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Tulsa 1000: a naturalistic study protocol for multilevel assessment and outcome prediction in a large psychiatric sample

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ABSTRACT

Introduction Although neuroscience has made tremendous progress towards 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 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 T-1000 is a naturalistic study that will recruit, assess and longitudinally follow 1000 participants, including healthy controls and treatment-seeking individuals with mood, anxiety, substance use and eating disorders. Each participant will undergo interview, behavioural, biomarker and neuroimaging assessments over the course of 1 year. The study goal is to determine how disorders of affect, substance use and eating behaviour organise across different levels of analysis (molecules, genes, cells, neural circuits, physiology, behaviour 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 multilevel latent variable analysis will be standardised assessments that can be developed into clinical tools to help clinicians predict outcomes and select the best intervention for each individual, thereby reducing the burden of mental disorders, and taking psychiatry a step closer towards personalised medicine.

Ethics and dissemination Ethical approval was obtained from Western Institutional Review Board 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; Pre-results.

Strengths and limitations of this study

- 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 uses novel statistical approaches to identify and replicate latent constructs within a large and complex dataset.
- The study does not include controlled treatment interventions and 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 with a cross-sectional study.
- The study recruitment aims to generate a representative sample of a local Midwestern community in the USA, including subsamples selected to represent the US community at large, however the results may not be generalisable to individuals with mood, substance use and eating disorders in other regions of the USA 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 US$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 (SU) and eating disorders (ED), which further exacerbate the cost and suffering associated with these disorders. The lifetime prevalence of ED is comparatively lower at <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, SU 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 non-linear such that as many as 50% of treatment-seeking individuals relapse within a month of last use. The neural basis and behavioural 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 use 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 behaviours.[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, behaviour, physiology, neural circuitry, genetics and clinically relevant psychopathology). The Tulsa 1000 (T-1000) aims to address these needs by determining how biological and objective behavioural measures can contribute to improving assessment and treatment of mental illness.

The overarching goal of this study is to use a dimensional psychopathological framework focused on mood-related, anxiety-related, eating-related and substance-related dysfunctions to identify latent variables that generalise across units of analyses, that is, 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, for example, severity of mood symptoms and network characteristics of resting state functional MRI (fMRI). 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 behavioural 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 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 online supplementary materials.

Cognitive system

The major constructs that were considered by the RDoC committee on cognitive systems included: (1) *attention,* that is, a set of processes that regulate access to capacity-limited systems, such as awareness, higher perceptual processes and motor action; (2) *perception*, that is, 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*, that is, the acquisition or encoding, storage, consolidation and retrieval of facts and events; (4) *language*, that is, a system of shared symbolic representations of the world, the self and abstract concepts that supports thought and communication; (5) *cognitive control*, that is, a system that modulates the operation of other cognitive and emotional systems, in the service of goal-directed behaviour, when prepotent modes of responding are not adequate to meet the demands of the current context; (6) *working memory*, that is, 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 hypothesised to be dysfunctional in individuals with SU problems.[39] However, it is unclear how dysfunctional cognitive control is associated with continuing SU, and how this affects relapse following a period of recovery from SU. 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 fMRI data, to investigate subtle behavioural 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 modelling 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 behaviour.[52–54] One important aspect of the arousal domain is the link to homeostatic drives and interoception. Different conceptualisations 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 generalised view that the anterior cingulate cortex (ACC), among other functions, orchestrates approach or avoidance behaviours 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 T-1000 study are: (a) symptoms, (b) paradigms/behaviour, (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 behaviour 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 T-1000 study.

Microbiome

The human body can be considered a superorganism 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 revolutionised 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 show 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 signalling 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, behavioural 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 (MA), SU and eating behaviours 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, SU or eating behaviours. 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, SU 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 (eg, 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 ED (anorexia nervosa and bulimia) are moderately heritable—in the region of 40%–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 ~5500 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 T-1000. Here, the proposed within-subject genetic analyses will emphasise the prediction of naturalistic clinical outcomes such as response to pharmacological and/or non-pharmacological treatment. Furthermore, the genetic data collected will be stored for future testing and combined with multiple phenotypes (eg, 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 characterised by activation of the innate immune system together with suppression of elements of the adaptive immune response.[82–87] However, progress has been limited by a disproportionate focus on a static and narrow aspect of innate immunity, that is, single time-point measurements of C reactive protein 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. Furthermore, 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 further our understanding of the nature of immune dysfunction in psychiatric illness and may lead to the identification of prognostic and/or predictive biomarkers that possess clinical utility.

