [101]
Trauma	Traumatic Events Questionnaire (TEQ) [102]
Trauma	Child Trauma Questionnaire (CTQ) [103]
Positive/Negative Valence	Positive and Negative Affect Schedule-Expanded Form (PANAS-X) [104]
Positive/Negative Valence	Behavioral Inhibition System/Behavioral Approach Scale (BIS/BAS) [105]
Positive Valence	TEPS anticipation/consumption/pleasure [106]
Positive Valence	UPPS Impulsive Behavior Scale[107]
Empathy-like	Interpersonal Reactivity Index (IRI) [108, 109]
Personality	Big Five Inventory (BFI) [110]
Arousal/Interoception	Toronto Alexithymia Scale (TAS) [111, 112]
Arousal/Interoception	Multidimensional Assessment of Interoceptive Awareness (MAIA) [58]

Eating Behaviors	Three Factor Eating Questionnaire (TFEQ) [113-115]
Eating Behaviors	Eating Disorders Diagnostic Scale (EDDS) [116]
Eating Behaviors	Simplified Nutritional Appetite Questionnaire (SNAQ) [117]
Physical Activity	International Physical Activity Questionnaire (IPAQ) [118]
Disability	World Health Organization (WHO) Disability Assessment Schedule [119]
Absenteeism/Presenteeism	WHO Health & Work Performance Questionnaire (WHOHPQ) [120]

Patient Reported Outcome Measurement Information System (PROMIS) Measures **[121, 122]**

Negative Valence	PROMIS Anxiety
Negative Valence	PROMIS Depression
Negative Valence	PROMIS Anger
Positive Valence	PROMIS/Neuro-QOL Positive Affect and Well-being
Cognitive	PROMIS Cognitive Abilities
Cognitive	PROMIS Cognitive General
Fatigue	PROMIS Fatigue
Sleep	PROMIS Sleep Disturbance
Sleep	PROMIS Sleep-related impairment
Alcohol	PROMIS Alcohol Use
Alcohol	PROMIS Alcohol: Negative Consequences
Alcohol	PROMIS Alcohol: Positive Consequences
Alcohol	PROMIS Alcohol: Negative Expectancies
Alcohol	PROMIS Alcohol: Positive Expectancies
Social	PROMIS Social Satisfaction DSA
Social	PROMIS Social Satisfaction Role
Social	PROMIS Ability to Participate Social
Social	PROMIS Emotional Support
Social	PROMIS Information Support
Social	PROMIS Instrument Support
Social	PROMIS Satisfaction Roles Activities
Social	PROMIS Social Isolation
Physical	PROMIS Physical Function
Pain	PROMIS Pain Interference
Pain	PROMIS PAIN Behavior
Sex	PROMIS Global Satisfaction with Sex Life
Sex	PROMIS Interest in Sex Activity
Nicotine	Nicotine Dependence
Nicotine	Coping Expectancies
Nicotine	Emotional and Sensory Expectancies
Nicotine	Health Expectancies
Nicotine	Psychosocial Expectancies
Nicotine	Social Motivations

Baseline Behavioral Session

Behavioral tests will be administered via computer interfaces, with the exception of neuropsychological testing which will be conducted face to face by an assessor. The neuropsychological assessments will be administered by trained clinical assistants, directly supervised by licensed clinical psychologists and board certified psychiatrists. Behavioral assessments will be conducted by trained research assistants. The behavioral session is expected to take about 4 hours to complete and can be split into 2 or more visits (Table 2).

Table 2. Behavioral and Neuropsychological Tasks

Domain	Task
Computational- Cognitive	Change Point Detection Task [123] Three Arm Bandit Task [124] Start/Stop Task [125]
Positive/Negative Valence	Implicit Approach/Avoidance Task [126] Attentional Bias/Dot Probe Task [127] Emotional Reactivity Task [128] Approach Avoidance Conflict Task [129]
Arousal/Interoception	Breath Hold Heartbeat Tapping Task Cold Pressor [130, 131]
Neuropsychology	WRAT Reading [132] DKEFS Color-Word Inhibition [133] DKEFS verbal fluency [133] WAIS-IV digit span [134] Finger Tapping Test WAIS-IV Digit Symbol Coding [134] California Verbal Learning Test [135]

Baseline Biomarkers

Table 3 summarizes the proposed biomarkers and biological specimens that will be obtained from blood samples and microbial samples of the subjects. It is expected to take approximately 30-45 minutes to complete sample collection.

Table 3. Examples of immune-related measurements

Immunophenotype	Reported Abnormality in Depression, Eating Disorders or Addiction Disorders	References
Cytokines	Elevations in pro-	[136-139]

	inflammatory cytokines	
PBMC Gene Expression	Increased mRNA expression of pro-inflammatory mediators	[140-143]
Kynurenine Pathway	Increased neurotoxic kynurenine metabolites	[144-147]
T-cells	Altered T-cell function and numbers	[148, 149]
Natural Killer Cells (NKC)	Reduced NKC function	[150-152]
Pathogens	Increased seropositivity for *T. gondii* and herpesviridae	[153, 154]

Baseline Neuroimaging

The session will consist of one 60 and one 120 minute scan in the MRI machine. One of the neuroimaging sessions will focus on structural differences in the brain and a second session will focus on functional differences. The neuroimaging sessions are expected to take approximately 4 hours total to complete and are split into two visits (Table 4).

Table 4. Baseline Neuroimaging Sessions

32 Channel Head Coil MRI Imaging: Structural & Perfusion
Participant Last Use Summary (PLUS)
3-plane localizer, asset calibration
T2-W Clinical Flair
T2-W Clinical FSE
T1-W Clinical MPRAGE
T1-W MPRAGE HI-RES
T2-W Propeller FSE HI-RES
Arterial Spin labeling
Diffusion Tensor Imaging
8 Channel Head Coil MRI, and fMRI with concurrent EEG
Task Training and Practice
Karolinska Sleepiness Scale: Pre-scan (KSS)
Participant Last Use Summary (PLUS)
EEG Cap Setup
MRI Anatomical scan (T1-W)
fMRI Monetary Incentive Delay Task (MID) **[155, 156]**
fMRI Stop Signal Task **[157]**
fMRI Resting State with eyes open
fMRI Interoceptive Attention Task **[158]**

fMRI Fear Conditioning/Extinction Task **[159]**
Karolinska Sleepiness Scale: Post-scan (KSS)

Quarterly Follow-up Session

These sessions will examine the course of outcomes in individuals with dysregulated mood and/or anxiety, substance use, or problematic eating behavior. These assessments will be brief in-person visits. The quarterly follow-up assessments will take approximately 1.5 hours every 3 months during the 12-month follow-up time period (Supplementary Table 1).

One-year Follow-up Session

This session will examine the course of outcomes 1 year after baseline. For neuropsychological assessment, alternative forms will be used as available. Assessments will be administered during in-person sessions that take approximately 7 hours to complete over 1 to 3 visits (Supplementary Table 2).

Biomarker measures

Blood Collection

We will investigate neuroendocrine, metabolic, inflammatory, and cardiovascular biomarkers associated with positive and negative valence domains, cognitive systems and arousal/interoceptive systems. These measures help to extend our multi-level analysis of NIMH RDoC constructs into the cellular and molecular units of analysis. Biochemical assays will be performed on biological samples collected at baseline and during the 1-year follow-up to quantify a range of biomarkers and their relationship with other variables and units of analysis.

Participants will have fasting blood drawn by venipuncture by a trained phlebotomist for the biomarker panels. This will be scheduled to occur the morning of one of the visits, or at a time convenient for the participant. Resting blood pressure and heart rate will be assessed. Additionally, in order to lay the foundation for future studies, we will also collect and process a small quantity of blood to be banked for potential future endocrine, immune and/or genomic analyses.

Sample collection, processing distribution and storage procedures

A trained phlebotomist will obtain all blood samples. Less than 150 mL of blood will be collected per subject during each session (baseline and 1-year follow-up), which is well within the safety limit of ~450 mL per blood draw. Samples for stem cells and genetics will be shipped to Rutgers University laboratory for processing and storage. Blood samples for plasma, serum, and peripheral blood mononuclear cells (PBMCs) will be transported to and processed at the University of Oklahoma Integrative Immunology Center (IIC) Laboratories. Plasma and serum

samples will be stored in secure freezers at -80°C. Freezers will be maintained in a specially equipped room with emergency backup power and an automated telephone alarm system that is programmed to call in case of failure. Additional aliquots of samples will be stored at -80°C should repeat analyses be required at a later date. PBMCs will be stored in liquid nitrogen dewars with liquid level monitors and alarms in a secure room at the University of Oklahoma IIC Laboratories.

Microbiome Collection

Participants will be asked to provide microbial samples during the biomarker session. All participants will be asked to provide forehead, mouth and stool samples.

A research assistant will provide the participant with an all-in-one sample collection kit system for collecting, stabilizing, transporting, and purifying samples which includes cotton-swabs, tubes labeled by body area, and step by step instructions.. Participants will be asked to perform the sampling themselves. Samples will be stored at the University of Oklahoma IIC Laboratories after initial processing until they are shipped to The University of San Diego-California for final processing and sample analysis.

Compensation

Subjects will receive the following payment for completing the study (Table 5):

Table 5. Compensation

SESSION	TIME	PAYMENT*
Interview and Demographic Information	4.5 hours	$90
Behavioral assessments & Computerized Tasks	4 hours	$80 $10-$20 reward
Biomarkers	30 minutes	$50
Neuroimaging & EEG & Setup	4 hours	$170 $0-$60 reward
3 month Follow up*	1.5 hours	$30
6 month Follow up	1.5 hours	$30
9 month Follow up	1.5 hours	$30
12 month Follow up	7 hours	$200 $10-20 reward
Total	23.5 hours	$700 to $780

DATA ANALYSIS

Behavioral and Psychophysiological Data Analyses

Self-report questionnaires, interviews, neuropsychological assessments, computer-based behavioral assessments, and psychophysiological assessments will be scored according to published methods (as cited in the Tables). These variables will then be used in conjunction with collected biological data in the latent variable approach. The analysis strategy consists of the following steps. First, the characteristics of all measures will be examined for deviation from normality prior to subsequent analyses. For each unit of analysis (self-report, behavior, physiology, circuits, biomarkers), separate principal components analyses (PCA) will be performed and a separate analysis will be conducted for each behavioral task to minimize task-specific factors in subsequent analysis steps. Next, the number of components for each analysis will be determined using a number of different approaches [160]. In particular, if the number of components to be extracted differed across the extraction approaches, both solutions will be explored [161, 162]. Component scores from each unit of analyses will be extracted for each participant and used for the following analyses.

MRI, EEG and fMRI Data Analysis

The basic structural and functional image processing will be done with the Analysis of Functional Neuroimages (AFNI) software package [163].

EEG-fMRI

The EEG data will be acquired simultaneously with the fMRI data and corrected for artifacts related to the gradient switching and cardiac ballistic effect using the template subtraction method [164-166] implemented in BrainVision Analyzer software (Brain Products GmbH, Munich, Germany).

During fMRI scans we will simultaneously record EEG using a 31-electrode cap attached to an MRI-compatible BrainAmp MR Plus amplifier. The sintered Ag/AgCl ring electrodes are mounted into a scalp cap according to the standard 10-5 system. All electrodes are referenced to the FCz position, while a ground electrode is located at the AFz position. One additional electrode will be placed on the subjects' back to monitor the electrocardiographic signal. The impedance of all electrodes will be maintained below 10 KΩ throughout the recording. The internal sampling clock of the EEG amplifier will be synchronized with the MRI scanner 10MHz master clock signal using the SyncBox device (Brain Products GmbH, Munich, Germany), in order to prevent variant sampling of imaging artifacts and to facilitate artifact correction [166]. The signals will be recorded at a sampling frequency of 5000 Hz with an analog filter (from 0.016 to 250 Hz) and a resolution of 0.1 µV.

Besides independent EEG measures of brain state, and EEG-informed fMRI data analysis, we will use EEG data to correct the effects of head movements in simultaneously acquired fMRI

data on a slice-by-slice basis [167]. This E-REMCOR, and recently developed automated version aE-REMCORE technique, will make it possible to regress out the effects of rapid head movements from unprocessed fMRI data on slice-by-slice basis prior to volume registration [168]. Thus, aE-REMCOR complements both the traditional fMRI volume registration approach, which performs better for slower head motions, and the RETROICOR method for slice-specific correction of fMRI cardiorespiratory artifacts [169]. EEG-informed fMRI analysis will allow us to better elucidate and characterize normal and pathological interactions between cerebral function and behavior, cognition or emotion.

fMRI Pre-Processing

Standard fMRI data pre-processing will include a slice-timing correction, signal scaling, spatial smoothing, physiological noise suppression [169, 170], and motion correction.

Task-based fMRI Analysis

First/Subject-Level Analyses

Multiple regression will be used to analyze individual subjects' data, with predictors in the model constructed by convolving each column of the task design matrix with a canonical hemodynamic response function. Regressors of non-interest will be included in all models to account for (1) head motion (6 motion variables), and (2) other sources causing drifts (each run's signal mean, linear, quadratic, and cubic signal trends). The beta weights and corresponding t-statistics for image contrasts of interest will be produced for group-level analyses.

Second/Group-Level Analyses

Both region of interest (ROI) and whole-brain analyses start with voxel-wise statistical tests using mixed-effects modeling on aggregations of maps of the subjects' beta-weights and beta-weight standard errors (AFNI's *3dMEMA* or in-house developed R code). This approach has the advantage of taking into account in the group analysis both effect estimates as well as their within- and between-subjects variances. Correction for multiple comparisons will be conducted as follows. Statistical maps will either be corrected using the false-discovery rate (FDR) or cluster level thresholds. For cluster level thresholds, AFNI's *3dClustSim* (with spatial autocorrelation function [acf] adjustments) will be used to identify the required cluster-size threshold, given a voxel-wise probability of $p < 0.001$, the smoothness of the residuals from the group level test, and the size of the region tested (either whole-brain or an a priori defined ROI).

Resting State fMRI Analysis

Pre-Processing

Data pre-processing will be conducted using afni_proc.py. The first three volumes of the functional scans will be discarded to allow the signal to reach T1 equilibrium, and a de-spiking algorithm will be used to remove any transient signal spikes from the data. Prior to slice time correction, physiological signals of non interest (pulse, respiration) will be removed using RETROICOR. For each subject, the remaining volumes will be corrected for differences in slice acquisition time; head motion will be corrected by rigid body translation and rotation; the third volume of the functional run will be co-registered to the anatomical coordinates of the participant's structural scan by linear warping, then normalized to the Talairach template and resampled to 2x2x2 mm^3 voxels.

First/Subject-Level Analyses

For each participant, the time courses of the residual images from the pre-processing step will be averaged across voxels within each ROI, and Pearson correlation coefficients will be computed between the mean signal time courses of pairs of ROIs. These correlation coefficients will be converted by Fisher *r*-to-*z* transformation, which will be used as predictors of treatment outcomes.

The identified brain activation at ROIs and/or functional connectivity z-scores will be analyzed by PCA, and the extracted principal component scores will be used with scores from other units of analyses.

General Unifying Statistical Approach

The goal of this project is to derive latent variables that adequately quantify the positive and negative valence, cognition, and interoception/arousal domains across different units of analyses collected at baseline. The analysis of the variables that are extracted from each unit will consist of three steps. First, a PCA will be conducted for each unit of analysis to determine the number of independent degrees of freedom contributing to the variance observed in each unit. We expect to extract at least two independent components. The action units that show the highest correlation with the components will be used for subsequent analyses. Second, we will conduct a confirmatory factor analysis with the variables from each unit of analysis that showed the highest correlation with the principal components of four proposed factors – positive valence system, negative valence system, arousal/interoceptive system, and cognitive system. We will subsequently test the statistical significance of the coefficients contributing to the factors. Finally, we will conduct a latent variable analysis as detailed below to relate one unit directly to another unit of analysis.

Statistical Analysis Plan

Baseline/Cross-sectional analyses

We will relate different units of analyses by regularized generalized canonical correlation analysis (RGCCA) [171]. Classical CCA identifies linear combinations of two sets of variables such that their correlations are maximized. RGCCA extends classical CCA from two sets of variables to multiple sets. When applied to multiple units of analyses, RGCCA identifies linear combinations (canonical variates) of principal component scores within each unit of analyses, such that the sum of correlations or covariance across canonical variates is maximized. The results of RGCCA can be demonstrated as a network that shows which unit of analyses are connected, and which are not. Moreover, the canonical correlations obtained from RGCCA can be used to define biotypes by cluster analysis from two sets of variables (clinical symptoms and resting state functional connectivity) to define biotypes [172]. These dimension-defined biotypes will be linked to the category-defined groups by cross tabulation.

Longitudinal analysis

The self-report outcomes will be measured at baseline and months 3, 6, 9, and 12, and these time trajectories will be compared between groups based on categorical diagnosis (comparison subjects, substance use disorders, mood disorders, and eating disorders) and between dimensionally-defined biotypes using models for longitudinal data – mixed effects and generalized estimating equations (GEE) models. No functional form will be assumed for the time trajectories and profile models will be used (i.e., time variable is treated as a factor in the model). The biotype/group effect will be measured as a time-by-group interaction. Comparisons between the time profiles of the groups will use appropriate Wald and likelihood ratio tests. In addition, linear time effects will be considered; these will be used if they are preferable to the profile models in model comparison using Akaike information criterion (AIC).

Statistical Power

We will base statistical power on two considerations: (1) power to estimate latent factor models with precisions, and (2) accuracy of prediction of outcomes using baseline variables and latent factors as predictors. Although controversial [173], typically one suggests that there should be at least n=10 subjects for each identified latent variable. In comparison, this study is likely to have up to n=100 subjects per latent construct. More recent recommendations for power take into account the quality of the indicators for the latent variables and the number of items per factor. For a moderate to low communality (conservative assumption), a sample size of n=300 would give an excellent coefficient of congruence of K=0.97. This allows for fitting latent factor models to each patient subgroup separately with adequate power [174]. We also compute power to predict the year follow-up clinical outcomes: assuming 100 healthy controls (HC), 100 eating disorder (ED), 500 mood/anxiety (MA), and 300 substance use (SU) participants at baseline and a uniform 20% attrition rate for each group at one-year follow-up (i.e., with

remaining 80, 80, 400, and 240 participants in the corresponding groups), we will have 80% power to detect effect sizes (Cohen's D for between-group differences in changes from baseline to 1-year follow-up) of 0.57 (ED vs. HC), 0.43 (MA vs. HC or ED), 0.45 (SU vs. HC or ED), 0.29 (MA vs. SU) at two-sided Type I error rate 0.05/6 = 0.008 (Bonferroni correction) in t-test for post hoc comparisons.

ETHICS and DISSEMINATION

Gender/minority/pediatric inclusion for research

Women and minorities will be included in the study without prejudice and represented according to the study population. Participants will be recruited from the greater metropolitan areas of Tulsa, Oklahoma and efforts will be made to ensure the subject population is representative of the gender, ethnicity and racial demographics of the region according to the US Census Bureau data. No participants under the age of 18 will be enrolled in the study.

Specimens, records, data collection

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study. Study consent records will be stored in the locked records room at the Laureate Institute for Brain Research. Only approved study personnel will have access to study records that contain any identifying information. Study data records and blood/urine/biological samples will be assigned code numbers and will not be individually identifiable. Code numbers are a combination of numbers and letters. The electronic data will be kept in a firewalled and password protected database on a secure server managed by LIBR. Vanderbilt University, with collaboration from a consortium of institutional partners, has developed a software toolset and workflow methodology for electronic collection and management of research and clinical trial data REDCap (Research Electronic Data Capture) [90] data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team with planning assistance from the information technology staff. The iterative development and testing process results in a well-planned data collection strategy for individual studies. REDCap servers are housed in a local data center at Laureate Institute for Brain Research and all web-based information transmission is encrypted. REDCap was developed specifically around HIPAA-Security guidelines and is recommended to LIBR researchers by both our Privacy Office and the Western Institutional Review Board (WIRB). REDCap has been disseminated for use locally at other institutions and currently supports 240+ academic/non-profit consortium partners on six continents and over 26,000 research end-users (www.project-redcap.org).

Records of the subject's participation in this study will be held confidential except as disclosure

is required by law or as described in the informed consent document (under "Confidentiality"). The study doctor, the sponsor or persons working on behalf of the sponsor, and under certain circumstances, the United States Food and Drug Administration (FDA) and WIRB will be able to inspect and copy confidential study-related records which identify the subject by name. Therefore, absolute confidentiality cannot be guaranteed. If the results of this study are published or presented at meetings, the subject will not be identified. Paper copies of consents, screening forms, the Research Privacy Form, and any other forms, testing results or papers containing Personally Identifiable Information (PII) will be stored in a secured medical records room with access granted only to authorized personnel.

Recruitment and consent procedure

Recruitment into the T-1000 study at the Laureate Institute for Brain Research will be ongoing for 4 years from January 2015 through December 2018. The study will be completed by December 2019 after the completion of the 1-year follow-ups from 2018. Study participants will be recruited through the clinical services of the Laureate Psychiatric Clinic and Hospital (LPCH), local service providers for behavioral health, mental health, and addiction and recovery (e.g. Family and Children's Services, 12&12 Inc., local psychiatrist and physician offices), and through online, newspaper, flyer, radio or other media advertisements in the Tulsa metropolitan area. Participants will also be recruited through a pre-approved LIBR Screening protocol (WIRB #20101611) and through the Laureate Institute for Brain Research REDCap database. Informed Consent will be obtained by members of the research team that have received training from the PI to obtain consent for this study. All participant interactions including consenting will be conducted in private interview/exam rooms. These exam rooms at LIBR are secured from public areas via combination locked doors that are only accessible to authorized personnel.

Expected outcomes

The final end-point of this analysis will be a set of standardized multi-level latent variables that can be developed into clinical tools to help clinicians predict illness course and recovery at the individual patient level following the implementation of standard treatment interventions. These variables, which will focus on the prediction of mood, anxiety, eating, or substance use psychopathology, will be investigated in a number of different ways. A first approach will determine how measures of each domain across different units of analyses (e.g., from molecules to mental processes) relate to one another. A second approach will involve indentifying whether they predict the progression and severity of symptoms over time (including natural recovery or worsening of symptoms). A third approach will examine whetherthey predict responses to independently-sought pharmacological or behavioral treatments. A fourth approach will be to investigate how these variables can be implemented in computational models of mental health to gain a better understanding of the underlying

processes driving psychopathology. Additional approaches and outcomes are expected to emerge in the process of conducting these examinations. By establishing a robust and reliable dimensional set of latent variables that quantify the positive and negative valence, cognition, and arousal/interoception RDoC domains, this project will take psychiatry a step closer towards personalized and biologically based medicine [28-30].

