Trial Protocol for "Positive affect treatment targets reward sensitivity: a randomized controlled trial"

Trial Registration

The trial was officially registered on clinicaltrials.gov on February 5th, 2018. The registry name is "Treatment for Affect Dimensions (TAD)" (Clinical Trials ID#: NCT03439748). This study is funded by the National Institute of Health (R61MH115138). Dr. Michelle G. Craske is the contact principal investigator (PI), and Drs. Alicia Meuret and Thomas Ritz are additional PIs of the study. Correspondence concerning this protocol should be addressed to Michelle G. Craske, Department of Psychology, University of California, Los Angeles, 405 Hilgard Avenue, Los Angeles, CA 90077 (email: mcraske@mednet.ucla.edu), or to Alicia E. Meuret, Department of Psychology, Southern Methodist University, Dallas, P.O. Box 750442, Dallas, TX 75275 (e-mail: ameuret@smu.edu).

Public Title: "Treatment for Affect Dimensions (TAD)"
Scientific Title: "Reward Sensitivity as a Mechanism of Positive Affect Treatment for Anhedonia"

Roles and Responsibilities

The Executive Committee of the three PIs (Drs. Craske, Meuret, and Ritz) will be chaired by Dr. Craske. The Executive Committee will hold weekly teleconference calls. Monthly calls will include key investigators as needed, including our biostatistician (Dr. Rosenfield), Consultants (Drs. Pizzagalli and Hollon) as well as research staff. In these monthly meetings, we will address issues of data collection, budget, recruitment, treatment delivery, data management and analysis, and training and ongoing review to maintain interrater reliability. Also, we will discuss human subjects' issues, especially the recruitment of minority participants.

The Executive Committee will review all publications and presentations derived from data garnered in this grant in order to ensure its quality. Assignment of publications and other academic products of this project will be decided on by the Executive Committee, with lead roles equitably rotated among the three PIs. Disagreements will be resolved by majority decision. At the end of the trial, each site will receive a cleaned and checked data file; however, all publications and presentations derived from that data in the future will be vetted within the Executive Committee prior to release.

Background and Significance

Affective neuroscience has identified two core systems that regulate thoughts and behaviors. The first is the approach or appetitive system, which motivates actions towards goals and rewards, and produces positive emotions such as enthusiasm and pride. The second is the withdrawal or defensive system, which motivates avoidance of aversive outcomes or punishments, and is linked with negative emotions. Despite the fundamental role played by both appetitive and defensive systems in depression and anxiety, treatment has focused largely upon decreasing withdrawal (and negative affect) rather than increasing approach (and positive affect). This study will test mechanisms of a novel, pilot-tested treatment specifically designed to target deficits in the appetitive system. This goal is aligned with the NIMH Research Domain Criteria (RDoC) initiative, in which the appetitive positive valence system is a critical dimension of psychopathology.

Low positive affect is increasingly recognized as a critical transdiagnostic feature of many mental health disorders[1, 2]. In the context of depression and anxiety, low positive affect is not only correlate but also a risk factor for onset[3-7] and is associated with poorer longitudinal course[8]. Furthermore, low positive affect is associated with suicidal ideation and the related construct of anhedonia (or markedly diminished interest or joy in usual activities) is a predictor of suicide ideation and attempt[9, 10], even when controlling for other cognitive and affective symptoms of

depression[11, 12]. Patients with depression view the restoration of positive mood as their primary treatment goal, over reducing negative symptoms[13]. Yet, treatments to date have not reliably improved positive affect. The goal of the current study was to test replicability of a novel treatment for positive affect and to evaluate processes underlying therapeutic effects.

Meta-analyses of evidence-based psychotherapies for depression (primarily cognitive–behavioral therapy and mindfulness-based cognitive therapy) yield low to moderate effects sizes for change in positive affect, with significant heterogeneity across studies[14]. Re-analyses of prior RCTs show that cognitive therapy and antidepressant medication normalized elevations in negative affect but had little effect on positive affect[15] and were less successful in raising positive affect than decreasing negative affect[16]. Even Behavioral Activation therapy, which aims to increase positive affect through response contingent positive reinforcement from rewarding activities[17] has limited effects on positive affect in the few studies in which such effects have been reported[18, 19]. This is perhaps not surprising since little attention has been given to how to conduct behavioral activation in a manner that maximizes rewarding, positive emotional experiences[20]. Pharmacological treatments have mixed effects and may even worsen positive emotions or responses to rewarding stimuli[21-24], although newer pharmacological approaches such as kappa-opioid antagonists and ketamine are showing promising effects[25, 26].