METHODS

Aims and objective

This is a multilevel, longitudinal observational study of healthy controls (HC) 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, SU and eating behaviour are organised across different units of analysis (genes, molecules, cells, neural circuits, physiology, behaviour and self-report) and different domains of functioning (positive and negative valence, cognition and arousal/interoception). On 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 (eg, 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 operating 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 MA, 300 SU, 100 ED and 100 mentally and physically HC participants. In order to obtain 1000 participants who complete the year-long study, we plan to enrol 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 and 38 kg/m^2. Subjects will be referred from local treatment facilities or seeking treatment for anxiety and/or depressive symptoms, problems related to SU or problems related to eating behaviour. As part of the inclusion criteria, MA, SU and ED participants must also screen positive for these conditions as indicated by a score on the Patient Health Questionnaire-9 ≥10 and/or Overall Anxiety Severity and Impairment Scale ≥8, drug abuse screening test-10 score >2 or Sick, Control, One, Fat, Food Questionnaire eating disorder screen score ≥2. Participants who meet criteria for one primary domain may also screen positive for one of the other study domains. HC 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, neurological, haematological, rheumatological or metabolic disturbance; or any other condition that, in the opinion of the investigator, would make participation not be in the best interest (eg, 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 Diagnostic and Statistical Manual of Mental Disorders (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, for example, anxiolytics, antipsychotics, antidepressants or mood stabilisers. 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 haemodynamic response (eg, 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, bypass surgery/coronary artery clips, hearing aid, heart valve replacement, shunt (ventricular or spinal), electrodes, metal plates/pins/screws/wires or neurostimulators/biostimulators, (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 min; (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 MRI (eg, due to claustrophobia), biopsy, blood draws or behavioural assessment. However, failing to complete some individual aspects of these assessment sessions will be acceptable (eg, being unwilling to answer individual items on some questionnaires or being unwilling to complete a behavioural task), (19) non-correctable vision or hearing problems. Once participants have been enrolled, they will be followed for the study duration even if they fulfil exclusion criteria for initial enrolment, for example, an individual with an SU 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, for example, 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, behaviour, 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, SU and eating behaviour 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 multilevel assessment based on the RDoC approach that consists of (a) a standardised diagnostic assessment, (b) self-report questionnaires assessing the positive and negative valence domains as well as interoception, (c) behavioural 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) fMRI 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 iPS and (i) genetic as well as epigenetic assessments. Subsequently, these individuals will be followed-up quarterly and for 1 year. At months 3, 6 and 9, only self-report assessments will be collected, and the participants will be re-assessed using a multidomain 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) utilisation 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 2-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 (eg, 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, SU or ED, it will be important to characterise how our findings map onto the 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 V.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, social anxiety disorder, post-traumatic stress disorder, generalised anxiety disorder, ED, obsessive-compulsive disorder and 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 behavioural testing session (session 2) and neuroimaging and biomarker testing sessions (sessions 3–5). During the behavioural session, participants will complete a battery of neuropsychological assessments, a set of cognitive tasks which have been selected based