Dissemination of results

Results from the study will be submitted to relevant journals for peer-reviewed publication and presented at national and/or international biomedical conferences.

Registration

In accordance with the recommendations of the International Committee of Medical Journal Editors, the proposed study is registered in a public registry (http://www.clinicaltrials.gov/, Trial Registration Number: NCT02450240).

Collaborators

University of Oklahoma

University of California-San Diego

Rutgers University

Contributors

All authors made a significant contribution to the conception and design of the study protocol. The protocol was written by MPP and TAV and critically reviewed by SK, JS, JB, JF, RA, HY and WKS. All authors gave permission and approval for publication.

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Competing Interests

None

Patient consent

Obtained

Ethics Approval

The study protocol is approved by the Western Institutional Review Board, Puyallup, Washington (WIRB, protocol number 194919).

Provenance and peer review

Not commissioned; externally peer reviewed.

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Figure 1. T1000 Workflow Schematic

Abbreviations (in alphabetical order): BOLD: Blood-Oxygen-Level-Dependent; DAST: Drug Abuse Screening Test; DTI: Diffusion Tensor Imaging; EEG: Electroencephalogram; MINI: Mini International Neuropsychiatric Interview; MRI: Magnetic Resonance Imaging; OASIS: Overall Anxiety Severity and Impairment Scale; PHQ-9: Patient Health Questionnaire; PROMIS: Patient Reported Outcome Measurement Information System; SCOFF: Sick, Control, One, Fat, Food Questionnaire; T1/T2: T1- weighted (longitudinal relaxation time) and T2-weighted (transverse relaxation time)

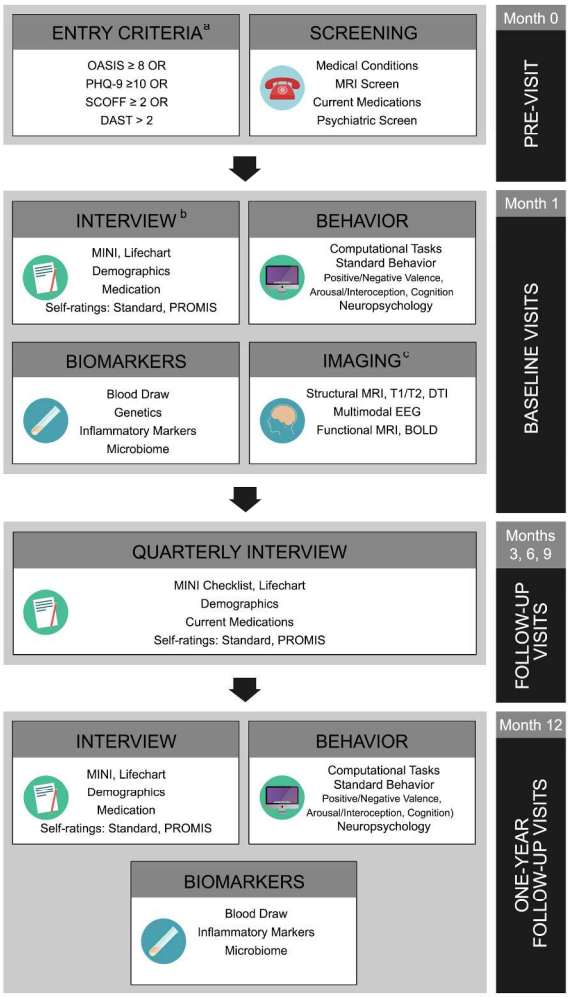

Figure 1. T1000 Workflow Schematic

215x279mm (300 x 300 DPI)

SUPPLEMENTARY MATERIALS

Positive and Negative Valence Domains

Positive Valence System

A central construct of the positive valence system is *approach motivation*, which can be defined as processes that regulate the direction and maintenance of approach behavior. The constructs of *reward seeking* and *reward sensitivity* are components of approach motivation. Reward sensitivity refers to the anticipation and receipt of positive stimuli. The primary neural mechanisms of reward sensitivity involve the ventral striatum (VS) and orbitofrontal cortex (OFC). These structures are involved in the processing of primary rewards, such as pleasant tastes [1], smells [2] or sights [3], as well as secondary (monetary) rewards [3-5]. The VS plays an important role in the anticipation of reward [6, 7] as well as the receipt of reward [4, 8]. The VS is part of a larger fronto-striatal circuit subserving reward-related processing that also includes the OFC, a subregion of the prefrontal cortex [9]. An important functional coupling exists between the VS and OFC [10]. Reward-processing also involves other neural regions, including the amygdala [11-13], dorsal anterior cingulate cortex (ACC) [14] and the hippocampus [15].

Relationship between reward sensitivity and the positive valence system: Extant evidence shows that individuals have deficits in positive affect (i.e., individuals with depressive disorders) show deficits in reward processing, at both the behavioral [16] and the neural levels [17]. At the behavioral level, individuals with major depression are less responsive to reward-relevant stimuli than non-depressed individuals and deficits in reward responding are associated with deficits in positive affect or the ability to experience pleasure [16, 18]. At the neural level, depression is associated with reduced activation in fronto-striatal circuits, namely the VS and caudate, during reward processing compared with healthy controls [17]. Anhedonia [19, 20] (or, the inability to experience pleasure) and reward-related processing [21] have been considered critical factors in the development of depression. Reward sensitivity in anxiety disorders has been less well studied. Similar to depression, evidence of reduced striatal activation during reward processing has been found in individuals diagnosed with

posttraumatic stress disorder (PTSD) compared with healthy controls [22, 23], particularly in relation to anhedonic features of PTSD (e.g., emotional numbing). Other studies, however, find evidence of heightened striatal activation during reward anticipation in some anxiety disorders [24]. This heterogeneity underscores the potential value of moving towards a dimensional understanding of reward sensitivity and positive valence system functioning in anxiety, mood, substance and eating disorders.

Negative Valence System

Responses to *acute threat* (fear) and *potential harm* (anxiety) were considered by the RDoC workshop committee to be central constructs within the negative valence system. One approach to measuring response to threat is via fear conditioning, which involves excitatory learning of conditioned stimulus vs. unconditioned stimulus (CS-US) associations [25, 26]. Research on fear learning uniquely adapts to translational neuroscience contexts because we understand with great precision the relevant neural processes in many species, including humans. The brain regions that have most consistently been associated with fear conditioning are the amygdala [27-31] and insular cortex [32]. In healthy adults, increased activity in the amygdala and insula is typically observed in response to the CS during conditioning. Response to loss was cited by the RDoC committee as another critical component process of the negative valence system, and may be particularly related to depression. Reward paradigms that include loss or punishment trials (e.g., losing money for incorrect responses [33-35]) can be used to measure behavioral and neural responses to loss anticipation and outcome. Research in healthy adults suggests that the ventral and dorsal striatum (caudate) are associated with anticipation and receipt of loss or punishment using these paradigms [33, 34].

Baseline Diagnostic and Demographic Assessment Measures

Patient Health Questionnaire (PHQ-9): The Patient Health Questionnaire (PHQ) is a self-administered diagnostic instrument for common mental disorders. The PHQ-9 is the depression module, which scores each of the 9 DSM-IV criteria as “0” (not at all) to “3” (nearly every day). Scores of 1-4 are considered minimal depression, 5-9 mild depression, 10-14 moderate depression, 15-19 moderately severe depression and 20-27 severe depression [36].

Overall Anxiety Severity and Impairment Scale (OASIS): The OASIS is a brief questionnaire (5 Items) that can be used as a continuous measure of anxiety-related severity and impairment across anxiety disorders. Each item is rated on a 5-point scale and the ratings are summed to obtain a total score. A cut-score of 8 has been shown to correctly classified 87% of individuals as having an anxiety diagnosis or not [37]. The OASIS has demonstrated excellent 1-month test–retest reliability, and convergent and divergent validity [38].

Drug Abuse Screening Test (DAST-10): The DAST-10 [39] is a brief version of the 28-item DAST designed to identify drug-use related problems in the previous year. It has demonstrated good internal consistency and temporal stability in psychiatric samples; the DAST-10 discriminates between psychiatric outpatient with or without drug use disorders (with scores between 2-4; [40]). This measure consists of 10 yes/no questions. Responding yes to score > 2 of the questions is considered an indicator that the individual should seek further evaluation for problematic drug use behaviors.

Sick, Control, One, Fat, Food Questionnaire (SCOFF): The SCOFF eating disorder screen was developed by British researchers as a screening tool for eating problems in a primary care setting [41]. It consists of 5 yes/no questions that inquire about eating behaviors and beliefs or obsessions with eating. Responding yes to ≥ 2 of the five items is considered an indicator that the participant should seek further evaluation for eating concerns.

Life chart interview: This interview was adapted from published methodologies for obtaining life histories of important life events relevant to mental health [42]. The purpose of this interview will be to obtain qualitative information regarding the temporal sequence of important events throughout the participant's life, which will be used to inform the structured diagnostic interview (MINI) and provide a more thorough and holistic understanding of the factors that have contributed to the individual's mental health. The Life Chart will ask questions pertaining to what important events happened during specific intervals of the person's life, including: (1) birth (2) childhood to the start of elementary school, (3) elementary school, (4) middle school to leaving/finishing high school (5) after high school to age 25 (6) ages 25-35 (7) ages 35-45 (8) ages 45-55. For each interval, subjects will be asked questions about potentially important events in their life, such as whether they moved, had any births or deaths in their

family, sought mental health treatment, etc. From this comprehensive list, the 0-3 most significantly life events will be selected from each time interval and the participant will be asked to rate their mood level (on a scale of 1-5) for those events as well as on average for that time interval. Participants may be asked to be audio recorded during the life chart interview. The recordings will be strictly optional and refusal will not impact participants' inclusion in the study. The recorded interviews will be used to develop reliability ratings among clinicians at LIBR and development of an event timeline. A visual timeline displaying the most significant events identified throughout their lifetime and their mood ratings throughout this time will be constructed and provided to the participant upon request.

Mini International Neuropsychiatric Interview (MINI Version 6.0): This is a widely used structured interview that assesses diagnostic criteria related to psychotic disorders, mood disorders, substance use disorders, and anxiety disorders. This interview will be used to assess symptoms and diagnostic criteria related to Axis I disorders. The MINI has been validated with the Structured Clinical Interview for DSM Axis I Diagnoses (SCID) with an average Kappa statistic of 0.67 across all 22 diagnoses measured on the MINI, and an average inter-rater reliability of 0.97 across diagnoses [43].

Demographics and Psychosocial Form: This form will ask participants to indicate their age, date of birth, contact information, ethnicity, race, gender, marital status and family makeup, language use, average income, education level, occupational and/or student status, and health insurance.

Assessment of Medical and Medication History: This form was created specifically for the purposes of this study and will ask questions related to medical and mental health diagnoses the participants has received currently or in the lifetime. This will involve a review of systems (e.g., constitutional, cardiovascular, respiratory) to inquire about previous or current problems, questions concerning in inpatient stays/treatments, surgeries, medications, and psychotherapies. For each mental health treatment, they will be asked to rate their compliance with that treatment. At the follow-up session, this interview will be repeated, but only in reference to the year of the study.

Diagnostic Review and Verification of Clinical Information: After completing the Assessment and Medication History, Life Charting, and MINI structured interview, each participant's information will be presented to a board certified psychiatrist for review, verification, and potential revision. This includes a targeted review of medical and psychiatric history and current medications for the purpose of identifying and correcting any collection errors. Participants for whom the DSM diagnosis is questionable will be re-evaluated in person by a board certified psychiatrist for independent diagnostic verification.

Edinburgh Handedness Inventory (EHI): The EHI is a self-report laterality scale that estimates the degree of right or left hand dominance during everyday activities [44].

Customary Drinking and Drug Use Record (CDDR [45] with Michigan Negative Reinforcement Questionnaire (MNRQ [46]): The CDDR provides current (past 3 months) and lifetime measures of 4 alcohol and other drug-related domains, including level of involvement, withdrawal characteristics, psychological/behavioral dependence symptoms, and negative consequences. The measure has been found to have good internal consistency, test-retest reliability, and construct validity [45]. The MNRQ was originally developed to assess beliefs about positive and negative consequences of smoking specifically and was found to have good reliability and validity in relation to diagnostic measures of nicotine dependence [47]. This measure has subsequently been adapted for use related to other substances of dependence and will be administered along with the CDDR in the current study to obtain measures of alcohol and drug use as well as participant beliefs concerning the consequences of that drug use.

Tulsa Head Injury Screen (THIS): The THIS is a questionnaire that asks participants about their history of head injuries and loss of consciousness.

Family History Screen (FHS): The FHS is a questionnaire that asks about the psychiatric history of the participant's family members, including biological parents, siblings and children.

Columbia-Suicide Severity Rating Scale (C-SSRS): The C-SSRS is a tool used to determine the presence of suicidal ideation or behavior in a participant [48].

Wong-Baker FACES Pain Rating Scale: This questionnaire is used to assess the current degree of physical pain being experienced by the participant [49].

Self-Report Measures

State-Trait Anxiety Inventory (STAI): This is a widely-used psychometric instrument designed to assess an individual's anxiety proneness. This measure has both a "state" subscale meant to measure temporary anxiety symptoms and a "trait" subscale meant to measure more long-standing anxiety proneness. Each subscale consists of 20 items using 4-point scales ("not at all" to "almost always"). The STAI is a validated measure with good internal consistencies for both subscales and has high test-retest reliability for the trait subscale and low to moderate test-retest reliability for the state measure [50].

Anxiety Sensitive Index (ASI-3): This instrument includes 18 items designed to measure the fear of arousal-related sensations, specifically along the dimensions/subscales of Physical, Cognitive, and Social Concerns. Each item is answered on a scale of 0-4 ("very little" to "very much"). The ASI-3 has been found to have adequate performance on several measures of reliability and validity [51].

Quick Inventory of Depressive Symptomatology (QIDS-SR): The QIDS-SR is a self-report 16 item assessment of the severity of depressive symptoms [52].

Simplified Nutritional Appetite Questionnaire (SNAQ): The SNAQ is a reliable tool with appraisal questions that focus on appetite and evaluating weight loss. [53]

Ruminative Responses Scale (RRS): This instrument is used to measure dispositional tendencies to ruminate in response to negative affect. It consists of 22 questions concerning how they respond to sad mood, which are focused on the self, on one's symptoms, and on the possible causes and consequences of the mood state (i.e., "Think 'why do I have problems other people don't have'?"). Responses are rated on a 4-point scale (e.g., 1 =almost never respond in this way; 4=almost always respond in this way). The RRS has three factor-analytically derived

subscales, including depression, brooding, and reflection. The RRS has been found to have good test–retest reliability (.67) and satisfactory convergent and predictive validity [54, 55].

Traumatic Events Questionnaire (TEQ) – Civilian Version: The Traumatic Events Questionnaire (TEQ) [56], assesses 11 specific traumatic events: (1) combat, (2) large fires/explosions, (3) serious industrial/farm accidents, (4) sexual assault, rape (forced unwanted sexual activity), (5) natural disasters, (6) violent crime, (7) adult abusive relationships, (8) physical/sexual child abuse, (9) witnessing someone being mutilated, seriously injured, or violently killed, (10) other life threatening situations, and (11) violent or unexpected death of a loved one. Two nonspecific questions, "other event" and "can't tell," complete the scale. Individuals are asked to indicate the frequency, severity (on a 7-point scale), and age at the time of the event. The scale has been found to have very high reliability (.91) and has been found to relate to PTSD, anxiety, and depressive symptoms [56].

Childhood Trauma Questionnaire, Short Form (CTQ-SF): This instrument is used to screen adolescents and adults for a history of child abuse and neglect. The CTQ has five subscales: (1) Physical abuse, (2) Sexual abuse, (3) Emotional abuse, (4) Physical neglect, and (5) Emotional neglect. The CTQ will be used to identify traumatic childhood conditions characteristic of the negative valence domain. The CTQ consists of 28 items which are rated on a 5 point scale (1=never true; 5=very often true). The full CTQ has been found to have good reliability and validity and the CTQ –SF was found to have good validity in reference to the full version [57].

Positive and Negative Affective Schedule- State/Trait (PANAS) [58]: The PANAS is a widely used measure comprising 20-items assessing activated forms of PA and NA using 5-point scales (1 = very slightly/not at all, 5 = extremely). To assess trait PA and NA, participants will be asked to respond according to how they have felt "during the past week". State PA and NA will be asked by asking participants to rate how they feel “right now (that is, at the present moment)”. The PANAS has high internal consistency and temporal stability (trait version). Correlational data support its convergent and discriminant validity. Confirmatory factor analyses support the construct validity of the PANAS.

Behavioral Inhibition and Activation Scales (BIS/BAS): The behavioral inhibition and activation scales (BIS/BAS) include 20-items assessing dispositional BIS and BAS sensitivities (i.e. avoidance and approach motives), which are hypothesized to reflect the negative and positive valence systems, respectively. Items are rated on four-point scales (1 = strongly disagree; 4 = strongly agree). The BAS has three subscales (Drive, Reward Responsiveness, and Fun Seeking); however, factor analyses support a single higher-order factor. The BIS/BAS has good test-retest reliability. Correlational data support the relative orthogonality and convergent, discriminant, and predictive validity of the subscales [59].

Temporal Experience of Pleasure Scale (TEPS): The TEPS is a recently developed measure of anticipatory pleasure and consummatory pleasure. It has 18 items, each of which are rated on a 6 point scale (e.g., 1=very false for me; 6=very true for me). Initial investigations with this measure indicate good validity and independence of the two subscales (anticipatory and consummatory; [60]).

UPPS Impulsive Behavior Scale (UPPS): The UPPS [61] was designed to measure impulsivity across dimensions of the Five Factor Model of personality. The scale has 45 items that use a 4-point scale, e.g., 1=; 4=) and has 4 subscales, including Premeditation (lack of), Urgency, Sensation Seeking, and Perseverance (lack of). The subscales have been shown to have good internal consistencies (.82-.91; [61]) and the measures has been shown to distinguish between subgroups of psychopathology compared to control groups [62].

Snaith-Hamilton Pleasure Scale (SHAPS): This instrument is used to measure hedonic capacity. It consists of 14 items, rated on a 4-point scale (1=Definitely Agree; 4=Strongly Disagree). This instrument has been found to have excellent internal consistency and adequate convergent and discriminant validity [63].

Interpersonal Reactivity Index (IRI): The IRI was developed to measure empathy, defined as the "reactions of one individual to the observed experiences of another". This is a 28-item measure, each rated on a 5-point Likert scale (1="Does not describe me well"; 5="Describes me very well"). The measure has 4 subscales, each made up of 7 different items. These subscales include Perspective Taking, Fantasy, Empathic Concern, and Personal Distress. Good internal

consistency. The scale has also been shown to have good construct validity with related measures [64, 65].

Big Five Inventory (BFI): The BFI measures an individual on the Big Five Factors (dimensions) of personality [152], which include (1) extraversion versus introversion, (2) agreeableness versus antagonism, (3) Conscientiousness vs. lack of direction, (4) neuroticism vs. emotional stability, (5) openness vs. closedness to experience. This measure has 44-items, each of which are rated on a 5-point scale (1=disagree strongly, 5= agree strongly). This measure has been shown to have high internal consistency, test-retest reliability, and good convergent and divergent validity with other Big Five measures [66].

Toronto Alexithymia Scale (TAS-20): The TAS is one of the most commonly used measures of alexithymia, or the difficulty identifying and describing emotions. This is a 20-item measure, with each rated on a 5-point scale (1=strongly disagree, 5=strongly agree). There are three subscales, including (1) Difficulty Describing Feelings, (2) Difficulty Identifying Feeling, and (3) Externally-Oriented Thinking. The TAS-20 has been shown to have good internal consistency (.81), test-retest reliability (.77), and adequate convergent and concurrent validity [67, 68].

Multidimensional Assessment of Interoceptive Awareness (MAIA): This measure was recently developed to measure trait interoceptive body awareness. It consists of 32 items, each rated on a 6-point scale (0=never, 6=always). There are 8 subscales, including: (1) Noticing, (2) Not-distracting, (3) Not-worrying, (4) Attention Regulation, (5) Emotional Awareness, (6) Self-regulation, (7) Body listening and (8) Trusting. The measure was found to have good measures of internal consistency on each subscale and showed adequate construct validity with other, related measures of emotional processing anxiety, and body awareness [69].

Three Factor Eating Questionnaire (TFEQ): The TFEQ was developed to measure three dimensions of human eating behavior: cognitive restraint of eating, disinhibition, and hunger. This is a 51-item measure, including 36 items with yes/no responses, 14 items on a 4-point scale (1=unlikely; 4=very likely), and one item of restraint on a 6-point scale (0="eat whatever you want, whenever you want"; 5="constantly limit food intake, never give in"). A subscale score is calculated for each of the three dimensions of human eating behavior. Cognitive Restraint is

designed to measure control over food intake. Disinhibition measures loss of control over eating. The Hunger scale concerns subjective feelings of hunger and food cravings. The TFEQ has been found to have high test-retest reliability and internal consistency, and adequate construct validity [70-72].

Eating Disorders Diagnostic Scale (EDDS): The EDDS [73] measures the presence of anorexia nervosa, bulimia nervosa and binge eating disorder. It was developed as a self-report measures based on the Eating Disorder Examination (EDE) and the eating disorder module of the Structured Clinical Interview for DSM-IV. The EDDS provides both full and subthreshold diagnoses as well as a continuous symptom composite score. It consists of 22 items, 4 of which are on a 6-point scale (1=not at all; 6=extremely), 9 of which are yes/no questions, 6 items that ask for frequency of events (e.g., episodes of uncontrolled eating) over the week or month; and 3 remaining questions asking for height, weight, and number of missed periods over the past 3 months. The EDDS was shown to have good test-retest reliability, internal consistency, and convergent validity with other eating-pathology scales [73]. Research has shown it to be sensitive as a screening measure in detecting change with eating disorder treatment and is predictive of the development of eating disorder symptoms and depression [74].