As noted by Dunn (2012)[27] little attention has been given to how to conduct behavioral activation, or psychological treatments in general, in a manner that maximizes positive emotional experience. We hypothesize therapeutic strategies which specifically target the mechanisms underlying low positive affect will lead to greater improvement in positive affect than extant treatments.

Low positive affect is a core feature of anhedonia (or diminished interest or joy in usual or pleasurable activities), and both low positive affect and anhedonia can be viewed as expressions of an underlying dysregulated reward system. The reward system affects the ability to anticipate or predict expected rewards; associates relative values and costs with rewards; determines the effort required to obtain rewards; integrates this information to decide whether it is worthwhile to obtain rewards and when to become motivated to perform the necessary actions to obtain rewards[28]. While there are many aspects of the reward system, including action selection/decision making, habit responding[29] and satiation, we focus on three frequently emphasized components[30]: 1) anticipation-motivation for reward, 2) initial responsiveness to reward attainment, and 3) reward learning.[31,28] The anticipation-motivation component drives adaptive behaviors towards rewarding stimuli (e.g., planning and looking forward to a vacation) and is related to the effort expended to receive reward. It is dominated by “wanting.” The initial attainment component refers to the pleasure or hedonic impact of rewarding stimuli (e.g., the pleasure whilst on vacation) and is dominated by “liking.” The learning component typically involves Pavlovian or instrumental associations and predictions about future rewards based on past experiences. Thomsen and colleagues[31] relate wanting, liking, and learning of reward to the appetitive, consummatory, and satiety phases of the pleasure cycle. Their model recognizes that each component serves a particular survival function, is associated with different behavioral outputs, and is supported by different brain networks (albeit with some overlapping areas).

Individuals who are depressed show deficits in anticipation-motivation, initial responsiveness to attainment and learning of reward across multiple indices.[32, 33] Furthermore, there is compelling evidence for linkages between reward hyposensitivity and low positive affect, mostly in the context of depression-related anhedonia.[34-37]

Anticipation-Motivation. (1) Self-report: Dysphoric individuals expect to feel less positive emotions in future positive events[38, 39] and report less positive emotion in anticipation of monetary rewards[37] compared to healthy controls, although the evidence is not entirely robust.[40] (2) Behavior: Trait anhedonia among healthy individuals correlates with choosing easy tasks for a small reward over harder tasks for larger rewards, indicative of less motivation (i.e., expenditure of effort) to gain reward.[41] Also, depressed individuals make fewer high reward/high effort choices

than healthy controls,[42] and importantly, the motivational effort they expend to obtain rewards decreases with higher anhedonia.[42, 43] (3) Psychophysiology: Monetary incentives have consistently been shown to be associated with cardiac acceleration.[44-47]Dysphoric individuals show less reliable acceleration of heart rate than healthy controls when performing memory or mental arithmetic tasks that are linked to monetary rewards[48-50]. (4) Neurophysiology: Depressed individuals show reduced activation in reward circuitries in anticipation of reward.[36,51—57] Importantly, reduced ventral striatum responsivity to incentive stimuli and reward expectancy-prediction error is particularly related to anhedonic symptoms[57—59].

Initial Responsiveness to Reward Attainment. (1) Self-report: Evidence for deficits in self-rated liking of reward as a function of depression is mixed. Some data fail to show deficits in liking of reward.[60—62] However, a meta-analysis of methodologically rigorous studies concluded that there was evidence for blunted self-reported positive emotion to positive stimuli in laboratory tasks in depressed individuals.[63] Importantly, lower levels of self-reported positive emotions to positive stimuli are more strongly related to anhedonia than to depression.[64,65] (2) Attention Bias: Depressed individuals show less attention to positive stimuli than controls as measured via response latency times in dot probe tasks and eye tracking.[64, 66-68] Attention to positive information is associated with positive affect but has not been linked to anhedonia per se.[69] (3) Psychophysiology: Anhedonia is associated with reduced cardiac acceleration while viewing pleasant pictorial stimuli[70] or during imagery of pleasant scripts.[71] (4) Neurophysiology: In depressed samples, ventral striatum and lateral global pallidus hypoactivity to positive stimuli[72—74] is strongly associated with symptoms of anhedonia.[72,74-77] These effects were specific to anhedonia above and beyond negative symptoms of anxiety or depression.[76,77]