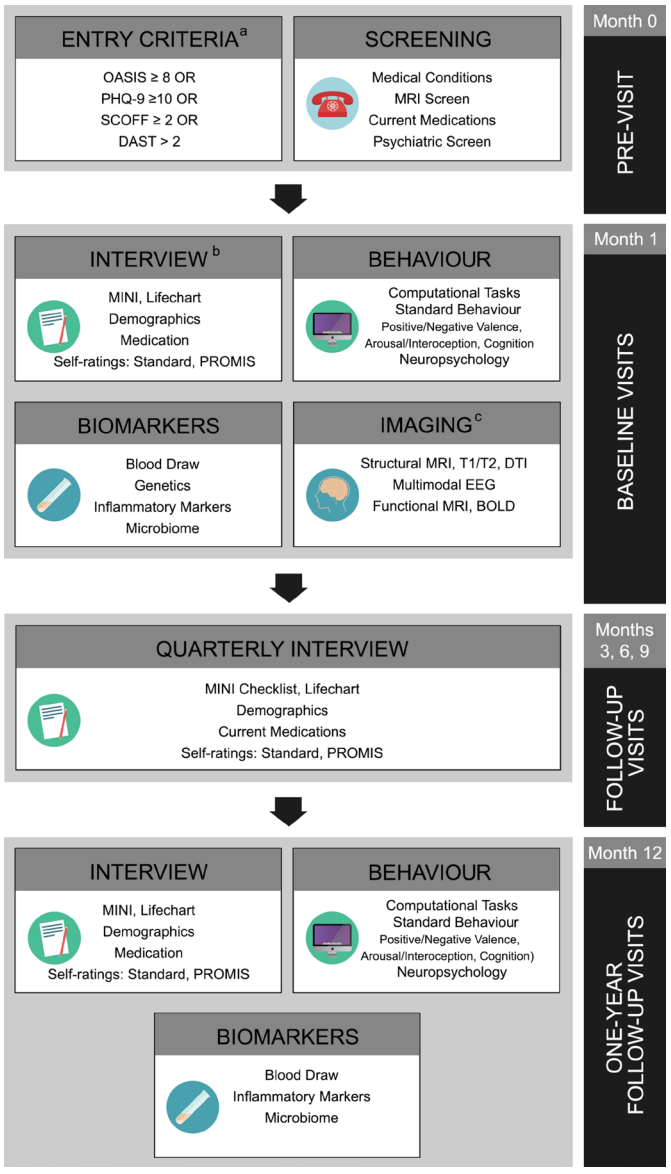

Figure 1 Tulsa 1000 workflow schematic. BOLD, blood oxygen level-dependent; DAST, drug abuse screening test; DTI, diffusion tensor imaging; EEG, electroencephalogram; MINI, Mini International Neuropsychiatric Interview; OASIS, Overall Anxiety Severity and Impairment Scale; PHQ-9, Patient Health Questionnaire; 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).

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 behavioural 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, fMRI and electroencephalogram (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 the Research Electronic Data Capture (REDCap).[90]

Study sessions

Detailed descriptions of the clinical, demographic, self-report, behavioural, neuropsychological and functional neuroimaging measures listed below are provided in the online 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 assessments is expected to take approximately 4.5 hours to complete and can be split into two or more visits.

Baseline behavioural session

Behavioural 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. Behavioural assessments will be conducted by trained research assistants. The behavioural session is expected to take about 4 hours to complete and can be split into two or more visits (table 2).

Baseline biomarkers

Table 3 summarises 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 min to complete sample collection.

Baseline neuroimaging

The session will consist of one 60 and one 120 min 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 (box).

Quarterly follow-up session

These sessions will examine the course of outcomes in individuals with dysregulated MA, SU or problematic eating behaviour. These assessments will be brief in-person visits.

Table 1 Baseline session: clinical interview, demographics and questionnaires

Domain	Assessment
Clinical rating scales and demographics	
Diagnosis	Mini International Neuropsychiatric Interview V.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[106]
Handedness	Edinburgh Handedness Inventory[107]
Compliance	Medication compliance
Compliance	Therapy compliance
Traumatic head injury	Tulsa head injury screen
Family psychiatric history	Family history screen[108]
Suicidal Ideation	Columbia-Suicide Severity Rating Scale[109 110]
Pain	Wong-Baker FACES Pain Rating Scale[111]
Self-report scales	
Negative valence	State Trait Anxiety Inventory[112]
Negative valence/ interoception	Anxiety Sensitivity Index[113]
Negative valence	Ruminative Responses Scale[114]
Depression	Quick Inventory of Depressive Symptomatology[115]
Trauma	Traumatic Events Questionnaire[116]
Trauma	Child Trauma Questionnaire[117]
Positive/ negative valence	Positive and Negative Affect Schedule-Expanded Form[118]
Positive/ negative valence	Behavioural Inhibition System/ Behavioural Approach Scale[119]
Positive valence	Temporal Experience of Pleasure Scale (TEPS) [120]
Positive valence	UPPS Impulsive Behavior Scale[121]
Empathy-like	Interpersonal Reactivity Index[122 123]
Personality	Big Five Inventory[124]
Arousal/ interoception	Toronto Alexithymia Scale[125 126]
Arousal/ interoception	Multidimensional Assessment of Interoceptive Awareness[58]
Eating behaviours	Three Factor Eating Questionnaire[127–129]
Eating behaviours	Eating Disorders Diagnostic Scale[130]
Eating behaviours	Simplified Nutritional Appetite Questionnaire[131]