International Physical Activity Questionnaires (IPAQ): The IPAQ is used to obtain internationally comparable data on health-related physical activity. Extensive reliability and validity testing has been undertaken in 12 countries (14 sites) across 6 continents since 2000. The short, self-administered format, for use with young and middle-aged adults, will be utilized – which has been shown to have adequate validity and reliability [75].

World Health Organization Disability Assessment Schedule (WHODAS): The WHODAS (12-item version) is a generic assessment instrument for health and disability, and covers 6 domains: (1) Cognition (understanding & communicating), (2) Mobility (moving & getting around), (3) Self-care (hygiene, dressing, eating & staying alone), (4) Getting along (interacting with other people), (5) Life activities (domestic responsibilities, leisure, work & school), and (6) Participation (joining in community activities). The WHODAS produces standardized disability levels and profiles, is applicable across cultures in adult populations, and has a direct conceptual link to the International Classification of Functioning, Disability and Health (ICF) [76].

World Health Organization Health and Work Performance Questionnaire (HPQ): The WHO HPQ is a 9-item questionnaire to evaluate absenteeism and presenteeism in the workplace as indirect costs of illness. The instrument includes questions regarding days (full or in part) of work missed due to personal physical or mental health, days of work missed for other reasons, arriving early or late to work or working on a day off, hours worked in the past 4 weeks and self-evaluations of job performance recently, over the past year, and in comparison to other employees [77] [78].

PROMIS® (Patient Reported Outcome Measurement Information System) Measures (http://www.nihpromis.org; [79, 80]): PROMIS is a U.S.-based cooperative group of research sites and centers of excellence, funded by NIH, and convened to develop and standardize patient outcome measures across studies and settings. The PROMIS measures were developed using item response theory and calibrated on a sample of 21,133 people, with the aim of providing highly reliable, precise measures of patient–reported health status for physical, mental, and social well–being. Most question banks utilize a 7-day recall period and five response options (e.g., 1=Not at all, 5=very much). All instruments developed to be used with computer adaptive testing (CAT) to reduce patient burden. With CAT, the specific construct item that best distinguished between individuals in their test populations is administered first. Based on the individual's response to this item, the computer picks what question will be administered next, and so on, until a reliable estimate of their total score on that construct can be determined. With this method, an average of 5 items is administered for each PROMIS construct listed, thus taking an estimate 1 minute or less to complete. The instruments have been reported to have good reliability and validity [79, 80].

Behavioral Tasks

Bandit Task*:* This task is included to apply Bayesian computational approaches that quantify how individuals switch between an "exploration" and "exploitation" strategy. Subjects have to sample from different choice options with unknown probabilities of success/failure with the goal of maximizing success. The optimal strategy is to start by trying all available options (exploration) to gauge the rate of success of each option, and to switch relatively early to only selecting the option with the highest likelihood of success (exploitation). Participants will

perform a total of 20 three-armed bandit games with a known number of trials (i.e., token) per game. For each game, participants will have 16 tokens (stacked in the middle of the screen) and will have to assign each token to one of three lotteries of their choice (white panels on left, right and middle of the screen). After placing each token, they will earn 1 point if the token turns green or zero points if the token turns red. Each token decision will last about 2 sec. After the button press, the chosen lottery is highlighted for 250ms, after which the token turns green or red to reveal the decision outcome. Participants will be instructed to find the most rewarding lottery and maximize the points earned in each game. Participants are paid an additional $5 or $10 based on the performance on this task.

Change Point Detection Task: For each trial, subjects will attempt to locate a target stimulus in one of three possible locations. The target stimulus consists of a patch of dots, which are predominantly moving in one direction. The other two locations have distractors with dots moving in the opposite direction. However, at the beginning of the trial, the patches of dots are hidden by white circles, which initially appear in the three locations. The subject first selects a location in which to see a patch of dots; a button press indicates the location of choice. The subject is then shown the patch of dots at the selected location, and asked to determine whether it is the target or the distractor. If the subject indicates that the patch is the target, the trial ends. If the subject believes the patch is a distractor, the subject can then indicate a second location to view, and be shown the patch of dots corresponding to the new location. The trial continues in this manner until the subject chooses the patch of dots which is believed to represent the target location. The position of the target location on each trial is determined by a probability distribution, such that one location is most likely to contain the target. It is therefore possible for the subject to learn over several trials which location is most likely to contain the target. However, at random intervals, the probability distribution will change, and a new location will become most likely to contain the target. The subject will then have to update their beliefs about the most likely location in which to locate the target. The experiment consists of 3 blocks with 60 trials per block. Prior to the experimental blocks, the subject will complete practice blocks until accuracy exceeds a certain threshold. Additionally, there is one block of 20 trials where all locations have equal probability that is used as a

baseline measure for response time. Response time and learning rate over time with each target location are the main variables of interest. Participants are paid an additional $5 or $10 based on the performance on this task.

Move-Go and Speed-Stop Task: Driving, as a common real-time motor task, is determined by both motivational factors (safety, time, etc.), and perceptual-motor limits (perceptual delay, motor delay, etc.). It has been shown that people with emotional disorders have impaired driving performance. For example, there have been growing evidence show that depression increases the odds ratio for car accidents and reduces driving performance in a driving simulator. It also has been shown that mood (influenced by music) can impact driving behavior in healthy population. Thus we propose to use a simulated driving task to collect behavioral data. The driving task has two separate components. The Move-Go component is used to measure perceptual and motor speed. In it, subjects are asked to attend to a car presented at the bottom of the screen. As soon as they perceive that the car has started to move, subjects are to move the joy stick all the way forward as quickly as possible. In the Speed-Stop component, subjects are instructed to drive a virtual car on a computer screen from an initial position to a stop sign as quickly as possible and stop as close to the stop-sign as possible without crossing the stop-sign, by pushing or pulling a joystick to control the velocity of the car. Each trial has a fixed time-window of 10 seconds. The car has a linear dynamic system, in which velocity is controlled by joystick position ($dXt = AXtdt + BUtdt$, in which Xt = [car position, car velocity], Ut = control action (car velocity based on joystick position), A = [0 1; 0 -.35], B = [0; 0.5]). This task will be used to estimate each individual's motivational component (goal state, accuracy/effort ratio) using computational models.

Implicit Approach Avoidance Task (AAT): Purpose: This task is designed to assess automatic action tendencies to approach or avoid positive, negative, and neutral stimuli [81]. Description: In this task, participants are asked to respond to a series of cues conveying positive, negative, or neutral emotional information (e.g., happy, angry, disgusted, neutral faces) by either pulling (approach) or pushing (avoidance) a joystick towards or away from themselves. Participants will see a picture in the center of the screen framed by either a blue or a yellow border. They will be instructed to pull the joystick towards themselves when the border is one color and to

push the joystick away when the border is the other (counterbalanced across subjects). Pushing the joystick results in the picture zooming out and pulling the joystick results in the picture zooming in, thereby creating the visual impression that the pictures are coming closer or moving away. Reaction times are calculated based on the duration from the time the picture appeared on the screen to the time it disappeared. An approach bias score is computed by subtracting each participant's mean response latency in the pull condition for a given stimulus type from their mean response latency in the corresponding push condition (e.g., positive faces-push minus positive faces-pull). The AAT is a well-established measure of implicit approach/avoidance behavioral tendencies [82].

Approach-avoidance conflict task (AAC): This computer-based task is designed to examine decision-making in the context of affective risk. For this task, the participant is presented with a series of decisions between two different outcomes. Each outcome is associated with either a positive or negative valenced image/sound pair (IAPS and IADS), and some amount of point or gains. The participant is not able to select with certainty one outcome over the other. Instead, only the probability of the two outcomes is chosen, in the range from 10-90%, depending on the subject's stated preference for the two outcomes on a 9 point scale. The standardized IAPS and IADS stimulus sets have been used extensively in emotion research and are reliable elicitors of affective arousal [83, 84]. Conflict trials are those in which a negative affective image is combined with point rewards, while the positive affective image is combined with no point rewards. There are three levels of conflict (2-point, 4-point, and 6-point). The main outcome variables of the task are: (1) mean approach behavioral for the different condition types (conflict, approach-only, and avoid-only). Before and after the task, participants rate their mood in terms of pleasantness, unpleasantness, and overall intensity on a visual analogue scale (VAS). After the task, participants complete a 14-item questionnaire asking questions about their experience of the task (i.e., "Overall, this task was enjoyable"), rating each item on a 1-7 Likert scale. This measure was originally developed by Dr. Robin Aupperle [85]. This task takes approximately 20 minutes to administer.

Modified Probe Detection Task (MPDT): Attentional bias for positive and negative information will be measured using a version of the modified probe detection task [86]). Each trial consists

of the identification of a cue location, brief presentation of a cue at that location (a small line oriented either horizontally or vertically), presentation of a pair of images (one representational, one non-representational), and presentation of a target, which is another line in either of two locations and is either horizontal or vertical. This target is presented until the participant responds, indicating whether the target is of the same or different orientation from the cue. Representational [86] stimuli will comprise IAPS images taken from positive, negative, or neutral valence sets. Each representational image is paired with one non-representational image, taken from a set of images of abstract art. Participants are presented with a total of 192 trials: 64 from each of positive, negative, and neutral images. The following traits are balanced across trials: representational image location, cue location, cue orientation, target location, target orientation, image duration (500 or 1000ms). The main outcome measures are the positive and negative engagement and disengagement biases [87].

Emotional Reactivity: This task consists of the presentation of 8 positive, 10 neutral, and 8 negative images. Each trial begins with a 20-26s fixation period, followed by presentation of one image for 6s. After each image, the participant makes valence and arousal ratings on a 7 point scale. During image presentation and sometimes during fixation, participants receive a ~95DB 50ms white noise sound meant to elicit a startle response [88]. The main purpose of this paradigm is to provide a reliable and validated assessment of psychophysiological responses to emotional stimuli and startle-eliciting stimuli [89]. The collection of psychophysiological recordings will therefore be integral to this task specifically.

Heartbeat Tapping: This task will contain four 1 minute trials, during which the participant has their eyes closed and is tapping a vmeter device [90].

Cold Pressor Challenge: This task will have each participant immerse their left hand in a circulating pool of water cooled to 6 degrees Celsius. Participants will be asked to keep their hand in the water for as long as they can tolerate, providing a brief measure of pain/stress tolerance and emotional reactivity/regulation. During each immersion participants will provide real-time ratings of their degree of pain unpleasantness/discomfort using the vmeter. The Cold

Pressor paradigm is the gold standard which has been repeatedly used over the past century to safely induce transient states of intense pain [91, 92]. Maximum trial length will be 2 minutes.

Breath Hold Challenge: This task will have participants undergo 2 expiratory breath holds, providing a brief measure of interoceptive distress tolerance and carbon dioxide sensitivity. The maximum trial length is 1 minute, and there will be a 2-minute rest between trials. Participants are instructed to hold their breath for as long as they can tolerate following a normal (not forced) exhalation. The duration of each breath hold will be calculated starting from the moment when they begin exhaling and ending the moment they start inhaling again.

Psychophysiological Recordings: Heart rate (ECG), respiration (RSP), skin conductance (SCR), and eye blink electromyogram (EMG) will be recorded continuously during each the behavioral tasks described above, using BIOPAC instrumentation (Lehigh, Pennsylvania). These physiological indices will also be measured during a 5-minute passive viewing task where subjects are presented with a slideshow of images of different flowers. The images are not expected to affect the physiological recordings, so data from this task are used as a physiological baseline to compare to the behavioral tasks. Measuring these indices during the behavioral tasks listed above will not add any time to the tasks themselves, but should take approximately 10-15 minutes for setup (i.e., to attach all electrodes, respiration belt, etc.).

BIOPAC Systems provides both hardware for collection of these measures (BioPac MP150 system) and software (AcqKnowledge software) for analyzing these measures. All of these measures are commonly used in emotional processing research and are relatively non-invasive. The use of all of these measures concurrently allows for a more thorough understanding of sympathetic and parasympathetic nervous system influences on physiological responses to negatively and positively-valenced stimuli, interoceptive stimuli, cognitive processing and decision-making.

Facial Expressions: Advances in computer vision and machine learning over the past 15 years have led to the emergence of technology for automatic analysis of affective behavior [93]. During this time, the Machine Perception Laboratory at UCSD (MPLab) has focused on development of systems for automatic analysis of facial behavior, including audio-visual speech

recognition [94-96] and recognition of facial expressions [95-99]. The output of the face detector is scaled to 90x90 and fed directly to the facial expression analysis system. First the face image is passed through a bank of Gabor filters at 8 orientations and 9 scales (2-32 pixels/cycle at 0.5 octave steps). The filterbank representations are then channeled to a classifier to code the image in terms of a set of expression dimensions. Research at the MPLab has demonstrated that performing feature selection on the Gabor filters prior to classification enhances both speed and accuracy. This approach combines feature selection based on Adaboost with feature integration using support vector machine. *Automatic Facial Expression Analysis*: A video camera will record each participant during the behavioral tasks described above in order to permit coding of facial expressions. Automatic facial expression analysis will be conducted by the EMOTIENT [100], software developed and validated by our collaborators at the Machine Perception Laboratory at UCSD (MPLab). EMOTIENT analysis corresponds to the well-validated Facial Action Coding System (FACS [101, 102]), a comprehensive method to objectively code facial expressions. EMOTIENT automatically codes the intensity of 26 component facial movements referred to as action units (Aus).

Neuropsychological Tasks

Wide Range Achievement Test (WRAT-4 reading): The WRAT-4 is an individually administered test of reading designed to measure general academic competence. The main variable of interest will be the total words pronounces correctly [103].

Delis-Kaplan Executive Function System (D-KEFS) Color-Word Inhibition Test: The D-KEFS Color-Word Inhibition Test is designed to assess verbal response inhibition and attentional switching. Participants are asked to name patches of colored ink (Color Naming subtest), read color-related words (Word Reading subtest), or to name the ink that color-related words are written in (Inhibition subtest). The speed at which participants complete the task and the number of mistakes made during completion are recorded. The main variables of interest for this study are the total time to complete the word reading, color naming, inhibition, and inhibition/switching subtests [104].

Delis-Kaplan Executive Function System (DKEFS) Verbal Fluency: This test is meant to measure information retrieval that is under conscious cognitive control and presumably an aspect of executive functions. On each of six one-minute trials, the examinee is asked to say as many distinct words as possible that meet a certain criterion. For the first three trials, the words must begin with a particular letter, for the next two trials, the words must belong to a particular semantic category, and for the last trial, words must alternate between two semantic categories. The main variable of interest is the total number of words correctly identified for the letter subtests and the semantic category subtests [104].

Wechsler Adult Intelligence Scale (WAIS-IV) Digit Span: This sub-test of the WAIS-IV is used to assess attention and working memory and requires participants to repeat a series of numbers in forwards and backwards order (Digit Span). The accuracy of their responses is recorded. The main variables of interest are the total score forward and backward [105].

Finger Tapping Test (FTT): The FTT is a neuropsychological test that examines motor functioning, specifically, motor speed and has also been shown as a sensitive measure of testing effort [106]. The main variables of interest are the average number of taps with the index finger per 10 seconds for dominant and non-dominant hands.

WAIS-IV Digit Symbol Coding [105] The Digit Symbol is a neuropsychological test of visuomotor speed and working memory. The test requires individuals to match a symbol to a number according to a key at the top of the page. The main variable of interest will be the number of symbols matched in the time limit (90 seconds).

California Verbal Learning Test (CVLT-II): The CVLT-II is used to evaluate verbal learning and memory. The CVLT consists of a list of 16 words from four semantic categories that is presented orally for five immediate recall trials (List A). Subsequent to the five learning trials of List A, a second 16-item word list (List B) is presented once. Free- and category-cued-recall trials of List A follow the immediate free-recall of List B. After a 20-min delay, free recall, cued recall, and a recognition trial of List A occur. The recognition trial contains the 16 target items from the first list along with 28 distractor items. During the recognition trial, the examiner presents each of the 44 items orally to the participant, who indicates whether or not the item was from the first

word list. The main variables of interests for this study are the immediate recall from Trials 1-5 List A, Immediate and Delayed free recall and cued recall of List A. In addition, as most patients (even those with neurological disorders) are expected to score above chance on Recognition, this test will also be used to assess whether participants are putting in sufficient effort towards testing.

Functional MRI Tasks

Reward Processing Task: To measure behavioral and neural responses to rewards and losses, participants will complete the monetary incentive delay task (MID), a well-established measure of reward processing [107, 108]. This task dissociates anticipatory and consummatory phases of reward processing and has been shown to reliably activate brain regions implicated in regulating approach-related response tendencies and reward sensitivity (e.g., ventral striatum). On each trial, participants are given a cue indicating potential reward (circle), loss (square), or no reward/loss (circle or square). In order to receive a specified reward or avoid a loss, participants are required to press a button within a certain duration of time (adapted for individual participant reaction times) following presentation of a white square (target cue). Task difficulty, based on reaction times collected during a practice session, is set such that each participant should succeed on ~66% of trials. The degree of potential reward or loss is varied on three levels indicated by the number of horizontal lines in a cue, i.e., one line indicates the lowest reward value (no reward), two lines an intermediate reward, and three lines the highest reward. For the MID task, participants can gain or lose points and earn an average of $30. The primary outcomes of interest will be: (1) anticipation of reward vs. no-reward, (2) receipt of reward outcomes vs. no-reward outcomes; (3) anticipation of loss vs. no-loss, and (4) receipt of loss outcomes vs. no-loss outcomes. The Monetary Incentive Delay Task will take about 18 minutes to complete.

Fear Conditioning Task: The fear conditioning task is based closely on the task successfully used by [109] to uncover neural bases of fear conditioning associated with trait anxiety [109]. The stimuli will consist of two neutral, non-social, abstract images as conditioned stimuli (CS), presented for 2 seconds at a time. Which image is the CS+ (paired with the unconditioned

stimulus (US) during fear acquisition) and which is the CS- (never paired with the US) will be counter-balanced across participants. The US will be a 1s scream beginning 500ms after image onset. In the 9-15 seconds between CS image presentations, participants will be engaged in a continuous performance task requiring a right or left button press in response to right or left facing arrows. This serves to increase engagement and attention in the inter-trial interval. The task will consist of three components: a brief familiarization period, fear acquisition, and fear extinction. First, the *familiarization phase* (2.5 minutes) involves five presentations of each CS with no instances of the US to provide a baseline and allow familiarization to the scanner environment. Next, the *acquisition phase* will be broken into two runs of 8 minutes each. Each run will consist of 15 presentations of the CS- and 20 presentations of the CS+: five with (CS+ paired) and 15 without (CS+ unpaired) the US. This follows Sehlmeyer et al. [110] and allows for an equal number of trials to be included in the analysis (the CS+ paired trials will be excluded from analysis so as to not confound processing of the CS+ with reactivity to the US). Finally, the *extinction phase* will involve 25 presentations of each CS with no instances of the US. Participants will rate their valence, arousal and anxiety level to each CS at four times during the task: after familiarization, halfway through acquisition, after acquisition, and after extinction. Trials will be presented in a fixed, pseudo-randomized order, constrained so that no more than two identical trials occur in a row.

Stop Signal (Inhibition) Task: At the onset of each trial, either an 'X' or an 'O' appears on a black background back-projected to the magnetic resonance imaging room. Participants are instructed to press, as quickly as possible, the left button when an 'X' appeared, and the right button when an 'O' appeared. They are also instructed not to press either button whenever they hear a tone during a trial (stop trials). Each trial lasts 1300 ms and each trial is separated by 200-ms inter-stimulus intervals (blank screen; see [111]). Individual response latency is used to denote the period of inhibitory processing and provide a subject-dependent jittered reference function. Participants perform six blocks of the task, each containing a total of 48 trials (12 stop and 36 nonstop trials in each block). Trial order is pseudo-randomized throughout the task and counterbalanced. Prior to scanning, participants perform the stop task in a behavioral testing session in order to determine their mean reaction time (RT) from 'X' and

'O' stimuli onset. Such individual measures are used to determine the stop signal delay (SSD) for the six different stop trial types. Specifically, stop signals are delivered at 0 (RT-0), 100 (RT-100), 200 (RT-200), 300 (RT-300), 400 (RT-400), or 500 (RT-500) ms less than the mean RT after the beginning of the trial, thus providing a range of difficulty level.

Interoceptive Attention Task: During this task, subjects alternate between two conditions: the interoception condition and the exteroception condition. During the interoception condition, the word "HEART" or "STOMACH" is presented on the screen and subjects are instructed to focus their attention on interoceptive sensations from that organ. For example, upon seeing the word "HEART", subjects focus on how intensely they can feel the sensation of their heart beating. During the exteroception control condition, the word "TARGET" is presented in the middle of the screen and the color of the word alternates from black to a lighter shade of gray every second. The subjects are instructed to focus their attention on the intensity of these color changes. Each task condition is presented in 10-second blocks, and half of the blocks are followed immediately by a 5-second response period during which the subject uses a visual scale (1-to-7) to rate the intensity of interoceptive sensations or exteroceptive color changes experienced during the preceding trial. Blocks are often separated by a variable inter-stimulus interval, during which subjects look at a fixation mark. Each run of the task begins with a 10-sec initial fixation period and ends with a 10-sec final fixation period. Subjects will perform 2 scanning runs, each lasting 360 seconds (including initial and final fixation periods).

MRI, EEG and fMRI Data Analysis

EEG-fMRI

Residual ballistocardiac artifacts in the EEG signals will be removed using the independent component analysis method. The de-noised data will be subsequently band-pass filtered from 1 Hz to 70 Hz, downsampled to 250 Hz, and re-referenced to the common average reference. For the EEG signals recorded outside the scanner, data will be similarly band-pass filtered from 1 Hz to 70 Hz, downsampled to 250 Hz, and re-referenced to the common average reference.

