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