Continued

Table 1 Continued

Domain	Assessment
Physical activity	International Physical Activity Questionnaire[132]
Disability	WHO Disability Assessment Schedule[133]
Absenteeism/ presenteeism	WHO Health & Work Performance Questionnaire[134]
Patient Reported Outcome Measurement Information System (PROMIS) measures[135 136]	
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 behaviour
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

Table 2 Behavioural and neuropsychological tasks

Domain	Task
Computational-cognitive	Change Point Detection Task[137]
	Three Arm Bandit Task[138]
	Start/Stop Task[139]
Positive/negative valence	Implicit Approach/Avoidance Task[140]
	Attentional Bias/Dot Probe Task[141]
	Emotional Reactivity Task[142]
	Approach Avoidance Conflict Task[143]
Arousal/ interoception	Breath Hold
	Heartbeat Tapping Task
	Cold Pressor[144 145]
Neuropsychology	Wide Range Achievement Test (WRAT) Reading[146]
	Delis-Kaplan Executive Function System (DKEFS) Color-Word Inhibition[147]
	DKEFS verbal fluency[147]
	Wechsler Adult Intelligence Scale (WAIS-IV) digit span[148]
	Finger Tapping Test
	WAIS-IV Digit Symbol Coding[148]
	California Verbal Learning Test[149]

The quarterly follow-up assessments will take approximately 1.5 hours every 3 months during the 12-month follow-up time period (see online 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 1–3 visits (online 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 multilevel 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

Table 3 Examples of immune-related measurements

Immunophenotype	Reported abnormality in depression, eating disorders or addiction disorders	References
Cytokines	Elevations in pro-inflammatory cytokines	150–153
PBMC gene expression	Increased mRNA expression of pro-inflammatory mediators	154–157
Kynurenine pathway	Increased neurotoxic kynurenine metabolites	158–161
T-cells	Altered T-cell function and numbers	162 163
Natural killer cells (NKC)	Reduced NKC function	164–166
Pathogens	Increased seropositivity for *Toxoplasma gondii* and herpesviridae	167 168

MRNA, messenger ribonucleic acid; PBMC, peripheral blood mononuclear cell.

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, stabilising, transporting and purifying samples which includes cotton-swabs, tubes labelled 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 payment for completing the study as mentioned in table 4.

Box Baseline neuroimaging sessions

32 channel head coil MRI: structural and perfusion

- Participant Last Use Summary (PLUS)
- 3-plane localiser, 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 labelling
- Diffusion tensor imaging

8 channel head coil MRI, and fMRI with concurrent EEG

- Task training and practice
- Karolinska Sleepiness Scale: prescan (KSS)
- PLUS
- EEG Cap Setup
- MRI anatomical scan (T1-W)
- fMRI Monetary Incentive Delay Task (MID)[169 170]
- fMRI Stop Signal Task[171]
- fMRI Resting State with eyes open
- fMRI Interoceptive Attention Task[172]
- fMRI Fear Conditioning/Extinction Task[173]
- KSS: postscan

Table 4 Compensation

Session	Time	Payment (US$)
Interview and demographic information	4.5 hours	90
Behavioural assessments and computerised tasks	4 hours	80 10–20 reward
Biomarkers	30 min	50
Neuroimaging and electroencephalogram and 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	700–780