Other types of EEG-informed fMRI analyses include: EEG band-pass correlation analysis with fMRI data (Fast Fourier transformation will be used to estimate EEG δ (1–3 Hz), θ (4–7 Hz), α (8-13 Hz), and β (13–30 Hz) frequency band spectral power, and its temporal changes during fMRI) [112], EEG microstate analysis in time and spatial domain (EEG temporal independent microstates and their spatial representation correlates with slow hemodynamic activity in brain resting state networks and their spatial maps) [113, 114], EEG-asymmetry analysis, and EEG-coherence analysis (e.g. quantify and correlate changes in EEG alpha band asymmetry and/or EEG coherence with fMRI data [115]), and behavioral measures [116].

fMRI Pre-Processing

For task fMRI analysis, a multivariate regressor approach will be used to relate changes in echo planar imaging (EPI) intensity to differences in task characteristics. The aE-REMCOR motion will be corrected on a slice by slice basis. fMRI data will be co-registered using a 3D-coregistration algorithm. Motion parameters will be obtained across the time series for each subject. Subjects will be excluded if the average in any one of these six parameters exceeds 2 standard deviations from the mean or if mean displacement exceeds the size of the voxel (4 mm). This assures that differences at group-level are not due to differences in movements during scanning. Motion parameters will be used as regressors to adjust EPI intensity changes due to motion artifacts. This has been shown to increase power in detecting task-related activation. All slices of the EPI scans will be temporally aligned following registration to ensure different relationships with the regressors are not due to the acquisition of different slices at different times during the repetition interval.

Resting State Pre-Processing

The six motion parameters from the image registration process will be used to construct a time series reflecting the Euclidean normalized derivatives of the motion, and any time point, plus one prior, where the derivative is greater than 0.2 or where more than 10% of brain voxels are considered as outliers will be censored. Nuisance variables will be regressed out of the normalized data and include the de-meaned motion parameters and their derivatives, the

average signal taken from a local eroded local white matter mask, the first 3 principal components of the lateral ventricles, and terms reflecting baseline drift.

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Supplementary Table 1. Quarterly Follow-up Assessments

QUARTERLY FOLLOW-UP ASSESSMENTS	
Domain	Description
STANDARD SCALES	
Demographics	Demographics and Psychosocial Form (update)
History	Assessment of Medical and Medication History (update)
History	Life chart interview (update)
Substance Use	Customary Drinking and Drug Use Record (CDDR)
Depression	Quick Inventory of Depressive Symptomatology (QIDS-SR)
Eating Behavior	Simplified Nutritional Appetite Questionnaire (SNAQ)
Compliance	Medication Compliance
Compliance	Therapy Compliance
Disability	World Health Organization Disability Assessment Schedule
Presenteeism/Absenteeism	(WHODAS)
Suicidal Ideation	WHO Health and Work Performance Questionnaire (WHO HPQ)
Pain	Columbia-Suicide Severity Rating Scale (C-SSRS)
	Wong-Baker FACES Pain Rating Scale
PROMIS MEASURES	
Negative Valence	PROMIS Anxiety
Negative Valence	PROMIS Depression
Negative Valence	PROMIS Anger
Positive Valence	PROMIS/Neuro-QOL Positive Affect and Well-being
Cognitive	PROMIS Cognitive Abilities
Cognitive	PROMIS Cognitive General
Fatigue	PROMIS Fatigue
Sleep	PROMIS Sleep Disturbance
Sleep	PROMIS Sleep-related Impairment
Alcohol	PROMIS Alcohol Use
Alcohol	PROMIS Alcohol: Negative Consequences
Alcohol	PROMIS Alcohol: Positive Consequences
Alcohol	PROMIS Alcohol: Negative Expectancies
Alcohol	PROMIS Alcohol: Positive Expectancies
Nicotine	Nicotine Dependence
Nicotine	Coping Expectancies
Nicotine	Emotional and Sensory Expectancies
Nicotine	Health Expectancies
Nicotine	Psychosocial Expectancies
Nicotine	Social Motivations
Social	PROMIS Social Satisfaction DSA
Social	PROMIS Social Satisfaction Role
Social	PROMIS Ability to Participate Social

Social	PROMIS Emotional Support
Social	PROMIS Information Support
Social	PROMIS Instrumental Support
Social	PROMIS Satisfaction Roles Activities
Social	PROMIS Social Isolation
Physical	PROMIS Physical Function
Pain	PROMIS Pain Interference
Pain	PROMIS PAIN Behavior
Sex	PROMIS Global Satisfaction with Sex Life
Sex	PROMIS Interest in Sex Activity

Supplementary Table 2. One-Year Follow-up Session

ONE-YEAR FOLLOW-UP SESSION	
Domain	Description
DIAGNOSTIC AND DEMOGRAPHIC ASSESSMENT	
Diagnosis	MINI 6.0
Demographics	Demographics and Psychosocial Form (update)
History	Assessment of Medical and Medication History (update)
History	Life chart interview (update)
Substance Use	Customary Drinking and Drug Use Record (CDDR)
Compliance	Medication Compliance
Compliance	Therapy Compliance
Suicidal Ideation	Columbia-Suicide Severity Rating Scale (C-SSRS)
Pain	Wong-Baker FACES Pain Rating Scale
STANDARD SELF-REPORT SCALES	
Negative Valence/Interoception	Anxiety Sensitive Index (ASI-3)
Negative Valence	Ruminative Responses Scale (RRS)
Positive / Negative Valence	Positive and Negative Affect Schedule-Expanded Form (PANAS)
Depression	Quick Inventory of Depressive Symptomatology (QIDS-SR)
Positive Valence	TEPS anticipation/consumption/ pleasure
Arousal / Interoception	Multidimensional Assessment of Interoceptive Awareness
Eating Behaviors	Eating Disorders Diagnostic Scale
Eating Behaviors	Simplified Nutritional Appetite Questionnaire (SNAQ)
Physical Activity	International Physical Activity Questionnaire (IPAQ)
Disability	World Health Organization Disability Assessment Schedule (WHODAS)
Trauma	Traumatic Events Questionnaire (TEQ)
Absenteeism/Presenteeism	WHO Health and Work Performance Questionnaire
PROMIS MEASURES	
Negative Valence	PROMIS Anxiety
Negative Valence	PROMIS Depression
Negative Valence	PROMIS Anger
Positive Valence	PROMIS/Neuro-QOL Positive Affect and Well-being
Cognitive	PROMIS Cog Abilities
Cognitive	PROMIS Cog General
Fatigue	PROMIS Fatigue
Sleep	PROMIS Sleep Disturbance
Sleep	PROMIS Sleep-related Impairment
Alcohol	PROMIS Alcohol Use
Alcohol	PROMIS Alcohol: Negative Consequences
Alcohol	PROMIS Alcohol: Positive Consequences

Alcohol	PROMIS Alcohol: Negative Expectancies
Alcohol	PROMIS Alcohol: Positive Expectancies
Nicotine	Nicotine Dependence
Nicotine	Coping Expectancies
Nicotine	Emotional and Sensory Expectancies
Nicotine	Health Expectancies
Nicotine	Psychosocial Expectancies
Nicotine	Social Motivations
Social	PROMIS Social Satisfaction DSA
Social	PROMIS Social Satisfaction Role
Social	PROMIS Ability to Participate Social
Social	PROMIS Emotional Support
Social	PROMIS Information Support
Social	PROMIS Instrumental Support
Social	PROMIS Satisfaction Roles Activities
Social	PROMIS Social Isolation
Physical	PROMIS Physical Function
Pain	PROMIS Pain Interference
Pain	PROMIS PAIN Behavior
Sex	PROMIS Global Satisfaction with Sex Life
Sex	PROMIS Interest in Sex Activity
	Physio Setup
Computational - cognitive	Change Point Detection Task
	Regular Bandit Task
	Start / Stop Task (Driving)
Positive / Negative Valence	Implicit Approach / Avoidance Task
	Attentional Bias / Dot Probe Task
	Emotional Reactivity Task
	Baseline Task
	Approach Avoidance Conflict Task
Arousal / Interoception	Breath hold
	Heartbeat Tapping Task
	Cold Pressor
Neuropsychology	WRAT reading
	DKEFS Color-Word Inhibition
	DKEFS verbal fluency
	WAIS-IV digit span
	Finger Tapping Test
	WAIS-IV Digit Symbol Coding
	California Verbal Learning Test
Biomarker and Microbiome	Repeat baseline measures, except for stem cells and genetics

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract **Pages 1-2**	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale **Pages 3-10**	2	Explain the scientific background and rationale for the investigation being reported
Objectives **Pages 10-11**	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design **Page 12**	4	Present key elements of study design early in the paper
Setting **Pages 13, 27**	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants **Pages 11, 13, 25-26**	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables **Pages 10-13**	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement **Pages 13-19, supplementary materials**	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias **Pages 26-27**	9	Describe any efforts to address potential sources of bias
Study size **Page 25**	10	Explain how the study size was arrived at
Quantitative variables **Pages 20-25**	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods **Pages 20-25**	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants N/A	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data N/A	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data N/A	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results N/A	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses N/A	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results N/A	18	Summarise key results with reference to study objectives
Limitations **Page 3**	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation N/A	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability **Page 3**	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding **Page 28**	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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The Tulsa 1000: A naturalistic study protocol for multi-level assessment and outcome prediction in a large psychiatric sample

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The Tulsa 1000: A naturalistic study protocol for multi-level assessment and outcome prediction in a large psychiatric sample

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ABSTRACT

Introduction: Although neuroscience has made tremendous progress toward understanding the basic neural circuitry underlying important processes such as attention, memory, and emotion, little progress has been made in applying these insights to psychiatric populations to make clinically meaningful treatment predictions. The overall aim of the Tulsa 1000 (T-1000) study is to use the NIMH Research Domain Criteria (RDoc) framework in order to establish a robust and reliable dimensional set of variables that quantifies the positive and negative valence, cognition, and arousal domains, including interoception, to generate clinically useful treatment predictions.

Methods and Analysis: The Tulsa 1000 is a naturalistic study that will recruit, assess, and longitudinally follow 1,000 participants, including healthy controls and treatment-seeking individuals with mood, anxiety, substance use, and eating disorders. Each participant will undergo interview, behavioral, biomarker and neuroimaging assessments over the course of one year. The study goal is to determine how disorders of affect, substance use, and eating behavior organize across different levels of analysis (molecules, genes, cells, neural circuits, physiology, behavior, and self-report) to predict symptom severity, treatment outcome, and long-term prognosis. The data will be used to generate computational models based on Bayesian statistics. The final end-point of this multi-level latent variable analysis will be standardized assessments that can be developed into clinical tools to help clinicians predict outcomes and select the best intervention foreach individual, thereby reducing the burden of mental disorders, and taking psychiatry a step closer toward personalized medicine.

Ethics and Dissemination: Ethical approval was obtained from Western Institutional Review Board (WIRB) screening protocol #20101611. The dissemination plan includes informing health professionals of results for clinical practice, submitting results to journals for peer-reviewed publication, presenting results at national and international conferences, and making the dataset available to researchers and mental health professionals.

Trial registration number: NCT02450240

STRENGTHS AND LIMITATIONS

Strengths

- The study uses a comprehensive approach across multiple units of analysis for phenotyping.
- The study focuses on a dimensional psychopathology that cuts across traditional psychiatric diagnoses.

- The study utilizes novel statistical approches to identify and replicate latent constructs within a large and complex dataset.

Limitations

- The study does not include controlled treatment interventions.
- The study is a longitudinal observational study, which requires large numbers of participants to yield statistically significant results and may experience higher attrition rates over the course of the study compared to a cross-sectional study.
- The study recruitment aims to generate a representative sample of a local Midwestern community in the United States, including subsamples selected to represent the United States community at large, however the results may not be generalizable to individuals with mood, substance use and eating disorders in other regions of the US or worldwide due to factors such as access to and quality of healthcare or demographic, social or cultural differences.

INTRODUCTION

Mood [1] and anxiety [2] disorders are the most common form of mental illness and represent one of the biggest health issues worldwide, accounting for approximately $16 trillion in lost productivity or 25% of the global gross domestic product over the next 20 years [3]. Epidemiological data estimate the lifetime prevalence of Major Depressive Disorder (MDD) at about 18% and the 12-month prevalence at 7% [4]. Both MDD and anxiety disorders are associated with significant medical comorbidities [5] including substance use and eating disorders, which further exacerbate the cost and suffering associated with these disorders. The lifetime prevalence of eating disorders is comparatively lower at less than 3.5% [6], however, individuals exhibit extreme changes in body physique together with some of the highest mortality rates of all psychiatric disorders [7, 8]. Furthermore, most patients fail to remit or recover following treatment and up to 20% remain chronically ill [9-12]. Similarly, substance use disorders are among the most disabling conditions worldwide [13, 14]. Recovery includes abstinence [15, 16] and remission [17] but may not be adequately captured as an all-or-nothing process [18]. Recovery rates can differ across the primary drug of choice [19] and are highly nonlinear such that as many as 50% of treatment-seeking individuals relapse within a month of last use. The neural basis and behavioral changes associated with recovery are poorly understood because very few sufficiently powered, neurobiologically-based prospective, longitudinal studies have been conducted [20-25]. The heterogeneity of psychiatric disorders and the limited ability to identify broadly efficacious interventions have provided an impetus to utilize dimensional approaches to help delineate distinct syndromes that better reflect the underlying neurobiology [26].

Although neuroscience has made tremendous progress in understanding the basic neural circuitry that underlies important processes such as attention, memory, and basic emotion processing, little progress has been made in applying these insights to psychiatric populations in order to make clinically meaningful predictions. This may be because the current diagnostic system for mental disorders is based on statistically aggregated categories relying solely on verbal report and clinically observable behaviors [27]. Unfortunately, the connection between psychiatric disorders and their underlying neurobiology has been difficult to establish. The NIMH Research Domain Criteria (RDoC) framework was developed as a heuristic approach to better integrate pathophysiology with psychopathology [26]. The RDoC initiative highlights two important goals for this objective: (1) psychiatric studies should transcend traditional diagnostic groups in order to adequately capture the inherent heterogeneity of symptomatology, and (2) clinical neuroscience and advanced statistical approaches should be used to determine the relationship between different units of analyses (self-report, behavior, physiology, neural circuitry, genetics, and clinically relevant psychopathology). The Tulsa 1000 aims to address these needs by determining how biological and objective behavioral measures can contribute to improving assessment and treatment of mental illness.

The overarching goal of this study is to utilized a dimensional psychopathological framework focused on mood, anxiety, eating and substance-related dysfunctions to identify latent variables that generalize across units of analyses, i.e. that can connect symptoms with underlying circuit dysfunctions and molecular abnormalities. We aim to establish a robust and reliable dimensional set of variables that quantify the positive and negative valence, cognition, and arousal/interoception RDoC domains based on a latent variable approach [28-30]. Moreover, we aim to make these data sets available for other investigators for novel analytic approaches aimed to delineate the relationship between variation within a particular domain, e.g. severity of mood symptoms and network characteristics of resting state functuional magnetic resonance imaging. These variables will be used to determine whether (a) measures of each domain (across different units of analyses) consistently relate to one another, (b) they predict the progression of symptoms over time (including natural recovery or worsening of symptoms), (c) they predict response to independently-sought pharmacological or behavioral treatments, and (d) they can be used in subsequent computational models of mental health to gain a more fundamental understanding of the pathology and predict illness course and recovery.

Overview of RDoC domains

Positive and Negative Valence Systems

Affect, or the tendency to experience a given emotion, is often subdivided into two domains [31]. Positive affect is the experience of positive emotions, such as happiness, excitement, elation, and enthusiasm. Negative affect is the experience of negative emotions, such as anger,

resentment, sadness, anxiety, and fear. Positive affect and negative affect systems represent dimensions of psychopathology identified by the RDoC work groups [32, 33]. For example, high negative affect is common to anxiety and depression, [34-36] and comorbid anxiety and depression is associated with more negative affect than each disorder alone [37]. Low positive affect is relatively specific to depression, although there also is some evidence of low positive affect in social anxiety [34, 38]. In addition, psychophysiological and neurobiological data indicate that the negative affect system is closely tied to threat sensitivity whereas the positive affect system is closely tied to reward sensitivity. More detailed information on specific constructs of the positive valence system, including approach motivation, reward seeking and reward sensitivity and constructs of the negative valence system, including acute threat, potential harm are described in the Supplementary Materials.

Cognitive System

The major constructs that were considered by the RDoC committee on cognitive systems included: (1) *attention,* i.e. a set of processes that regulate access to capacity-limited systems, such as awareness, higher perceptual processes, and motor action; (2) *perception*, i.e. process(es) that perform computations on sensory data to construct and transform representations of the external environment to make predictions and guide action; (3) *declarative memory*, i.e. the acquisition or encoding, storage, consolidation, and retrieval of facts and events; (4) *language*, i.e. a system of shared symbolic representations of the world, the self and abstract concepts that supports thought and communication; (5) *cognitive control*, i.e. a system that modulates the operation of other cognitive and emotional systems, in the service of goal-directed behavior, when prepotent modes of responding are not adequate to meet the demands of the current context; (6) *working memory*, i.e. the active maintenance and flexible updating of goal/task relevant information (items, goals, strategies, etc.) in a form that has limited capacity and resists interference.

The T-1000 focuses primarily on two constructs within the cognitive system (a) *cognitive control* and (b) *attention*. Inhibitory control, the ability to suppress a prepotent action, is an important cognitive control process, and is hypothesized to be dysfunctional in individuals with substance use problems [39]. However, it is unclear how dysfunctional cognitive control is associated with continuing substance use, and how this affects relapse following a period of recovery from substance use. For example, prior investigations have shown inhibitory control deficits in stimulant dependent individuals and moderate correlations with drug use indices [40-45].

In this study protocol, we will combine Bayesian ideal observer model-based analysis with fast, event-related functional magnetic resonance imaging (fMRI) data, to investigate subtle behavioral and neural differences among the target populations. Bayesian ideal observer models have been widely applied to the study of choice in uncertain environments, and to

identify potential neural markers of the iterative processes of belief update underlying such models [46, 47]. Subsequent modeling studies have shown that such a framework is readily adapted to various aspects of executive function, including attentional and inhibitory control [48-51].

Arousal/Interoceptive System

Arousal is defined as a continuum of sensitivity of the organism to stimuli, both external and internal. Interoception refers to how the brain receives, processes, and integrates internal signals from the body to affect motivated behavior [52-54]. One important aspect of the arousal domain is the link to homeostatic drives and interoception. Different conceptualizations of interoception have included its definition as the state of the individual at a particular point in time [55], or as the sensing of body-related information in terms of awareness [56], or as the accuracy of the sensing process [57], or as a trait phenomenon [58]. It is therefore a multifaceted process operating across numerous physiological and neural organ systems [59, 60]. Interoception provides an anatomical framework for identifying pathways focused on modulating the internal state of the individual. The anterior insula is predominately activated by effortful cognitive processing, whereas the posterior region is mostly activated by interoceptive sensory signals [61]. The insula is thought to be the central nervous system hub for interoceptive processing. There is an emerging generalized view that the anterior cingulate cortex (ACC), among other functions, orchestrates approach or avoidance behaviors in response to particular internal body states that involve homeostatic perturbations [62]. This function of the ACC is supported by the strong functional [63] and anatomical [64] connections between the anterior insula and the ACC. Taken together, the insula and ACC receive information about the individual's current body state and use this information to predict future body states and select actions that will help maintain bodily homeostasis.

Based on the RDoC criteria described above, the primary units of analyses for the Tulsa 1000 study are: (a) symptoms, (b) paradigms / behavior, (c) physiology, (d) circuits, and (e) molecules. These units of analysis will be assessed via clinical and self-report interviews of past and current psychiatric symptoms, computational tasks of behavior and neuropsychology, biomarkers for genetics inflammation and the microbiome, and structural and functional neuroimaging . There are several new emerging areas that either provide opportunities to examine how individual domains are affected by biological influences other than the individual or have the potential to yield cellular models of diseases. Next, these other units of analysis are described further and specific examples are provided for the relationship to at least one of the diagnostic groups in the Tulsa 1000 study.

Microbiome

The human body can be considered a super-organism composed of 10 times more microbial cells than our body cells. A meta-genomic study of the human microbiome has shown that microbial cells contain 150 times more genes than our own genome and make up an extraordinarily diverse set of over 1000 bacterial species [65]. Our understanding of the vast collection of microbes that live on and inside us (*microbiota*) and their collective genes (*microbiome*) has been revolutionized by culture-independent 'metagenomic' techniques and DNA sequencing technologies. Gut microbiota play an important role in health and disease and can be considered a 'microbial organ' [66]. Each individual's microbiota shows significant variability across body habitats and time, which may provide clues as to how microbiome changes cause or prevent disease [67].

The interaction between microbiota and human organs has been extended recently to brain-gut interactions [68]. The brain can influence enteric microbiota indirectly, via changes in gastrointestinal motility and secretion, and intestinal permeability, or directly, via signaling molecules released into the gut lumen from cells in the lamina propria [69]. There is emerging preclinical evidence that variations in the composition of gut microbes may be associated with changes in the normal functioning of the nervous system [70]. Explorations of the microbiome thus offer new insight into our neurodevelopment, behavioral phenotypes, and perhaps disorders affecting complex processes, such as cognition, personality, mood, sleep and eating.

Human induced pluripotent stem (hiPS) cells

The molecular mechanisms responsible for dysregulated mood and anxiety, substance use, and eating behaviors are not well understood and few defining characteristics of diseased neurons have been identified. We intend to address this by generating dopamine cells (or neurons) that have been derived from a subset of individuals with extreme phenotypes of depression and/or anxiety, substance use, or eating behaviors. We aim to create cell-based human models for psychiatric disorders by directly reprogramming blood cells into human induced pluripotent stem (hiPS) cells in both healthy individuals and those with clinically-significant complaints related to affect, substance use, or eating [71-73]. We aim to identify specific neuronal defects associated with dopamine neurons *in vitro* and demonstrate the reversibility of the disease phenotype in human neurons, with the expectation to ultimately screen chemical libraries to identify novel therapeutic targets. The goal of these experiments is to identify key molecular events involved in the dysregulation of these target populations and to exploit these as possible points of intervention.

Genetics and Epigenetics

In humans, there is considerable evidence that anxiety and depression are moderately heritable and influenced by multiple genes. Most experts now believe that it is highly unlikely that there are "genes for psychiatric disorders". Rather, genes involved in susceptibility to psychiatric disorders can best be understood at the level of more basic biological processes (e.g., neuronal

cell migrations during development) and/or mental function in the context of particular life experiences that are requisite for the expression of psychopathology.

Data from twin and adoption studies indicate that major depressive disorder (MDD), addiction disorders, and eating disorders (anorexia nervosa and bulimia) are moderately heritable - in the region of 40% to 60% - suggestive of a significant genetic contribution [74-76]. Clearly identifying the genetic variants that are associated with risk for developing these disorders would be helpful for predicting who is at risk of becoming ill and increasing our understanding of the pathophysiological basis of these disorders. Unfortunately, given the heterogeneity and complexity of MDD and anorexia nervosa, even well-powered genome-wide association study (GWAS) datasets of ~10,000 cases and ~10,000 controls and ~5,500 cases and ~20,000 controls, respectively, have failed to identify alleles that achieve genome-wide significance [77, 78].

A more tractable approach than the traditional case-control association study is offered by large scale longitudinal designs such as the Tulsa 1000. Here the proposed within-subject genetic analyses will emphasize the prediction of naturalistic clinical outcomes such as response to pharmacological and/or non-pharmacological treatment. Further, the genetic data collected will be stored for future testing and combined with multiple phenotypes (e.g. neuroimaging, clinical, cognitive assessments, and other bioassays) to provide an integrated theoretical perspective on the genetic basis for disorders of mood, anxiety, eating and addiction [79-81].

Immunophenotyping

Data from several different fields of study suggest that at least a subset of individuals with depression and other psychiatric illnesses show immunological dysregulation characterized by activation of the innate immune system together with suppression of elements of the adaptive immune response (reviewed in [82-87]). However, progress has been limited by a disproportionate focus on a static and narrow aspect of innate immunity, i.e. single time-point measurements of CRP or cytokines to the exclusion of other potentially informative markers of innate and adaptive immune function. Here, we will leverage the T-1000 design to obtain a wide-range of immunophenotypes both at baseline and post-treatment. Further, the range of tasks embedded within the T-1000 will provide a rich opportunity to examine the effect of experimental manipulations on immune function. The data obtained will not only further our understanding of the nature of immune dysfunction in psychiatric illness but may lead to the identification of prognostic and/or predictive biomarkers that possess clinical utility.

METHODS

Aims and Objective

This is a multi-level, longitudinal observational study of healthy controls and treatment-seeking individuals with mental health problems in Tulsa and the surrounding regions of Oklahoma. The overall aim is to obtain a comprehensive assessment based on RDoC principles, in order to:

(1) Determine relationships among variables assessing positive/negative valence, cognition, and arousal/interoception domains in order to derive latent variables that describe psychopathology across units of analysis and diagnostic groups.

(2) Investigate whether latent factors can be used to generate clinically meaningful outcome predictions across different domains and diagnostic groups.

Thus, this study has the potential to substantially improve our understanding of how disorders of mood, anxiety, substance use, and eating behavior are organized across different units of analysis (genes, molecules, cells, neural circuits, physiology, behavior, and self-report) and different domains of functioning (positive and negative valence, cognition, and arousal/interoception). Upon completion, we will aim to have robust and reliable dimensional measures that quantify these relationships among different units of analysis and different domains of functioning. The latent constructs will be the main outcome variables of this protocol. The baseline assessments will be used with individual-based prediction methods (e.g., random forests or support vector machines) to develop predictors. These predictors will be evaluated with test-specific statistics such as positive and negative likelihood ratios and standard measures such as area under the Receiver Operation Characteristic curve and area under Precision-Recall curve to determine which baseline measure or combination of measures best predicts clinical outcomes. Ultimately, the aim is to develop a set of assessments that can be used as a clinical tool to enhance outcome prediction for the clinician. These measures may also serve as an aid to determine who would likely benefit from different interventions.

Participants

We propose to collect complete datasets on a total of 1000 participants with approximately 500 mood and/or anxiety, 300 substance use, 100 eating disorder and 100 mentally and physically healthy control participants. In order to obtain 1000 participants who complete the year-long study, we plan to enroll up to 1400 participants between January 2015 and December 2018. Subjects will be between 18 and 55 years of age and have a body mass index between 17-38kg/m^2. Subjects will be referred from local treatment facilities or seeking treatment for anxiety and/or depressive symptoms, problems related to substance use, or problems related to eating behavior. As part of the inclusion criteria, mood/anxiety, substance, and eating disorder participants must also screen positive for these conditions as indicated by a score on the Patient Health Questionnaire (PHQ-9) ≥ 10 and/or Overall Anxiety Severity and Impairment Scale (OASIS) ≥ 8, (DAST-10) score > 2 or Sick, Control, One, Fat, Food Questionnaire eating disorder screen (SCOFF) score ≥ 2. Participants who meet criteria for one primary domain may

also screen positive for one of the other study domains. Healthy control participants will screen negative for these inclusion measures.

Exclusion Criteria

The following exclusion criteria will apply: (1) inability to provide informed consent, (2) no telephone or easy access to telephone, (3) history of unstable liver or renal insufficiency; glaucoma; significant and unstable cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, rheumatologic, or metabolic disturbance; or any other condition that, in the opinion of the investigator, would make participation not be in the best interest (e.g., compromise the well-being) of the subject or that could prevent, limit, or confound the protocol-specified assessments, (4) a positive test for drugs of abuse, including alcohol (breath test), cocaine, marijuana, opiates, amphetamines, methamphetamines, phencyclidine, benzodiazepines, barbiturates, methadone, and oxycodone, (5) has any of the following DSM-5 disorders: schizophrenia spectrum and other psychotic disorders, bipolar and related disorders, obsessive-compulsive and related disorders, (6) moderate to severe traumatic brain injury or other neurocognitive disorder with evidence of neurological deficits, neurological disorders, or severe or unstable medical conditions that might be compromised by participation in the study (to be determined by primary care provider), (7) active suicidal ideation with intent or plan, (8) change in the dose or prescription of a medication within the 6 weeks before enrolling in the study that could affect brain functioning, e.g., anxiolytics, antipsychotics, antidepressants, or mood stabilizers. However, we expect there to be changes in the dosing and prescription of medications during the course of the study protocol. This will be acceptable for the study and participants will be asked to inform the investigators of any treatments they undergo during their time in the study, (9) prescription of a medication outside of the accepted range, as determined by the best clinical practices and current research, (10) taking drugs that affect the fMRI hemodynamic response (e.g., methylphenidate, acetazolamide, excessive caffeine intake > 1000 mg/day), (11) MRI contraindications including: cardiac pacemaker, metal fragments in eyes/skin/body (shrapnel), aortic/aneurysm clips, prosthesis, by-pass surgery/coronary artery clips, hearing aid, heart valve replacement, shunt (ventricular or spinal), electrodes, metal plates/pins/screws/wires, or neuro/bio-stimulators, (12) persons who have ever been a professional metal worker/welder, history of eye surgery/eyes washed out because of metal, vision problems uncorrectable with lenses, (13) inability to lie still on one's back for 60-120 minutes; (14) prior neurosurgery, (15) tattoos or cosmetic makeup with metal dyes, (16) unwillingness to remove body piercings, (17) pregnancy, (18) unwillingness or inability to complete any of the major aspects of the study protocol, including magnetic resonance imaging (e.g., due to claustrophobia), biopsy, blood draws, or behavioral assessment. However, failing to complete some individual aspects of these assessment sessions will be acceptable (e.g., being unwilling to answer individual items on some questionnaires or being unwilling to

complete a behavioral task), (19) non-correctable vision or hearing problems. Once participants have been enrolled, they will be followed for the study duration even if they fulfill exclusion criteria for initial enrollment, e.g. an individual with a substance use disorder who was initially abstinent but experiences a relapse and presents with a positive drug screen during a follow-up session. However, subjects will be excluded if the investigators determine that participation would interfere with the individual's treatment or might negatively affect the outcome of the underlying disorder, e.g. an individual with a mood disorder who reports active suicidal ideation with intent or plan during a follow-up session.

Study design

The study's dependent variables will focus on the *positive and negative valence systems, cognition, and arousal/interoception domains* proposed by the RDoC [32, 33]. Using self-report, behavior, physiology, neural circuit, cell, molecule, and gene unit of analysis measures, we will apply these constructs to a clinical population of individuals with dysregulation of affect, substance use, and eating behavior recruited from treatment providers across different sites in the community. Through the application of latent variable analysis, we will derive latent constructs of positive and negative valence, cognition, and arousal/interoception system functioning that cut across units of analyses and diagnostic groups. Subjects will undergo a multi-level assessment based on the RDoC approach that consists of (a) a standardized diagnostic assessment , (b) self-report questionnaires assessing the positive and negative valence domains as well as interoception, (c) behavioral tasks assessing positive and negative valence, cognition, and interoception, (d) physiological measurements consisting of skin conductance, facial emotion expression monitoring, heart rate, respiration and eye-blink startle response, (e) functional magnetic resonance imaging focusing on reward-related processing, fear conditioning and extinction, cognitive control and inhibition, and interoceptive processing, (f) biomarker assessment, (g) microbiome assessment, (h) blood to derive induced pluripotent stem cells (IPS), (i) and genetic as well as epigenetic assessments. Subsequently, these individuals will be followed up quarterly and for one year. At months 3, 6, and 9, only self-report assessments will be collected, and the participants and will be re-assessed using a multi-domain assessment of functioning, which will include: (a) symptom severity and duration, (b) subjective well-being, (c) psychosocial function, (c) occupational function, (d) physical health, (e) utilization of mental health resources (treatment), and (f) adherence to treatment.

The workflow schematic in Figure 1 describes the overall outline of the T-1000 study and the measures obtained at different points in time.

Potential subjects will be screened by phone or in-person using the Western Institutional Review Board (WIRB) screening protocol 20101611. Once an individual has been identified as a potential subject in the T-1000, he or she will complete two to six in-person sessions within a

two-week time period. However, completion of these sessions may be broken into more or less visits depending on what works best for the participant's schedule. The order of the baseline assessments may also be modified to ensure timely and efficient completion, given individual differences in completion times for the various measures (e.g., variability in how long individuals may take to complete self-report measures).

Although entry into the study is not based on meeting diagnostic criteria for a particular mood, anxiety, substance use, or eating disorder, it will be important to characterize how our findings map onto the Diagnostic and Statistical Manual of Mental Disorders (DSM) (using DSM-5 criteria)[88]. Accordingly, patients will complete a diagnostic interview with study personnel, using an abbreviated version of the Mini International Neuropsychiatric Interview (MINI Version 6.0) [89]. The MINI was chosen over other diagnostic interviews because of its relative brevity, good inter-rater reliability, and suitability for use by an interviewer with limited training. We will include sections on panic disorder (PD), social anxiety disorder (SAD), posttraumatic stress disorder (PTSD), generalized anxiety disorder (GAD), eating disorders (ED), obsessive-compulsive disorder (OCD), and major depressive disorder (MDD) and several modules to provide further clinical information or to determine ineligibility (suicidality, manic/hypomanic episode, and psychotic disorders).

After completing the MINI and satisfying study criteria, the subjects will complete a wide range of self-assessments that are targeted to probe the positive and negative valence domains, cognitive systems and interoceptive systems. Subjects included in the study will return for a behavioral testing session (session 2) and neuroimaging and biomarker testing sessions (sessions 3-5). During the behavioral session participants will complete a battery of neuropsychological assessments, a set of cognitive tasks which have been selected based on underlying computational models, a modified dot probe detection task, an approach/avoidance conflict task, and an emotional reactivity task in which they view blocks of emotional images. Interoception will be probed using a series of heartbeat perception tasks, an inspiratory breathhold experiment, and a cold pressor test. State affect and physiology will be assessed throughout the behavioral session procedures. The biomarker session will include a blood draw, microbiome collection, physical measurements including height, weight, body composition assessment, hip/waist ratio, and vital signs (pulse, blood pressure). The structural MRI, functional MRI and EEG session will include high resolution anatomical brain scans, a resting state functional scan and task-based functional scans targeting neural systems associated with reward, attention, inhibition, interoception and fear conditioning.

The details of each session are listed in Table 1: the first column indicates which construct will be examined, the second column lists the name of the test. All self-report assessment measures will be administered electronically through REDCap [90].

Study Sessions

Detailed descriptions of the clinical, demographic, self-report, behavioral, neuropsychological and functional neuroimaging measures listed below are provided in the Supplementary Materials.

The Baseline Session

Clinical interview, demographics, and questionnaires detailed in Table 1 will be administered by masters or nurse level assistants who are supervised by licensed clinical psychologists and board certified psychiatrists. The clinical portion of the baseline assessements is expected to take approximately 4.5 hours to complete and can be split into two or more visits.

Table 1. Baseline Session: Clinical Interview, Demographics and Questionnaires

Domain	Assessment
Clinical Rating Scales and Demographics	
Diagnosis	MINI 6.0 [91]
Demographics	Demographics and Psychosocial Form
History	Assessment of Medical and Medication History
History	Life chart interview
Substance Use	Customary Drinking and Drug Use Record (CDDR) [92]
Handedness	Edinburgh Handedness Inventory [93]
Compliance	Medication Compliance
Compliance	Therapy Compliance
Traumatic Head Injury	Tulsa Head Injury Screen
Family Psychiatric History	Family History Screen (FHS) [94]
Suicidal Ideation	Columbia-Suicide Severity Rating Scale (C-SSRS) [95, 96]
Pain	Wong-Baker FACES Pain Rating Scale [97]
Self-Report Scales	
Negative Valence	State Trait Anxiety Inventory (STAI) [98]
Negative Valence/Interoception	Anxiety Sensitivity Index (ASI-3) [99]
Negative Valence	Ruminative Responses Scale (RRS) [100]
Depression	Quick Inventory of Depressive Symptomatology [101]
Trauma	Traumatic Events Questionnaire (TEQ) [102]
Trauma	Child Trauma Questionnaire (CTQ) [103]
Positive/Negative Valence	Positive and Negative Affect Schedule-Expanded Form (PANAS-X) [104]
Positive/Negative Valence	Behavioral Inhibition System/Behavioral Approach Scale (BIS/BAS) [105]
Positive Valence	TEPS anticipation/consumption/pleasure [106]
Positive Valence	UPPS Impulsive Behavior Scale[107]

Empathy-like	Interpersonal Reactivity Index (IRI) [108, 109]
Personality	Big Five Inventory (BFI) [110]
Arousal/Interoception	Toronto Alexithymia Scale (TAS) [111, 112]
Arousal/Interoception	Multidimensional Assessment of Interoceptive Awareness (MAIA) [58]
Eating Behaviors	Three Factor Eating Questionnaire (TFEQ) [113-115]
Eating Behaviors	Eating Disorders Diagnostic Scale (EDDS) [116]
Eating Behaviors	Simplified Nutritional Appetite Questionnaire (SNAQ) [117]
Physical Activity	International Physical Activity Questionnaire (IPAQ) [118]
Disability	World Health Organization (WHO) Disability Assessment Schedule [119]
Absenteeism/Presenteeism	WHO Health & Work Performance Questionnaire (WHOHPQ) [120]

Patient Reported Outcome Measurement Information System (PROMIS) Measures **[121, 122]**	
Negative Valence	PROMIS Anxiety
Negative Valence	PROMIS Depression
Negative Valence	PROMIS Anger
Positive Valence	PROMIS/Neuro-QOL Positive Affect and Well-being
Cognitive	PROMIS Cognitive Abilities
Cognitive	PROMIS Cognitive General
Fatigue	PROMIS Fatigue
Sleep	PROMIS Sleep Disturbance
Sleep	PROMIS Sleep-related impairment
Alcohol	PROMIS Alcohol Use
Alcohol	PROMIS Alcohol: Negative Consequences
Alcohol	PROMIS Alcohol: Positive Consequences
Alcohol	PROMIS Alcohol: Negative Expectancies
Alcohol	PROMIS Alcohol: Positive Expectancies
Social	PROMIS Social Satisfaction DSA
Social	PROMIS Social Satisfaction Role
Social	PROMIS Ability to Participate Social
Social	PROMIS Emotional Support
Social	PROMIS Information Support
Social	PROMIS Instrument Support
Social	PROMIS Satisfaction Roles Activities
Social	PROMIS Social Isolation
Physical	PROMIS Physical Function
Pain	PROMIS Pain Interference
Pain	PROMIS PAIN Behavior
Sex	PROMIS Global Satisfaction with Sex Life
Sex	PROMIS Interest in Sex Activity
Nicotine	Nicotine Dependence
Nicotine	Coping Expectancies

Nicotine	Emotional and Sensory Expectancies
Nicotine	Health Expectancies
Nicotine	Psychosocial Expectancies
Nicotine	Social Motivations

Baseline Behavioral Session

Behavioral tests will be administered via computer interfaces, with the exception of neuropsychological testing which will be conducted face to face by an assessor. The neuropsychological assessments will be administered by trained clinical assistants, directly supervised by licensed clinical psychologists and board certified psychiatrists. Behavioral assessments will be conducted by trained research assistants. The behavioral session is expected to take about 4 hours to complete and can be split into 2 or more visits (Table 2).

Table 2. Behavioral and Neuropsychological Tasks

Domain	**Task**
Computational- Cognitive	Change Point Detection Task [123] Three Arm Bandit Task [124] Start/Stop Task [125]
Positive/Negative Valence	Implicit Approach/Avoidance Task [126] Attentional Bias/Dot Probe Task [127] Emotional Reactivity Task [128] Approach Avoidance Conflict Task [129]
Arousal/Interoception	Breath Hold Heartbeat Tapping Task Cold Pressor [130, 131]
Neuropsychology	WRAT Reading [132] DKEFS Color-Word Inhibition [133] DKEFS verbal fluency [133] WAIS-IV digit span [134] Finger Tapping Test WAIS-IV Digit Symbol Coding [134] California Verbal Learning Test [135]

Baseline Biomarkers

Table 3 summarizes the proposed biomarkers and biological specimens that will be obtained from blood samples and microbial samples of the subjects. It is expected to take approximately 30-45 minutes to complete sample collection.

Table 3. Examples of immune-related measurements

Immunophenotype	Reported Abnormality in Depression, Eating Disorders or Addiction Disorders	References
Cytokines	Elevations in pro-inflammatory cytokines	[136-139]
PBMC Gene Expression	Increased mRNA expression of pro-inflammatory mediators	[140-143]
Kynurenine Pathway	Increased neurotoxic kynurenine metabolites	[144-147]
T-cells	Altered T-cell function and numbers	[148, 149]
Natural Killer Cells (NKC)	Reduced NKC function	[150-152]
Pathogens	Increased seropositivity for *T. gondii* and herpesviridae	[153, 154]

Baseline Neuroimaging

The session will consist of one 60 and one 120 minute scan in the MRI machine. One of the neuroimaging sessions will focus on structural differences in the brain and a second session will focus on functional differences. The neuroimaging sessions are expected to take approximately 4 hours total to complete and are split into two visits (Table 4).

Table 4. Baseline Neuroimaging Sessions

32 Channel Head Coil MRI Imaging: Structural & Perfusion
Participant Last Use Summary (PLUS)
3-plane localizer, asset calibration
T2-W Clinical Flair
T2-W Clinical FSE
T1-W Clinical MPRAGE
T1-W MPRAGE HI-RES
T2-W Propeller FSE HI-RES
Arterial Spin labeling
Diffusion Tensor Imaging
8 Channel Head Coil MRI, and fMRI with concurrent EEG
Task Training and Practice
Karolinska Sleepiness Scale: Pre-scan (KSS)
Participant Last Use Summary (PLUS)
EEG Cap Setup
MRI Anatomical scan (T1-W)

fMRI Monetary Incentive Delay Task (MID) **[155, 156]**
fMRI Stop Signal Task **[157]**
fMRI Resting State with eyes open
fMRI Interoceptive Attention Task **[158]**
fMRI Fear Conditioning/Extinction Task **[159]**
Karolinska Sleepiness Scale: Post-scan (KSS)

Quarterly Follow-up Session

These sessions will examine the course of outcomes in individuals with dysregulated mood and/or anxiety, substance use, or problematic eating behavior. These assessments will be brief in-person visits. The quarterly follow-up assessments will take approximately 1.5 hours every 3 months during the 12-month follow-up time period (Supplementary Table 1).

One-year Follow-up Session

This session will examine the course of outcomes 1 year after baseline. For neuropsychological assessment, alternative forms will be used as available. Assessments will be administered during in-person sessions that take approximately 7 hours to complete over 1 to 3 visits (Supplementary Table 2).

Biomarker measures

Blood Collection

We will investigate neuroendocrine, metabolic, inflammatory, and cardiovascular biomarkers associated with positive and negative valence domains, cognitive systems and arousal/interoceptive systems. These measures help to extend our multi-level analysis of NIMH RDoC constructs into the cellular and molecular units of analysis. Biochemical assays will be performed on biological samples collected at baseline and during the 1-year follow-up to quantify a range of biomarkers and their relationship with other variables and units of analysis.

Participants will have fasting blood drawn by venipuncture by a trained phlebotomist for the biomarker panels. This will be scheduled to occur the morning of one of the visits, or at a time convenient for the participant. Resting blood pressure and heart rate will be assessed. Additionally, in order to lay the foundation for future studies, we will also collect and process a small quantity of blood to be banked for potential future endocrine, immune and/or genomic analyses.

Sample collection, processing distribution and storage procedures

A trained phlebotomist will obtain all blood samples. Less than 150 mL of blood will be collected per subject during each session (baseline and 1-year follow-up), which is well within the safety limit of ~450 mL per blood draw. Samples for stem cells and genetics will be shipped

to Rutgers University laboratory for processing and storage. Blood samples for plasma, serum, and peripheral blood mononuclear cells (PBMCs) will be transported to and processed at the University of Oklahoma Integrative Immunology Center (IIC) Laboratories. Plasma and serum samples will be stored in secure freezers at -80°C. Freezers will be maintained in a specially equipped room with emergency backup power and an automated telephone alarm system that is programmed to call in case of failure. Additional aliquots of samples will be stored at -80°C should repeat analyses be required at a later date. PBMCs will be stored in liquid nitrogen dewars with liquid level monitors and alarms in a secure room at the University of Oklahoma IIC Laboratories.

Microbiome Collection

Participants will be asked to provide microbial samples during the biomarker session. All participants will be asked to provide forehead, mouth and stool samples.