DATA ANALYSIS

Behavioural and psychophysiological data analyses

Self-report questionnaires, interviews, neuropsychological assessments, computer-based behavioural assessments and psychophysiological assessments will be scored according to published methods (as cited in tables 1 and 2). 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, behaviour, physiology, circuits, biomarkers), separate principal components analyses (PCA) will be performed and a separate analysis will be conducted for each behavioural task to minimise task-specific factors in subsequent analysis steps. Next, the number of components for each analysis will be determined using a number of different approaches.[91] In particular, if the number of components to be extracted differed across the extraction approaches, both solutions will be explored.[92 93] 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.[94]

EEG-fMRI

The EEG data will be acquired simultaneously with the fMRI data and corrected for artefacts related to the gradient switching and cardiac ballistic effect using the template subtraction method[95–97] 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 synchronised with the MRI scanner 10 MHz master clock signal using the SyncBox device (Brain Products GmbH, Munich, Germany), in order to prevent variant sampling of imaging artefacts and to facilitate artefact correction.[97] The signals will be recorded at a sampling frequency of 5000 Hz with an analogue 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.[98] 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.[99] 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 artefacts.[100] EEG-informed fMRI analysis will allow us to better elucidate and characterise normal and pathological interactions between cerebral function and behaviour, cognition or emotion.

fMRI preprocessing

Standard fMRI data preprocessing will include a slice-timing correction, signal scaling, spatial smoothing, physiological noise suppression[100 101] and motion correction.

Task-based fMRI analysis

First/subject-level analyses

Multiple regression will be used to analyse individual subjects' data, with predictors in the model constructed by convolving each column of the task design matrix with a canonical haemodynamic response function. Regressors of non-interest will be included in all models to account for (1) head motion (six 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 modelling 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-subject and between-subject variances. Correction for multiple comparisons will be conducted as follows. Statistical maps will either be corrected using the false-discovery rate or cluster level thresholds. For cluster level thresholds, AFNI's *3dClustSim* (with spatial autocorrelation function 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

Preprocessing

Data preprocessing 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 despiking 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 coregistered to the anatomical coordinates of the participant's structural scan by linear warping, then normalised to the Talairach template and resampled to 2×2×2 mm^3 voxels.

First/subject-level analyses

For each participant, the time courses of the residual images from the preprocessing step will be averaged across voxels within each ROI, and Pearson's 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 analysed 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 df 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 regularised generalised canonical correlation analysis (RGCCA).[102] Classical CCA identifies linear combinations of two sets of variables such that their correlations are maximised. 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 maximised. 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.[103] 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, SU disorders, mood disorders and ED) and between dimensionally defined biotypes using models for longitudinal data—mixed effects and generalised estimating equations models. No functional form will be assumed for the time trajectories and profile models will be used (ie, 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.

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,[104] 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.[105] We also compute power to predict the year follow-up clinical outcomes: assuming 100 HC, 100 ED, 500 MA and 300 SU participants at baseline and a uniform 20% attrition rate for each group at 1-year follow-up (ie, 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/paediatric 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 years 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 fulfil the objectives of the study. Study consent records will be stored in the locked records room at the Laureate Institute for Brain Research (LIBR). 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[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 centre at LIBR and all web-based information transmission is encrypted. REDCap was developed specifically around Health Insurance Portability and Accountability Act of 1996 (HIPAA)-Security guidelines and is recommended to LIBR researchers by both our Privacy Office and the 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 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 authorised 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, local service providers for behavioural health, mental health and addiction and recovery (eg, 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 preapproved LIBR Screening protocol (WIRB #20101611) and through the LIBR 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 authorised personnel.

Expected outcomes

The final end point of this analysis will be a set of standardised multilevel 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 SU 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 (eg, from molecules to mental processes) relate to one another. A second approach will involve identifying whether they predict the progression and severity of symptoms over time (including natural recovery or worsening of symptoms). A third approach will examine whether they predict responses to independently sought pharmacological or behavioural 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 personalised and biologically based medicine.[28–30]

Collaborators University of Oklahoma, University of California San Diego, Rutgers University.

Contributors All authors made significant contributions to the conception and design of the study protocol. The protocol was written by MPP and TAV and critically reviewed by SSK, JS, JB, JSF, RLA, H-WY and WKS. All authors gave permission and approval for publication.

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