A research assistant will provide the participant with an all-in-one sample collection kit system for collecting, stabilizing, transporting, and purifying samples which includes cotton-swabs, tubes labeled by body area, and step by step instructions.. Participants will be asked to perform the sampling themselves. Samples will be stored at the University of Oklahoma IIC Laboratories after initial processing until they are shipped to The University of San Diego-California for final processing and sample analysis.

Compensation

Subjects will receive the following payment for completing the study (Table 5):

Table 5. Compensation

SESSION	TIME	PAYMENT*
Interview and Demographic Information	4.5 hours	$90
Behavioral assessments & Computerized Tasks	4 hours	$80 $10-$20 reward
Biomarkers	30 minutes	$50
Neuroimaging & EEG & Setup	4 hours	$170 $0-$60 reward
3 month Follow up*	1.5 hours	$30
6 month Follow up	1.5 hours	$30
9 month Follow up	1.5 hours	$30
12 month Follow up	7 hours	$200 $10-20 reward
Total	23.5 hours	$700 to $780

DATA ANALYSIS

Behavioral and Psychophysiological Data Analyses

Self-report questionnaires, interviews, neuropsychological assessments, computer-based behavioral assessments, and psychophysiological assessments will be scored according to published methods (as cited in the Tables). These variables will then be used in conjunction with collected biological data in the latent variable approach. The analysis strategy consists of the following steps. First, the characteristics of all measures will be examined for deviation from normality prior to subsequent analyses. For each unit of analysis (self-report, behavior, physiology, circuits, biomarkers), separate principal components analyses (PCA) will be performed and a separate analysis will be conducted for each behavioral task to minimize task-specific factors in subsequent analysis steps. Next, the number of components for each analysis will be determined using a number of different approaches [160]. In particular, if the number of components to be extracted differed across the extraction approaches, both solutions will be explored [161, 162]. Component scores from each unit of analyses will be extracted for each participant and used for the following analyses.

MRI, EEG and fMRI Data Analysis

The basic structural and functional image processing will be done with the Analysis of Functional Neuroimages (AFNI) software package [163].

EEG-fMRI

The EEG data will be acquired simultaneously with the fMRI data and corrected for artifacts related to the gradient switching and cardiac ballistic effect using the template subtraction method [164-166] implemented in BrainVision Analyzer software (Brain Products GmbH, Munich, Germany).

During fMRI scans we will simultaneously record EEG using a 31-electrode cap attached to an MRI-compatible BrainAmp MR Plus amplifier. The sintered Ag/AgCl ring electrodes are mounted into a scalp cap according to the standard 10-5 system. All electrodes are referenced to the FCz position, while a ground electrode is located at the AFz position. One additional electrode will be placed on the subjects' back to monitor the electrocardiographic signal. The impedance of all electrodes will be maintained below 10 KΩ throughout the recording. The internal sampling clock of the EEG amplifier will be synchronized with the MRI scanner 10MHz master clock signal using the SyncBox device (Brain Products GmbH, Munich, Germany), in order to prevent variant sampling of imaging artifacts and to facilitate artifact correction [166]. The signals will be recorded at a sampling frequency of 5000 Hz with an analog filter (from 0.016 to 250 Hz) and a resolution of 0.1 µV.

Besides independent EEG measures of brain state, and EEG-informed fMRI data analysis, we will use EEG data to correct the effects of head movements in simultaneously acquired fMRI data on a slice-by-slice basis [167]. This E-REMCOR, and recently developed automated version aE-REMCORE technique, will make it possible to regress out the effects of rapid head movements from unprocessed fMRI data on slice-by-slice basis prior to volume registration [168]. Thus, aE-REMCOR complements both the traditional fMRI volume registration approach, which performs better for slower head motions, and the RETROICOR method for slice-specific correction of fMRI cardiorespiratory artifacts [169]. EEG-informed fMRI analysis will allow us to better elucidate and characterize normal and pathological interactions between cerebral function and behavior, cognition or emotion.

fMRI Pre-Processing

Standard fMRI data pre-processing will include a slice-timing correction, signal scaling, spatial smoothing, physiological noise suppression [169, 170], and motion correction.

Task-based fMRI Analysis

First/Subject-Level Analyses

Multiple regression will be used to analyze individual subjects' data, with predictors in the model constructed by convolving each column of the task design matrix with a canonical hemodynamic response function. Regressors of non-interest will be included in all models to account for (1) head motion (6 motion variables), and (2) other sources causing drifts (each run's signal mean, linear, quadratic, and cubic signal trends). The beta weights and corresponding t-statistics for image contrasts of interest will be produced for group-level analyses.

Second/Group-Level Analyses

Both region of interest (ROI) and whole-brain analyses start with voxel-wise statistical tests using mixed-effects modeling on aggregations of maps of the subjects' beta-weights and beta-weight standard errors (AFNI's *3dMEMA* or in-house developed R code). This approach has the advantage of taking into account in the group analysis both effect estimates as well as their within- and between-subjects variances. Correction for multiple comparisons will be conducted as follows. Statistical maps will either be corrected using the false-discovery rate (FDR) or cluster level thresholds. For cluster level thresholds, AFNI's *3dClustSim* (with spatial autocorrelation function [acf] adjustments) will be used to identify the required cluster-size threshold, given a voxel-wise probability of $p < 0.001$, the smoothness of the residuals from the group level test, and the size of the region tested (either whole-brain or an a priori defined ROI).

Resting State fMRI Analysis

Pre-Processing

Data pre-processing will be conducted using afni_proc.py. The first three volumes of the functional scans will be discarded to allow the signal to reach T1 equilibrium, and a de-spiking algorithm will be used to remove any transient signal spikes from the data. Prior to slice time correction, physiological signals of non interest (pulse, respiration) will be removed using RETROICOR. For each subject, the remaining volumes will be corrected for differences in slice acquisition time; head motion will be corrected by rigid body translation and rotation; the third volume of the functional run will be co-registered to the anatomical coordinates of the participant's structural scan by linear warping, then normalized to the Talairach template and resampled to 2x2x2 mm^3 voxels.

First/Subject-Level Analyses

For each participant, the time courses of the residual images from the pre-processing step will be averaged across voxels within each ROI, and Pearson correlation coefficients will be computed between the mean signal time courses of pairs of ROIs. These correlation coefficients will be converted by Fisher *r*-to-*z* transformation, which will be used as predictors of treatment outcomes.

The identified brain activation at ROIs and/or functional connectivity z-scores will be analyzed by PCA, and the extracted principal component scores will be used with scores from other units of analyses.

General Unifying Statistical Approach

The goal of this project is to derive latent variables that adequately quantify the positive and negative valence, cognition, and interoception/arousal domains across different units of analyses collected at baseline. The analysis of the variables that are extracted from each unit will consist of three steps. First, a PCA will be conducted for each unit of analysis to determine the number of independent degrees of freedom contributing to the variance observed in each unit. We expect to extract at least two independent components. The action units that show the highest correlation with the components will be used for subsequent analyses. Second, we will conduct a confirmatory factor analysis with the variables from each unit of analysis that showed the highest correlation with the principal components of four proposed factors – positive valence system, negative valence system, arousal/interoceptive system, and cognitive system. We will subsequently test the statistical significance of the coefficients contributing to the factors. Finally, we will conduct a latent variable analysis as detailed below to relate one unit directly to another unit of analysis.

Statistical Analysis Plan

Baseline/Cross-sectional analyses

We will relate different units of analyses by regularized generalized canonical correlation analysis (RGCCA) [171]. Classical CCA identifies linear combinations of two sets of variables such that their correlations are maximized. RGCCA extends classical CCA from two sets of variables to multiple sets. When applied to multiple units of analyses, RGCCA identifies linear combinations (canonical variates) of principal component scores within each unit of analyses, such that the sum of correlations or covariance across canonical variates is maximized. The results of RGCCA can be demonstrated as a network that shows which unit of analyses are connected, and which are not. Moreover, the canonical correlations obtained from RGCCA can be used to define biotypes by cluster analysis from two sets of variables (clinical symptoms and resting state functional connectivity) to define biotypes [172]. These dimension-defined biotypes will be linked to the category-defined groups by cross tabulation.

Longitudinal analysis

The self-report outcomes will be measured at baseline and months 3, 6, 9, and 12, and these time trajectories will be compared between groups based on categorical diagnosis (comparison subjects, substance use disorders, mood disorders, and eating disorders) and between dimensionally-defined biotypes using models for longitudinal data – mixed effects and generalized estimating equations (GEE) models. No functional form will be assumed for the time trajectories and profile models will be used (i.e., time variable is treated as a factor in the model). The biotype/group effect will be measured as a time-by-group interaction. Comparisons between the time profiles of the groups will use appropriate Wald and likelihood ratio tests. In addition, linear time effects will be considered; these will be used if they are preferable to the profile models in model comparison using Akaike information criterion (AIC).

Statistical Power

We will base statistical power on two considerations: (1) power to estimate latent factor models with precisions, and (2) accuracy of prediction of outcomes using baseline variables and latent factors as predictors. Although controversial [173], typically one suggests that there should be at least n=10 subjects for each identified latent variable. In comparison, this study is likely to have up to n=100 subjects per latent construct. More recent recommendations for power take into account the quality of the indicators for the latent variables and the number of items per factor. For a moderate to low communality (conservative assumption), a sample size of n=300 would give an excellent coefficient of congruence of K=0.97. This allows for fitting latent factor models to each patient subgroup separately with adequate power [174]. We also compute power to predict the year follow-up clinical outcomes: assuming 100 healthy controls

(HC), 100 eating disorder (ED), 500 mood/anxiety (MA), and 300 substance use (SU) participants at baseline and a uniform 20% attrition rate for each group at one-year follow-up (i.e., with remaining 80, 80, 400, and 240 participants in the corresponding groups), we will have 80% power to detect effect sizes (Cohen's D for between-group differences in changes from baseline to 1-year follow-up) of 0.57 (ED vs. HC), 0.43 (MA vs. HC or ED), 0.45 (SU vs. HC or ED), 0.29 (MA vs. SU) at two-sided Type I error rate 0.05/6 = 0.008 (Bonferroni correction) in t-test for post hoc comparisons.

ETHICS and DISSEMINATION

Gender/minority/pediatric inclusion for research

Women and minorities will be included in the study without prejudice and represented according to the study population. Participants will be recruited from the greater metropolitan areas of Tulsa, Oklahoma and efforts will be made to ensure the subject population is representative of the gender, ethnicity and racial demographics of the region according to the US Census Bureau data. No participants under the age of 18 will be enrolled in the study.

Specimens, records, data collection

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study. Study consent records will be stored in the locked records room at the Laureate Institute for Brain Research. Only approved study personnel will have access to study records that contain any identifying information. Study data records and blood/urine/biological samples will be assigned code numbers and will not be individually identifiable. Code numbers are a combination of numbers and letters. The electronic data will be kept in a firewalled and password protected database on a secure server managed by LIBR. Vanderbilt University, with collaboration from a consortium of institutional partners, has developed a software toolset and workflow methodology for electronic collection and management of research and clinical trial data REDCap (Research Electronic Data Capture) [90] data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team with planning assistance from the information technology staff. The iterative development and testing process results in a well-planned data collection strategy for individual studies. REDCap servers are housed in a local data center at Laureate Institute for Brain Research and all web-based information transmission is encrypted. REDCap was developed specifically around HIPAA-Security guidelines and is recommended to LIBR researchers by both our Privacy Office and the Western Institutional Review Board (WIRB). REDCap has been disseminated for use locally at other institutions and currently supports 240+ academic/non-profit consortium partners on six continents and over 26,000 research end-users (www.project-redcap.org).

Records of the subject's participation in this study will be held confidential except as disclosure is required by law or as described in the informed consent document (under "Confidentiality"). The study doctor, the sponsor or persons working on behalf of the sponsor, and under certain circumstances, the United States Food and Drug Administration (FDA) and WIRB will be able to inspect and copy confidential study-related records which identify the subject by name. Therefore, absolute confidentiality cannot be guaranteed. If the results of this study are published or presented at meetings, the subject will not be identified. Paper copies of consents, screening forms, the Research Privacy Form, and any other forms, testing results or papers containing Personally Identifiable Information (PII) will be stored in a secured medical records room with access granted only to authorized personnel.

Recruitment and consent procedure

Recruitment into the T-1000 study at the Laureate Institute for Brain Research will be ongoing for 4 years from January 2015 through December 2018. The study will be completed by December 2019 after the completion of the 1-year follow-ups from 2018. Study participants will be recruited through the clinical services of the Laureate Psychiatric Clinic and Hospital (LPCH), local service providers for behavioral health, mental health, and addiction and recovery (e.g. Family and Children's Services, 12&12 Inc., local psychiatrist and physician offices), and through online, newspaper, flyer, radio or other media advertisements in the Tulsa metropolitan area. Participants will also be recruited through a pre-approved LIBR Screening protocol (WIRB #20101611) and through the Laureate Institute for Brain Research REDCap database. Informed Consent will be obtained by members of the research team that have received training from the PI to obtain consent for this study. All participant interactions including consenting will be conducted in private interview/exam rooms. These exam rooms at LIBR are secured from public areas via combination locked doors that are only accessible to authorized personnel.

Expected outcomes

The final end-point of this analysis will be a set of standardized multi-level latent variables that can be developed into clinical tools to help clinicians predict illness course and recovery at the individual patient level following the implementation of standard treatment interventions. These variables, which will focus on the prediction of mood, anxiety, eating, or substance use psychopathology, will be investigated in a number of different ways. A first approach will determine how measures of each domain across different units of analyses (e.g., from molecules to mental processes) relate to one another. A second approach will involve indentifying whether they predict the progression and severity of symptoms over time (including natural recovery or worsening of symptoms). A third approach will examine whetherthey predict responses to independently-sought pharmacological or behavioral

treatments. A fourth approach will be to investigate how these variables can be implemented in computational models of mental health to gain a better understanding of the underlying processes driving psychopathology. Additional approaches and outcomes are expected to emerge in the process of conducting these examinations. By establishing a robust and reliable dimensional set of latent variables that quantify the positive and negative valence, cognition, and arousal/interoception RDoC domains, this project will take psychiatry a step closer towards personalized and biologically based medicine [28-30].

Dissemination of results

Results from the study will be submitted to relevant journals for peer-reviewed publication and presented at national and/or international biomedical conferences.

Registration

In accordance with the recommendations of the International Committee of Medical Journal Editors, the proposed study is registered in a public registry (http://www.clinicaltrials.gov/, Trial Registration Number: NCT02450240).

Collaborators

University of Oklahoma

University of California-San Diego

Rutgers University

Contributors

All authors made a significant contribution to the conception and design of the study protocol. The protocol was written by MPP and TAV and critically reviewed by SK, JS, JB, JF, RA, HY and WKS. All authors gave permission and approval for publication.

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Competing Interests

None

Patient consent

Obtained

Ethics Approval

The study protocol is approved by the Western Institutional Review Board, Puyallup, Washington (WIRB, protocol number 194919).

Provenance and peer review

Not commissioned; externally peer reviewed.

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Figure 1. T1000 Workflow Schematic

Abbreviations (in alphabetical order): BOLD: Blood-Oxygen-Level-Dependent; DAST: Drug Abuse Screening Test; DTI: Diffusion Tensor Imaging; EEG: Electroencephalogram; MINI: Mini International Neuropsychiatric Interview; MRI: Magnetic Resonance Imaging; OASIS: Overall Anxiety Severity and Impairment Scale; PHQ-9: Patient Health Questionnaire; PROMIS: Patient Reported Outcome Measurement Information System; SCOFF: Sick, Control, One, Fat, Food Questionnaire; T1/T2: T1- weighted (longitudinal relaxation time) and T2-weighted (transverse relaxation time)

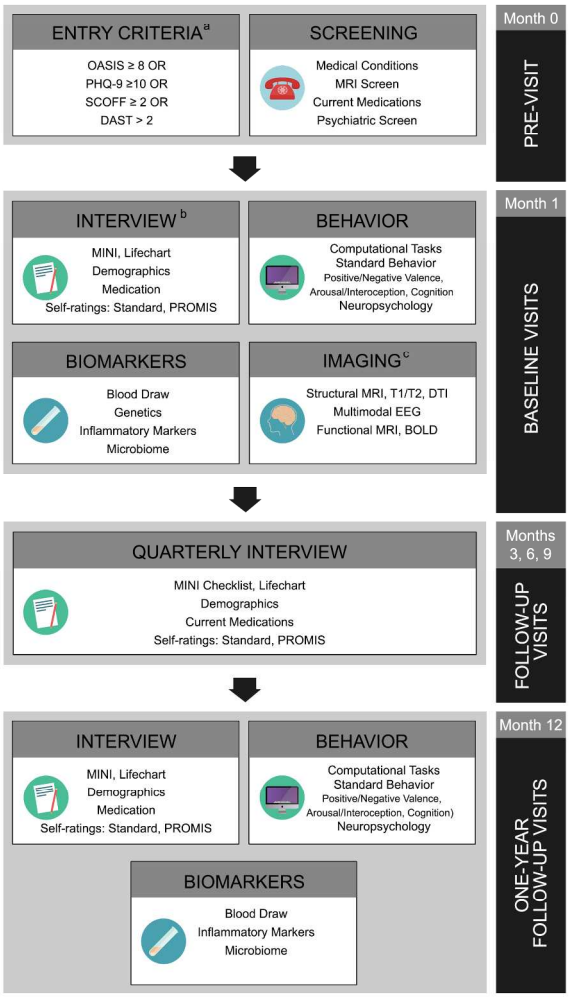

Figure 1. T1000 Workflow Schematic

215x279mm (300 x 300 DPI)

SUPPLEMENTARY MATERIALS

Positive and Negative Valence Domains

Positive Valence System

A central construct of the positive valence system is *approach motivation*, which can be defined as processes that regulate the direction and maintenance of approach behavior. The constructs of *reward seeking* and *reward sensitivity* are components of approach motivation. Reward sensitivity refers to the anticipation and receipt of positive stimuli. The primary neural mechanisms of reward sensitivity involve the ventral striatum (VS) and orbitofrontal cortex (OFC). These structures are involved in the processing of primary rewards, such as pleasant tastes [1], smells [2] or sights [3], as well as secondary (monetary) rewards [3-5]. The VS plays an important role in the anticipation of reward [6, 7] as well as the receipt of reward [4, 8]. The VS is part of a larger fronto-striatal circuit subserving reward-related processing that also includes the OFC, a subregion of the prefrontal cortex [9]. An important functional coupling exists between the VS and OFC [10]. Reward-processing also involves other neural regions, including the amygdala [11-13], dorsal anterior cingulate cortex (ACC) [14] and the hippocampus [15].

Relationship between reward sensitivity and the positive valence system: Extant evidence shows that individuals have deficits in positive affect (i.e., individuals with depressive disorders) show deficits in reward processing, at both the behavioral [16] and the neural levels [17]. At the behavioral level, individuals with major depression are less responsive to reward-relevant stimuli than non-depressed individuals and deficits in reward responding are associated with deficits in positive affect or the ability to experience pleasure [16, 18]. At the neural level, depression is associated with reduced activation in fronto-striatal circuits, namely the VS and caudate, during reward processing compared with healthy controls [17]. Anhedonia [19, 20] (or, the inability to experience pleasure) and reward-related processing [21] have been considered critical factors in the development of depression. Reward sensitivity in anxiety disorders has been less well studied. Similar to depression, evidence of reduced striatal activation during reward processing has been found in individuals diagnosed with

posttraumatic stress disorder (PTSD) compared with healthy controls [22, 23], particularly in relation to anhedonic features of PTSD (e.g., emotional numbing). Other studies, however, find evidence of heightened striatal activation during reward anticipation in some anxiety disorders [24]. This heterogeneity underscores the potential value of moving towards a dimensional understanding of reward sensitivity and positive valence system functioning in anxiety, mood, substance and eating disorders.

Negative Valence System

Responses to *acute threat* (fear) and *potential harm* (anxiety) were considered by the RDoC workshop committee to be central constructs within the negative valence system. One approach to measuring response to threat is via fear conditioning, which involves excitatory learning of conditioned stimulus vs. unconditioned stimulus (CS-US) associations [25, 26]. Research on fear learning uniquely adapts to translational neuroscience contexts because we understand with great precision the relevant neural processes in many species, including humans. The brain regions that have most consistently been associated with fear conditioning are the amygdala [27-31] and insular cortex [32]. In healthy adults, increased activity in the amygdala and insula is typically observed in response to the CS during conditioning. Response to loss was cited by the RDoC committee as another critical component process of the negative valence system, and may be particularly related to depression. Reward paradigms that include loss or punishment trials (e.g., losing money for incorrect responses [33-35]) can be used to measure behavioral and neural responses to loss anticipation and outcome. Research in healthy adults suggests that the ventral and dorsal striatum (caudate) are associated with anticipation and receipt of loss or punishment using these paradigms [33, 34].

Baseline Diagnostic and Demographic Assessment Measures

Patient Health Questionnaire (PHQ-9): The Patient Health Questionnaire (PHQ) is a self-administered diagnostic instrument for common mental disorders. The PHQ-9 is the depression module, which scores each of the 9 DSM-IV criteria as “0” (not at all) to “3” (nearly every day). Scores of 1-4 are considered minimal depression, 5-9 mild depression, 10-14 moderate depression, 15-19 moderately severe depression and 20-27 severe depression [36].

Overall Anxiety Severity and Impairment Scale (OASIS): The OASIS is a brief questionnaire (5 Items) that can be used as a continuous measure of anxiety-related severity and impairment across anxiety disorders. Each item is rated on a 5-point scale and the ratings are summed to obtain a total score. A cut-score of 8 has been shown to correctly classified 87% of individuals as having an anxiety diagnosis or not [37]. The OASIS has demonstrated excellent 1-month test–retest reliability, and convergent and divergent validity [38].

Drug Abuse Screening Test (DAST-10): The DAST-10 [39] is a brief version of the 28-item DAST designed to identify drug-use related problems in the previous year. It has demonstrated good internal consistency and temporal stability in psychiatric samples; the DAST-10 discriminates between psychiatric outpatient with or without drug use disorders (with scores between 2-4; [40]). This measure consists of 10 yes/no questions. Responding yes to score > 2 of the questions is considered an indicator that the individual should seek further evaluation for problematic drug use behaviors.

Sick, Control, One, Fat, Food Questionnaire (SCOFF): The SCOFF eating disorder screen was developed by British researchers as a screening tool for eating problems in a primary care setting [41]. It consists of 5 yes/no questions that inquire about eating behaviors and beliefs or obsessions with eating. Responding yes to ≥ 2 of the five items is considered an indicator that the participant should seek further evaluation for eating concerns.

Life chart interview: This interview was adapted from published methodologies for obtaining life histories of important life events relevant to mental health [42]. The purpose of this interview will be to obtain qualitative information regarding the temporal sequence of important events throughout the participant's life, which will be used to inform the structured diagnostic interview (MINI) and provide a more thorough and holistic understanding of the factors that have contributed to the individual's mental health. The Life Chart will ask questions pertaining to what important events happened during specific intervals of the person's life, including: (1) birth (2) childhood to the start of elementary school, (3) elementary school, (4) middle school to leaving/finishing high school (5) after high school to age 25 (6) ages 25-35 (7) ages 35-45 (8) ages 45-55. For each interval, subjects will be asked questions about potentially important events in their life, such as whether they moved, had any births or deaths in their

family, sought mental health treatment, etc. From this comprehensive list, the 0-3 most significantly life events will be selected from each time interval and the participant will be asked to rate their mood level (on a scale of 1-5) for those events as well as on average for that time interval. Participants may be asked to be audio recorded during the life chart interview. The recordings will be strictly optional and refusal will not impact participants' inclusion in the study. The recorded interviews will be used to develop reliability ratings among clinicians at LIBR and development of an event timeline. A visual timeline displaying the most significant events identified throughout their lifetime and their mood ratings throughout this time will be constructed and provided to the participant upon request.

Mini International Neuropsychiatric Interview (MINI Version 6.0): This is a widely used structured interview that assesses diagnostic criteria related to psychotic disorders, mood disorders, substance use disorders, and anxiety disorders. This interview will be used to assess symptoms and diagnostic criteria related to Axis I disorders. The MINI has been validated with the Structured Clinical Interview for DSM Axis I Diagnoses (SCID) with an average Kappa statistic of 0.67 across all 22 diagnoses measured on the MINI, and an average inter-rater reliability of 0.97 across diagnoses [43].

Demographics and Psychosocial Form: This form will ask participants to indicate their age, date of birth, contact information, ethnicity, race, gender, marital status and family makeup, language use, average income, education level, occupational and/or student status, and health insurance.

Assessment of Medical and Medication History: This form was created specifically for the purposes of this study and will ask questions related to medical and mental health diagnoses the participants has received currently or in the lifetime. This will involve a review of systems (e.g., constitutional, cardiovascular, respiratory) to inquire about previous or current problems, questions concerning in inpatient stays/treatments, surgeries, medications, and psychotherapies. For each mental health treatment, they will be asked to rate their compliance with that treatment. At the follow-up session, this interview will be repeated, but only in reference to the year of the study.

Diagnostic Review and Verification of Clinical Information: After completing the Assessment and Medication History, Life Charting, and MINI structured interview, each participant's information will be presented to a board certified psychiatrist for review, verification, and potential revision. This includes a targeted review of medical and psychiatric history and current medications for the purpose of identifying and correcting any collection errors. Participants for whom the DSM diagnosis is questionable will be re-evaluated in person by a board certified psychiatrist for independent diagnostic verification.

Edinburgh Handedness Inventory (EHI): The EHI is a self-report laterality scale that estimates the degree of right or left hand dominance during everyday activities [44].

Customary Drinking and Drug Use Record (CDDR [45] with Michigan Negative Reinforcement Questionnaire (MNRQ [46]): The CDDR provides current (past 3 months) and lifetime measures of 4 alcohol and other drug-related domains, including level of involvement, withdrawal characteristics, psychological/behavioral dependence symptoms, and negative consequences. The measure has been found to have good internal consistency, test-retest reliability, and construct validity [45]. The MNRQ was originally developed to assess beliefs about positive and negative consequences of smoking specifically and was found to have good reliability and validity in relation to diagnostic measures of nicotine dependence [47]. This measure has subsequently been adapted for use related to other substances of dependence and will be administered along with the CDDR in the current study to obtain measures of alcohol and drug use as well as participant beliefs concerning the consequences of that drug use.

Tulsa Head Injury Screen (THIS): The THIS is a questionnaire that asks participants about their history of head injuries and loss of consciousness.

Family History Screen (FHS): The FHS is a questionnaire that asks about the psychiatric history of the participant's family members, including biological parents, siblings and children.

Columbia-Suicide Severity Rating Scale (C-SSRS): The C-SSRS is a tool used to determine the presence of suicidal ideation or behavior in a participant [48].

Wong-Baker FACES Pain Rating Scale: This questionnaire is used to assess the current degree of physical pain being experienced by the participant [49].

Self-Report Measures

State-Trait Anxiety Inventory (STAI): This is a widely-used psychometric instrument designed to assess an individual's anxiety proneness. This measure has both a "state" subscale meant to measure temporary anxiety symptoms and a "trait" subscale meant to measure more long-standing anxiety proneness. Each subscale consists of 20 items using 4-point scales ("not at all" to "almost always"). The STAI is a validated measure with good internal consistencies for both subscales and has high test-retest reliability for the trait subscale and low to moderate test-retest reliability for the state measure [50].

Anxiety Sensitive Index (ASI-3): This instrument includes 18 items designed to measure the fear of arousal-related sensations, specifically along the dimensions/subscales of Physical, Cognitive, and Social Concerns. Each item is answered on a scale of 0-4 ("very little" to "very much"). The ASI-3 has been found to have adequate performance on several measures of reliability and validity [51].

Quick Inventory of Depressive Symptomatology (QIDS-SR): The QIDS-SR is a self-report 16 item assessment of the severity of depressive symptoms [52].

Simplified Nutritional Appetite Questionnaire (SNAQ): The SNAQ is a reliable tool with appraisal questions that focus on appetite and evaluating weight loss. [53]

Ruminative Responses Scale (RRS): This instrument is used to measure dispositional tendencies to ruminate in response to negative affect. It consists of 22 questions concerning how they respond to sad mood, which are focused on the self, on one's symptoms, and on the possible causes and consequences of the mood state (i.e., "Think 'why do I have problems other people don't have'?"). Responses are rated on a 4-point scale (e.g., 1 =almost never respond in this way; 4=almost always respond in this way). The RRS has three factor-analytically derived

subscales, including depression, brooding, and reflection. The RRS has been found to have good test–retest reliability (.67) and satisfactory convergent and predictive validity [54, 55].

Traumatic Events Questionnaire (TEQ) – Civilian Version: The Traumatic Events Questionnaire (TEQ) [56], assesses 11 specific traumatic events: (1) combat, (2) large fires/explosions, (3) serious industrial/farm accidents, (4) sexual assault, rape (forced unwanted sexual activity), (5) natural disasters, (6) violent crime, (7) adult abusive relationships, (8) physical/sexual child abuse, (9) witnessing someone being mutilated, seriously injured, or violently killed, (10) other life threatening situations, and (11) violent or unexpected death of a loved one. Two nonspecific questions, "other event" and "can't tell," complete the scale. Individuals are asked to indicate the frequency, severity (on a 7-point scale), and age at the time of the event. The scale has been found to have very high reliability (.91) and has been found to relate to PTSD, anxiety, and depressive symptoms [56].

Childhood Trauma Questionnaire, Short Form (CTQ-SF): This instrument is used to screen adolescents and adults for a history of child abuse and neglect. The CTQ has five subscales: (1) Physical abuse, (2) Sexual abuse, (3) Emotional abuse, (4) Physical neglect, and (5) Emotional neglect. The CTQ will be used to identify traumatic childhood conditions characteristic of the negative valence domain. The CTQ consists of 28 items which are rated on a 5 point scale (1=never true; 5=very often true). The full CTQ has been found to have good reliability and validity and the CTQ –SF was found to have good validity in reference to the full version [57].

Positive and Negative Affective Schedule- State/Trait (PANAS) [58]: The PANAS is a widely used measure comprising 20-items assessing activated forms of PA and NA using 5-point scales (1 = very slightly/not at all, 5 = extremely). To assess trait PA and NA, participants will be asked to respond according to how they have felt "during the past week". State PA and NA will be asked by asking participants to rate how they feel “right now (that is, at the present moment)”. The PANAS has high internal consistency and temporal stability (trait version). Correlational data support its convergent and discriminant validity. Confirmatory factor analyses support the construct validity of the PANAS.

Behavioral Inhibition and Activation Scales (BIS/BAS): The behavioral inhibition and activation scales (BIS/BAS) include 20-items assessing dispositional BIS and BAS sensitivities (i.e. avoidance and approach motives), which are hypothesized to reflect the negative and positive valence systems, respectively. Items are rated on four-point scales (1 = strongly disagree; 4 = strongly agree). The BAS has three subscales (Drive, Reward Responsiveness, and Fun Seeking); however, factor analyses support a single higher-order factor. The BIS/BAS has good test-retest reliability. Correlational data support the relative orthogonality and convergent, discriminant, and predictive validity of the subscales [59].

Temporal Experience of Pleasure Scale (TEPS): The TEPS is a recently developed measure of anticipatory pleasure and consummatory pleasure. It has 18 items, each of which are rated on a 6 point scale (e.g., 1=very false for me; 6=very true for me). Initial investigations with this measure indicate good validity and independence of the two subscales (anticipatory and consummatory; [60]).

UPPS Impulsive Behavior Scale (UPPS): The UPPS [61] was designed to measure impulsivity across dimensions of the Five Factor Model of personality. The scale has 45 items that use a 4-point scale, e.g., 1=; 4=) and has 4 subscales, including Premeditation (lack of), Urgency, Sensation Seeking, and Perseverance (lack of). The subscales have been shown to have good internal consistencies (.82-.91; [61]) and the measures has been shown to distinguish between subgroups of psychopathology compared to control groups [62].

Snaith-Hamilton Pleasure Scale (SHAPS): This instrument is used to measure hedonic capacity. It consists of 14 items, rated on a 4-point scale (1=Definitely Agree; 4=Strongly Disagree). This instrument has been found to have excellent internal consistency and adequate convergent and discriminant validity [63].

Interpersonal Reactivity Index (IRI): The IRI was developed to measure empathy, defined as the "reactions of one individual to the observed experiences of another". This is a 28-item measure, each rated on a 5-point Likert scale (1="Does not describe me well"; 5="Describes me very well"). The measure has 4 subscales, each made up of 7 different items. These subscales include Perspective Taking, Fantasy, Empathic Concern, and Personal Distress. Good internal

consistency. The scale has also been shown to have good construct validity with related measures [64, 65].

Big Five Inventory (BFI): The BFI measures an individual on the Big Five Factors (dimensions) of personality [152], which include (1) extraversion versus introversion, (2) agreeableness versus antagonism, (3) Conscientiousness vs. lack of direction, (4) neuroticism vs. emotional stability, (5) openness vs. closedness to experience. This measure has 44-items, each of which are rated on a 5-point scale (1=disagree strongly, 5= agree strongly). This measure has been shown to have high internal consistency, test-retest reliability, and good convergent and divergent validity with other Big Five measures [66].

Toronto Alexithymia Scale (TAS-20): The TAS is one of the most commonly used measures of alexithymia, or the difficulty identifying and describing emotions. This is a 20-item measure, with each rated on a 5-point scale (1=strongly disagree, 5=strongly agree). There are three subscales, including (1) Difficulty Describing Feelings, (2) Difficulty Identifying Feeling, and (3) Externally-Oriented Thinking. The TAS-20 has been shown to have good internal consistency (.81), test-retest reliability (.77), and adequate convergent and concurrent validity [67, 68].

Multidimensional Assessment of Interoceptive Awareness (MAIA): This measure was recently developed to measure trait interoceptive body awareness. It consists of 32 items, each rated on a 6-point scale (0=never, 6=always). There are 8 subscales, including: (1) Noticing, (2) Not-distracting, (3) Not-worrying, (4) Attention Regulation, (5) Emotional Awareness, (6) Self-regulation, (7) Body listening and (8) Trusting. The measure was found to have good measures of internal consistency on each subscale and showed adequate construct validity with other, related measures of emotional processing anxiety, and body awareness [69].

Three Factor Eating Questionnaire (TFEQ): The TFEQ was developed to measure three dimensions of human eating behavior: cognitive restraint of eating, disinhibition, and hunger. This is a 51-item measure, including 36 items with yes/no responses, 14 items on a 4-point scale (1=unlikely; 4=very likely), and one item of restraint on a 6-point scale (0="eat whatever you want, whenever you want"; 5="constantly limit food intake, never give in"). A subscale score is calculated for each of the three dimensions of human eating behavior. Cognitive Restraint is

designed to measure control over food intake. Disinhibition measures loss of control over eating. The Hunger scale concerns subjective feelings of hunger and food cravings. The TFEQ has been found to have high test-retest reliability and internal consistency, and adequate construct validity [70-72].

Eating Disorders Diagnostic Scale (EDDS): The EDDS [73] measures the presence of anorexia nervosa, bulimia nervosa and binge eating disorder. It was developed as a self-report measures based on the Eating Disorder Examination (EDE) and the eating disorder module of the Structured Clinical Interview for DSM-IV. The EDDS provides both full and subthreshold diagnoses as well as a continuous symptom composite score. It consists of 22 items, 4 of which are on a 6-point scale (1=not at all; 6=extremely), 9 of which are yes/no questions, 6 items that ask for frequency of events (e.g., episodes of uncontrolled eating) over the week or month; and 3 remaining questions asking for height, weight, and number of missed periods over the past 3 months. The EDDS was shown to have good test-retest reliability, internal consistency, and convergent validity with other eating-pathology scales [73]. Research has shown it to be sensitive as a screening measure in detecting change with eating disorder treatment and is predictive of the development of eating disorder symptoms and depression [74].

International Physical Activity Questionnaires (IPAQ): The IPAQ is used to obtain internationally comparable data on health-related physical activity. Extensive reliability and validity testing has been undertaken in 12 countries (14 sites) across 6 continents since 2000. The short, self-administered format, for use with young and middle-aged adults, will be utilized – which has been shown to have adequate validity and reliability [75].

World Health Organization Disability Assessment Schedule (WHODAS): The WHODAS (12-item version) is a generic assessment instrument for health and disability, and covers 6 domains: (1) Cognition (understanding & communicating), (2) Mobility (moving & getting around), (3) Self-care (hygiene, dressing, eating & staying alone), (4) Getting along (interacting with other people), (5) Life activities (domestic responsibilities, leisure, work & school), and (6) Participation (joining in community activities). The WHODAS produces standardized disability levels and profiles, is applicable across cultures in adult populations, and has a direct conceptual link to the International Classification of Functioning, Disability and Health (ICF) [76].

World Health Organization Health and Work Performance Questionnaire (HPQ): The WHO HPQ is a 9-item questionnaire to evaluate absenteeism and presenteeism in the workplace as indirect costs of illness. The instrument includes questions regarding days (full or in part) of work missed due to personal physical or mental health, days of work missed for other reasons, arriving early or late to work or working on a day off, hours worked in the past 4 weeks and self-evaluations of job performance recently, over the past year, and in comparison to other employees [77] [78].

PROMIS® (Patient Reported Outcome Measurement Information System) Measures (http://www.nihpromis.org; [79, 80]): PROMIS is a U.S.-based cooperative group of research sites and centers of excellence, funded by NIH, and convened to develop and standardize patient outcome measures across studies and settings. The PROMIS measures were developed using item response theory and calibrated on a sample of 21,133 people, with the aim of providing highly reliable, precise measures of patient–reported health status for physical, mental, and social well–being. Most question banks utilize a 7-day recall period and five response options (e.g., 1=Not at all, 5=very much). All instruments developed to be used with computer adaptive testing (CAT) to reduce patient burden. With CAT, the specific construct item that best distinguished between individuals in their test populations is administered first. Based on the individual's response to this item, the computer picks what question will be administered next, and so on, until a reliable estimate of their total score on that construct can be determined. With this method, an average of 5 items is administered for each PROMIS construct listed, thus taking an estimate 1 minute or less to complete. The instruments have been reported to have good reliability and validity [79, 80].

Behavioral Tasks

Bandit Task*:* This task is included to apply Bayesian computational approaches that quantify how individuals switch between an "exploration" and "exploitation" strategy. Subjects have to sample from different choice options with unknown probabilities of success/failure with the goal of maximizing success. The optimal strategy is to start by trying all available options (exploration) to gauge the rate of success of each option, and to switch relatively early to only selecting the option with the highest likelihood of success (exploitation). Participants will

perform a total of 20 three-armed bandit games with a known number of trials (i.e., token) per game. For each game, participants will have 16 tokens (stacked in the middle of the screen) and will have to assign each token to one of three lotteries of their choice (white panels on left, right and middle of the screen). After placing each token, they will earn 1 point if the token turns green or zero points if the token turns red. Each token decision will last about 2 sec. After the button press, the chosen lottery is highlighted for 250ms, after which the token turns green or red to reveal the decision outcome. Participants will be instructed to find the most rewarding lottery and maximize the points earned in each game. Participants are paid an additional $5 or $10 based on the performance on this task.

Change Point Detection Task: For each trial, subjects will attempt to locate a target stimulus in one of three possible locations. The target stimulus consists of a patch of dots, which are predominantly moving in one direction. The other two locations have distractors with dots moving in the opposite direction. However, at the beginning of the trial, the patches of dots are hidden by white circles, which initially appear in the three locations. The subject first selects a location in which to see a patch of dots; a button press indicates the location of choice. The subject is then shown the patch of dots at the selected location, and asked to determine whether it is the target or the distractor. If the subject indicates that the patch is the target, the trial ends. If the subject believes the patch is a distractor, the subject can then indicate a second location to view, and be shown the patch of dots corresponding to the new location. The trial continues in this manner until the subject chooses the patch of dots which is believed to represent the target location. The position of the target location on each trial is determined by a probability distribution, such that one location is most likely to contain the target. It is therefore possible for the subject to learn over several trials which location is most likely to contain the target. However, at random intervals, the probability distribution will change, and a new location will become most likely to contain the target. The subject will then have to update their beliefs about the most likely location in which to locate the target. The experiment consists of 3 blocks with 60 trials per block. Prior to the experimental blocks, the subject will complete practice blocks until accuracy exceeds a certain threshold. Additionally, there is one block of 20 trials where all locations have equal probability that is used as a

baseline measure for response time. Response time and learning rate over time with each target location are the main variables of interest. Participants are paid an additional $5 or $10 based on the performance on this task.

Move-Go and Speed-Stop Task: Driving, as a common real-time motor task, is determined by both motivational factors (safety, time, etc.), and perceptual-motor limits (perceptual delay, motor delay, etc.). It has been shown that people with emotional disorders have impaired driving performance. For example, there have been growing evidence show that depression increases the odds ratio for car accidents and reduces driving performance in a driving simulator. It also has been shown that mood (influenced by music) can impact driving behavior in healthy population. Thus we propose to use a simulated driving task to collect behavioral data. The driving task has two separate components. The Move-Go component is used to measure perceptual and motor speed. In it, subjects are asked to attend to a car presented at the bottom of the screen. As soon as they perceive that the car has started to move, subjects are to move the joy stick all the way forward as quickly as possible. In the Speed-Stop component, subjects are instructed to drive a virtual car on a computer screen from an initial position to a stop sign as quickly as possible and stop as close to the stop-sign as possible without crossing the stop-sign, by pushing or pulling a joystick to control the velocity of the car. Each trial has a fixed time-window of 10 seconds. The car has a linear dynamic system, in which velocity is controlled by joystick position ($dXt = AXtdt + BUtdt$, in which Xt = [car position, car velocity], Ut = control action (car velocity based on joystick position), A = [0 1; 0 -.35], B = [0; 0.5]). This task will be used to estimate each individual's motivational component (goal state, accuracy/effort ratio) using computational models.

Implicit Approach Avoidance Task (AAT): Purpose: This task is designed to assess automatic action tendencies to approach or avoid positive, negative, and neutral stimuli [81]. Description: In this task, participants are asked to respond to a series of cues conveying positive, negative, or neutral emotional information (e.g., happy, angry, disgusted, neutral faces) by either pulling (approach) or pushing (avoidance) a joystick towards or away from themselves. Participants will see a picture in the center of the screen framed by either a blue or a yellow border. They will be instructed to pull the joystick towards themselves when the border is one color and to

push the joystick away when the border is the other (counterbalanced across subjects). Pushing the joystick results in the picture zooming out and pulling the joystick results in the picture zooming in, thereby creating the visual impression that the pictures are coming closer or moving away. Reaction times are calculated based on the duration from the time the picture appeared on the screen to the time it disappeared. An approach bias score is computed by subtracting each participant's mean response latency in the pull condition for a given stimulus type from their mean response latency in the corresponding push condition (e.g., positive faces-push minus positive faces-pull). The AAT is a well-established measure of implicit approach/avoidance behavioral tendencies [82].

Approach-avoidance conflict task (AAC): This computer-based task is designed to examine decision-making in the context of affective risk. For this task, the participant is presented with a series of decisions between two different outcomes. Each outcome is associated with either a positive or negative valenced image/sound pair (IAPS and IADS), and some amount of point or gains. The participant is not able to select with certainty one outcome over the other. Instead, only the probability of the two outcomes is chosen, in the range from 10-90%, depending on the subject's stated preference for the two outcomes on a 9 point scale. The standardized IAPS and IADS stimulus sets have been used extensively in emotion research and are reliable elicitors of affective arousal [83, 84]. Conflict trials are those in which a negative affective image is combined with point rewards, while the positive affective image is combined with no point rewards. There are three levels of conflict (2-point, 4-point, and 6-point). The main outcome variables of the task are: (1) mean approach behavioral for the different condition types (conflict, approach-only, and avoid-only). Before and after the task, participants rate their mood in terms of pleasantness, unpleasantness, and overall intensity on a visual analogue scale (VAS). After the task, participants complete a 14-item questionnaire asking questions about their experience of the task (i.e., "Overall, this task was enjoyable"), rating each item on a 1-7 Likert scale. This measure was originally developed by Dr. Robin Aupperle [85]. This task takes approximately 20 minutes to administer.

Modified Probe Detection Task (MPDT): Attentional bias for positive and negative information will be measured using a version of the modified probe detection task [86]). Each trial consists

of the identification of a cue location, brief presentation of a cue at that location (a small line oriented either horizontally or vertically), presentation of a pair of images (one representational, one non-representational), and presentation of a target, which is another line in either of two locations and is either horizontal or vertical. This target is presented until the participant responds, indicating whether the target is of the same or different orientation from the cue. Representational [86] stimuli will comprise IAPS images taken from positive, negative, or neutral valence sets. Each representational image is paired with one non-representational image, taken from a set of images of abstract art. Participants are presented with a total of 192 trials: 64 from each of positive, negative, and neutral images. The following traits are balanced across trials: representational image location, cue location, cue orientation, target location, target orientation, image duration (500 or 1000ms). The main outcome measures are the positive and negative engagement and disengagement biases [87].

Emotional Reactivity: This task consists of the presentation of 8 positive, 10 neutral, and 8 negative images. Each trial begins with a 20-26s fixation period, followed by presentation of one image for 6s. After each image, the participant makes valence and arousal ratings on a 7 point scale. During image presentation and sometimes during fixation, participants receive a ~95DB 50ms white noise sound meant to elicit a startle response [88]. The main purpose of this paradigm is to provide a reliable and validated assessment of psychophysiological responses to emotional stimuli and startle-eliciting stimuli [89]. The collection of psychophysiological recordings will therefore be integral to this task specifically.

Heartbeat Tapping: This task will contain four 1 minute trials, during which the participant has their eyes closed and is tapping a vmeter device [90].

Cold Pressor Challenge: This task will have each participant immerse their left hand in a circulating pool of water cooled to 6 degrees Celsius. Participants will be asked to keep their hand in the water for as long as they can tolerate, providing a brief measure of pain/stress tolerance and emotional reactivity/regulation. During each immersion participants will provide real-time ratings of their degree of pain unpleasantness/discomfort using the vmeter. The Cold

Pressor paradigm is the gold standard which has been repeatedly used over the past century to safely induce transient states of intense pain [91, 92]. Maximum trial length will be 2 minutes.

Breath Hold Challenge: This task will have participants undergo 2 expiratory breath holds, providing a brief measure of interoceptive distress tolerance and carbon dioxide sensitivity. The maximum trial length is 1 minute, and there will be a 2-minute rest between trials. Participants are instructed to hold their breath for as long as they can tolerate following a normal (not forced) exhalation. The duration of each breath hold will be calculated starting from the moment when they begin exhaling and ending the moment they start inhaling again.

Psychophysiological Recordings: Heart rate (ECG), respiration (RSP), skin conductance (SCR), and eye blink electromyogram (EMG) will be recorded continuously during each the behavioral tasks described above, using BIOPAC instrumentation (Lehigh, Pennsylvania). These physiological indices will also be measured during a 5-minute passive viewing task where subjects are presented with a slideshow of images of different flowers. The images are not expected to affect the physiological recordings, so data from this task are used as a physiological baseline to compare to the behavioral tasks. Measuring these indices during the behavioral tasks listed above will not add any time to the tasks themselves, but should take approximately 10-15 minutes for setup (i.e., to attach all electrodes, respiration belt, etc.).

BIOPAC Systems provides both hardware for collection of these measures (BioPac MP150 system) and software (AcqKnowledge software) for analyzing these measures. All of these measures are commonly used in emotional processing research and are relatively non-invasive. The use of all of these measures concurrently allows for a more thorough understanding of sympathetic and parasympathetic nervous system influences on physiological responses to negatively and positively-valenced stimuli, interoceptive stimuli, cognitive processing and decision-making.

Facial Expressions: Advances in computer vision and machine learning over the past 15 years have led to the emergence of technology for automatic analysis of affective behavior [93]. During this time, the Machine Perception Laboratory at UCSD (MPLab) has focused on development of systems for automatic analysis of facial behavior, including audio-visual speech

recognition [94-96] and recognition of facial expressions [95-99]. The output of the face detector is scaled to 90x90 and fed directly to the facial expression analysis system. First the face image is passed through a bank of Gabor filters at 8 orientations and 9 scales (2-32 pixels/cycle at 0.5 octave steps). The filterbank representations are then channeled to a classifier to code the image in terms of a set of expression dimensions. Research at the MPLab has demonstrated that performing feature selection on the Gabor filters prior to classification enhances both speed and accuracy. This approach combines feature selection based on Adaboost with feature integration using support vector machine. *Automatic Facial Expression Analysis*: A video camera will record each participant during the behavioral tasks described above in order to permit coding of facial expressions. Automatic facial expression analysis will be conducted by the EMOTIENT [100], software developed and validated by our collaborators at the Machine Perception Laboratory at UCSD (MPLab). EMOTIENT analysis corresponds to the well-validated Facial Action Coding System (FACS [101, 102]), a comprehensive method to objectively code facial expressions. EMOTIENT automatically codes the intensity of 26 component facial movements referred to as action units (Aus).

Neuropsychological Tasks

Wide Range Achievement Test (WRAT-4 reading): The WRAT-4 is an individually administered test of reading designed to measure general academic competence. The main variable of interest will be the total words pronounces correctly [103].

Delis-Kaplan Executive Function System (D-KEFS) Color-Word Inhibition Test: The D-KEFS Color-Word Inhibition Test is designed to assess verbal response inhibition and attentional switching. Participants are asked to name patches of colored ink (Color Naming subtest), read color-related words (Word Reading subtest), or to name the ink that color-related words are written in (Inhibition subtest). The speed at which participants complete the task and the number of mistakes made during completion are recorded. The main variables of interest for this study are the total time to complete the word reading, color naming, inhibition, and inhibition/switching subtests [104].

Delis-Kaplan Executive Function System (DKEFS) Verbal Fluency: This test is meant to measure information retrieval that is under conscious cognitive control and presumably an aspect of executive functions. On each of six one-minute trials, the examinee is asked to say as many distinct words as possible that meet a certain criterion. For the first three trials, the words must begin with a particular letter, for the next two trials, the words must belong to a particular semantic category, and for the last trial, words must alternate between two semantic categories. The main variable of interest is the total number of words correctly identified for the letter subtests and the semantic category subtests [104].

Wechsler Adult Intelligence Scale (WAIS-IV) Digit Span: This sub-test of the WAIS-IV is used to assess attention and working memory and requires participants to repeat a series of numbers in forwards and backwards order (Digit Span). The accuracy of their responses is recorded. The main variables of interest are the total score forward and backward [105].

Finger Tapping Test (FTT): The FTT is a neuropsychological test that examines motor functioning, specifically, motor speed and has also been shown as a sensitive measure of testing effort [106]. The main variables of interest are the average number of taps with the index finger per 10 seconds for dominant and non-dominant hands.

WAIS-IV Digit Symbol Coding [105] The Digit Symbol is a neuropsychological test of visuomotor speed and working memory. The test requires individuals to match a symbol to a number according to a key at the top of the page. The main variable of interest will be the number of symbols matched in the time limit (90 seconds).

California Verbal Learning Test (CVLT-II): The CVLT-II is used to evaluate verbal learning and memory. The CVLT consists of a list of 16 words from four semantic categories that is presented orally for five immediate recall trials (List A). Subsequent to the five learning trials of List A, a second 16-item word list (List B) is presented once. Free- and category-cued-recall trials of List A follow the immediate free-recall of List B. After a 20-min delay, free recall, cued recall, and a recognition trial of List A occur. The recognition trial contains the 16 target items from the first list along with 28 distractor items. During the recognition trial, the examiner presents each of the 44 items orally to the participant, who indicates whether or not the item was from the first

word list. The main variables of interests for this study are the immediate recall from Trials 1-5 List A, Immediate and Delayed free recall and cued recall of List A. In addition, as most patients (even those with neurological disorders) are expected to score above chance on Recognition, this test will also be used to assess whether participants are putting in sufficient effort towards testing.

Functional MRI Tasks

Reward Processing Task: To measure behavioral and neural responses to rewards and losses, participants will complete the monetary incentive delay task (MID), a well-established measure of reward processing [107, 108]. This task dissociates anticipatory and consummatory phases of reward processing and has been shown to reliably activate brain regions implicated in regulating approach-related response tendencies and reward sensitivity (e.g., ventral striatum). On each trial, participants are given a cue indicating potential reward (circle), loss (square), or no reward/loss (circle or square). In order to receive a specified reward or avoid a loss, participants are required to press a button within a certain duration of time (adapted for individual participant reaction times) following presentation of a white square (target cue). Task difficulty, based on reaction times collected during a practice session, is set such that each participant should succeed on ~66% of trials. The degree of potential reward or loss is varied on three levels indicated by the number of horizontal lines in a cue, i.e., one line indicates the lowest reward value (no reward), two lines an intermediate reward, and three lines the highest reward. For the MID task, participants can gain or lose points and earn an average of $30. The primary outcomes of interest will be: (1) anticipation of reward vs. no-reward, (2) receipt of reward outcomes vs. no-reward outcomes; (3) anticipation of loss vs. no-loss, and (4) receipt of loss outcomes vs. no-loss outcomes. The Monetary Incentive Delay Task will take about 18 minutes to complete.

Fear Conditioning Task: The fear conditioning task is based closely on the task successfully used by [109] to uncover neural bases of fear conditioning associated with trait anxiety [109]. The stimuli will consist of two neutral, non-social, abstract images as conditioned stimuli (CS), presented for 2 seconds at a time. Which image is the CS+ (paired with the unconditioned

stimulus (US) during fear acquisition) and which is the CS- (never paired with the US) will be counter-balanced across participants. The US will be a 1s scream beginning 500ms after image onset. In the 9-15 seconds between CS image presentations, participants will be engaged in a continuous performance task requiring a right or left button press in response to right or left facing arrows. This serves to increase engagement and attention in the inter-trial interval. The task will consist of three components: a brief familiarization period, fear acquisition, and fear extinction. First, the *familiarization phase* (2.5 minutes) involves five presentations of each CS with no instances of the US to provide a baseline and allow familiarization to the scanner environment. Next, the *acquisition phase* will be broken into two runs of 8 minutes each. Each run will consist of 15 presentations of the CS- and 20 presentations of the CS+: five with (CS+ paired) and 15 without (CS+ unpaired) the US. This follows Sehlmeyer et al. [110] and allows for an equal number of trials to be included in the analysis (the CS+ paired trials will be excluded from analysis so as to not confound processing of the CS+ with reactivity to the US). Finally, the *extinction phase* will involve 25 presentations of each CS with no instances of the US. Participants will rate their valence, arousal and anxiety level to each CS at four times during the task: after familiarization, halfway through acquisition, after acquisition, and after extinction. Trials will be presented in a fixed, pseudo-randomized order, constrained so that no more than two identical trials occur in a row.

Stop Signal (Inhibition) Task: At the onset of each trial, either an 'X' or an 'O' appears on a black background back-projected to the magnetic resonance imaging room. Participants are instructed to press, as quickly as possible, the left button when an 'X' appeared, and the right button when an 'O' appeared. They are also instructed not to press either button whenever they hear a tone during a trial (stop trials). Each trial lasts 1300 ms and each trial is separated by 200-ms inter-stimulus intervals (blank screen; see [111]). Individual response latency is used to denote the period of inhibitory processing and provide a subject-dependent jittered reference function. Participants perform six blocks of the task, each containing a total of 48 trials (12 stop and 36 nonstop trials in each block). Trial order is pseudo-randomized throughout the task and counterbalanced. Prior to scanning, participants perform the stop task in a behavioral testing session in order to determine their mean reaction time (RT) from 'X' and

'O' stimuli onset. Such individual measures are used to determine the stop signal delay (SSD) for the six different stop trial types. Specifically, stop signals are delivered at 0 (RT-0), 100 (RT-100), 200 (RT-200), 300 (RT-300), 400 (RT-400), or 500 (RT-500) ms less than the mean RT after the beginning of the trial, thus providing a range of difficulty level.

Interoceptive Attention Task: During this task, subjects alternate between two conditions: the interoception condition and the exteroception condition. During the interoception condition, the word "HEART" or "STOMACH" is presented on the screen and subjects are instructed to focus their attention on interoceptive sensations from that organ. For example, upon seeing the word "HEART", subjects focus on how intensely they can feel the sensation of their heart beating. During the exteroception control condition, the word "TARGET" is presented in the middle of the screen and the color of the word alternates from black to a lighter shade of gray every second. The subjects are instructed to focus their attention on the intensity of these color changes. Each task condition is presented in 10-second blocks, and half of the blocks are followed immediately by a 5-second response period during which the subject uses a visual scale (1-to-7) to rate the intensity of interoceptive sensations or exteroceptive color changes experienced during the preceding trial. Blocks are often separated by a variable inter-stimulus interval, during which subjects look at a fixation mark. Each run of the task begins with a 10-sec initial fixation period and ends with a 10-sec final fixation period. Subjects will perform 2 scanning runs, each lasting 360 seconds (including initial and final fixation periods).

MRI, EEG and fMRI Data Analysis

EEG-fMRI

Residual ballistocardiac artifacts in the EEG signals will be removed using the independent component analysis method. The de-noised data will be subsequently band-pass filtered from 1 Hz to 70 Hz, downsampled to 250 Hz, and re-referenced to the common average reference. For the EEG signals recorded outside the scanner, data will be similarly band-pass filtered from 1 Hz to 70 Hz, downsampled to 250 Hz, and re-referenced to the common average reference.

Other types of EEG-informed fMRI analyses include: EEG band-pass correlation analysis with fMRI data (Fast Fourier transformation will be used to estimate EEG δ (1–3 Hz), θ (4–7 Hz), α (8-13 Hz), and β (13–30 Hz) frequency band spectral power, and its temporal changes during fMRI) [112], EEG microstate analysis in time and spatial domain (EEG temporal independent microstates and their spatial representation correlates with slow hemodynamic activity in brain resting state networks and their spatial maps) [113, 114], EEG-asymmetry analysis, and EEG-coherence analysis (e.g. quantify and correlate changes in EEG alpha band asymmetry and/or EEG coherence with fMRI data [115]), and behavioral measures [116].

fMRI Pre-Processing

For task fMRI analysis, a multivariate regressor approach will be used to relate changes in echo planar imaging (EPI) intensity to differences in task characteristics. The aE-REMCOR motion will be corrected on a slice by slice basis. fMRI data will be co-registered using a 3D-coregistration algorithm. Motion parameters will be obtained across the time series for each subject. Subjects will be excluded if the average in any one of these six parameters exceeds 2 standard deviations from the mean or if mean displacement exceeds the size of the voxel (4 mm). This assures that differences at group-level are not due to differences in movements during scanning. Motion parameters will be used as regressors to adjust EPI intensity changes due to motion artifacts. This has been shown to increase power in detecting task-related activation. All slices of the EPI scans will be temporally aligned following registration to ensure different relationships with the regressors are not due to the acquisition of different slices at different times during the repetition interval.

Resting State Pre-Processing

The six motion parameters from the image registration process will be used to construct a time series reflecting the Euclidean normalized derivatives of the motion, and any time point, plus one prior, where the derivative is greater than 0.2 or where more than 10% of brain voxels are considered as outliers will be censored. Nuisance variables will be regressed out of the normalized data and include the de-meaned motion parameters and their derivatives, the

average signal taken from a local eroded local white matter mask, the first 3 principal components of the lateral ventricles, and terms reflecting baseline drift.

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Supplementary Table 1. Quarterly Follow-up Assessments

QUARTERLY FOLLOW-UP ASSESSMENTS	
Domain	Description
STANDARD SCALES	
Demographics	Demographics and Psychosocial Form (update)
History	Assessment of Medical and Medication History (update)
History	Life chart interview (update)
Substance Use	Customary Drinking and Drug Use Record (CDDR)
Depression	Quick Inventory of Depressive Symptomatology (QIDS-SR)
Eating Behavior	Simplified Nutritional Appetite Questionnaire (SNAQ)
Compliance	Medication Compliance
Compliance	Therapy Compliance
Disability	World Health Organization Disability Assessment Schedule
Presenteeism/Absenteeism	(WHODAS)
Suicidal Ideation	WHO Health and Work Performance Questionnaire (WHO HPQ)
Pain	Columbia-Suicide Severity Rating Scale (C-SSRS)
	Wong-Baker FACES Pain Rating Scale
PROMIS MEASURES	
Negative Valence	PROMIS Anxiety
Negative Valence	PROMIS Depression
Negative Valence	PROMIS Anger
Positive Valence	PROMIS/Neuro-QOL Positive Affect and Well-being
Cognitive	PROMIS Cognitive Abilities
Cognitive	PROMIS Cognitive General
Fatigue	PROMIS Fatigue
Sleep	PROMIS Sleep Disturbance
Sleep	PROMIS Sleep-related Impairment
Alcohol	PROMIS Alcohol Use
Alcohol	PROMIS Alcohol: Negative Consequences
Alcohol	PROMIS Alcohol: Positive Consequences
Alcohol	PROMIS Alcohol: Negative Expectancies
Alcohol	PROMIS Alcohol: Positive Expectancies
Nicotine	Nicotine Dependence
Nicotine	Coping Expectancies
Nicotine	Emotional and Sensory Expectancies
Nicotine	Health Expectancies
Nicotine	Psychosocial Expectancies
Nicotine	Social Motivations
Social	PROMIS Social Satisfaction DSA
Social	PROMIS Social Satisfaction Role
Social	PROMIS Ability to Participate Social

Social	PROMIS Emotional Support
Social	PROMIS Information Support
Social	PROMIS Instrumental Support
Social	PROMIS Satisfaction Roles Activities
Social	PROMIS Social Isolation
Physical	PROMIS Physical Function
Pain	PROMIS Pain Interference
Pain	PROMIS PAIN Behavior
Sex	PROMIS Global Satisfaction with Sex Life
Sex	PROMIS Interest in Sex Activity

Supplementary Table 2. One-Year Follow-up Session

ONE-YEAR FOLLOW-UP SESSION	
Domain	Description
DIAGNOSTIC AND DEMOGRAPHIC ASSESSMENT	
Diagnosis	MINI 6.0
Demographics	Demographics and Psychosocial Form (update)
History	Assessment of Medical and Medication History (update)
History	Life chart interview (update)
Substance Use	Customary Drinking and Drug Use Record (CDDR)
Compliance	Medication Compliance
Compliance	Therapy Compliance
Suicidal Ideation	Columbia-Suicide Severity Rating Scale (C-SSRS)
Pain	Wong-Baker FACES Pain Rating Scale
STANDARD SELF-REPORT SCALES	
Negative Valence/Interoception	Anxiety Sensitive Index (ASI-3)
Negative Valence	Ruminative Responses Scale (RRS)
Positive / Negative Valence	Positive and Negative Affect Schedule-Expanded Form (PANAS)
Depression	Quick Inventory of Depressive Symptomatology (QIDS-SR)
Positive Valence	TEPS anticipation/consumption/ pleasure
Arousal / Interoception	Multidimensional Assessment of Interoceptive Awareness
Eating Behaviors	Eating Disorders Diagnostic Scale
Eating Behaviors	Simplified Nutritional Appetite Questionnaire (SNAQ)
Physical Activity	International Physical Activity Questionnaire (IPAQ)
Disability	World Health Organization Disability Assessment Schedule (WHODAS)
Trauma	Traumatic Events Questionnaire (TEQ)
Absenteeism/Presenteeism	WHO Health and Work Performance Questionnaire
PROMIS MEASURES	
Negative Valence	PROMIS Anxiety
Negative Valence	PROMIS Depression
Negative Valence	PROMIS Anger
Positive Valence	PROMIS/Neuro-QOL Positive Affect and Well-being
Cognitive	PROMIS Cog Abilities
Cognitive	PROMIS Cog General
Fatigue	PROMIS Fatigue
Sleep	PROMIS Sleep Disturbance
Sleep	PROMIS Sleep-related Impairment
Alcohol	PROMIS Alcohol Use
Alcohol	PROMIS Alcohol: Negative Consequences
Alcohol	PROMIS Alcohol: Positive Consequences

Alcohol	PROMIS Alcohol: Negative Expectancies
Alcohol	PROMIS Alcohol: Positive Expectancies
Nicotine	Nicotine Dependence
Nicotine	Coping Expectancies
Nicotine	Emotional and Sensory Expectancies
Nicotine	Health Expectancies
Nicotine	Psychosocial Expectancies
Nicotine	Social Motivations
Social	PROMIS Social Satisfaction DSA
Social	PROMIS Social Satisfaction Role
Social	PROMIS Ability to Participate Social
Social	PROMIS Emotional Support
Social	PROMIS Information Support
Social	PROMIS Instrumental Support
Social	PROMIS Satisfaction Roles Activities
Social	PROMIS Social Isolation
Physical	PROMIS Physical Function
Pain	PROMIS Pain Interference
Pain	PROMIS PAIN Behavior
Sex	PROMIS Global Satisfaction with Sex Life
Sex	PROMIS Interest in Sex Activity
	Physio Setup
Computational - cognitive	Change Point Detection Task
	Regular Bandit Task
	Start / Stop Task (Driving)
Positive / Negative Valence	Implicit Approach / Avoidance Task
	Attentional Bias / Dot Probe Task
	Emotional Reactivity Task
	Baseline Task
	Approach Avoidance Conflict Task
Arousal / Interoception	Breath hold
	Heartbeat Tapping Task
	Cold Pressor
Neuropsychology	WRAT reading
	DKEFS Color-Word Inhibition
	DKEFS verbal fluency
	WAIS-IV digit span
	Finger Tapping Test
	WAIS-IV Digit Symbol Coding
	California Verbal Learning Test
Biomarker and Microbiome	Repeat baseline measures, except for stem cells and genetics

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract **Pages 1-2**	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale **Pages 3-10**	2	Explain the scientific background and rationale for the investigation being reported
Objectives **Pages 10-11**	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design **Page 12**	4	Present key elements of study design early in the paper
Setting **Pages 13, 27**	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants **Pages 11, 13, 25-26**	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables **Pages 10-13**	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement **Pages 13-19, supplementary materials**	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias **Pages 26-27**	9	Describe any efforts to address potential sources of bias
Study size **Page 25**	10	Explain how the study size was arrived at
Quantitative variables **Pages 20-25**	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods **Pages 20-25**	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants N/A	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data N/A	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data N/A	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results N/A	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses N/A	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results N/A	18	Summarise key results with reference to study objectives
Limitations **Page 3**	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation N/A	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability **Page 3**	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding **Page 28**	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.