Reward Learning. (1) Behavior: The propensity to develop a response bias to stimuli that are more frequently rewarded is less likely to develop over time as a function of higher depressive symptoms.[78-80] Importantly, impairments in response bias formation among clinically depressed individuals correlate with self-reported anhedonia.[78-79,81] Furthermore, reduced reward learning predicted elevated anhedonia symptoms one month later[78] and depressed adults with poor (as compared to relatively intact) reward learning were almost 8 times more likely to remain symptomatic at the end of SSRI or psychotherapy.[79] (2) Neurophysiology: Depressed individuals and remitted individuals show reduced activation in reward circuitries during reward learning[82-83,] and poor reversal learning after unexpected reward delivery in depressed individuals is associated with deficits in the ventral striatum.[84] The monetary incentive delay task also reveals lower activation in the dorsal caudate (an area connected with feedback driven contingency learning) in depressed individuals.[74] There is some evidence for blunted ventral striatal responses to Pavlovian[83] and instrumental conditioning tasks[85] in depression with neural responses correlating with self-reported anhedonia.[82,85]

Given the evidence cited, a treatment that specifically targets three cardinal sub-domains of reward sensitivity within the RDoC Positive Valence Systems, Anticipation-Motivation, Initial Responsiveness to Reward Attainment, and Reward Learning, may be particularly potent for low positive affect. As noted, existing psychological treatments mostly target negative affect and while behavioral activation is designed to increase engagement in pleasant activities, little attention has been given to optimization of positive emotions during the planning and conduct of such activities.[27,86] Drawing from affective neuroscience and experimental psychopathology, we developed a treatment that specifically targets reward hyposensitivity, coined Positive Affect Treatment (PAT).[87] In our previous randomized controlled trial88, PAT was compared to cognitive behavior therapy that targeted reductions in negative affect (termed Negative Affect Treatment, NAT) for individuals with moderate to severe depression or anxiety. PAT resulted in higher positive affect, lower negative affect and less severe depression and anxiety at six months.

Specific Aims

The goal is to evaluate whether Positive Affect Treatment (PAT) leads to significantly higher positive affect, lower interviewer-rated anhedonia, and lower symptoms of depression and anxiety (outcome measures) than cognitive behavioral therapy that focuses on negative affect (called Negative Affect Treatment, NAT). A second goal is to evaluate whether PAT leads to greater (1) reward anticipation-motivation, (2) initial reward responsiveness or (3) reward learning (reward targets) compared to NAT. A third goal is to evaluate whether changes in reward targets correlate with changes in outcome measures (i.e., self-reported positive affect, clinician-rated anhedonia, and symptoms of depression and anxiety. Targets will be assessed before, twice during, and posttreatment, using physiological, behavioral, cognitive and subjective/experiential measures. Participants will be individuals who score above clinical cut-offs on (1) low positive affect, (2) depression or anxiety, and (3) functioning.

Aim 1: Test of Replicability of Efficacy. Hypothesis: PAT leads to significantly higher positive affect, lower interviewer-rated anhedonia and lower symptoms of depression and anxiety than NAT.

Aim 2: Target Engagement. Hypothesis: PAT leads to significantly greater reward approach-motivation, initial responsiveness to reward attainment, or reward learning than NAT.

Aim 3: Target Engagement Covariation with Outcome. Hypothesis: Improvements from pre- to post-treatment in reward anticipation-motivation, initial reward responsiveness or reward learning significantly covary with improvements in positive affect, interviewer-rated anhedonia, and symptoms of depression and anxiety .

Methods

Trial Design

This will be a multi-site, assessor-blinded, parallel, 2-arm, stratified (medicated, y/n), randomized (1:1) clinical superiority trial, for help-seeking adults with moderate to severe depression or anxiety, functional impairment, and low positive affect.

Participants

Participants will be recruited in the U.S. A brief study description will be distributed via lab websites, social media, clinicaltrials.gov, and brochures to local agencies. A 3-stage standardized screening process will begin with online screening of demographic, medical and symptomatic eligibility criteria. Eligible persons then will complete a more in-depth phone screen by study staff who detailed study procedures. The third stage will involve a SCID-5 Research Version[90] (for exclusion criteria) conducted by reliability-certified advanced research associates, with consensus diagnosis overseen by experienced clinicians. Cross-site consistency for diagnostic interviews will be maintained by (1) annual joint teleconference among interviewers and PIs to discuss diagnostic issues, and (2) cross-site consistency checks, in which 20% of the audio or video-taped interviews at each site will be randomly selected to be blindly rated by interviewers of the other site.

Inclusion criteria will consist of (1) aged 18 to 65 years old, (2) English-speaking, (3) low positive affect indexed by $\leq$ 24 on the Positive Affect Subscale of the Positive and Negative Affect Schedule (PANAS-P),[89] or 1SD below the population mean[90] (4) Depression, Anxiety and Stress Scales[91] scores of ≥ 11 for depression, ≥ 6 for anxiety or ≥ 10 for stress to represent moderate to severe symptom severity,[92] (5) ≥5 on any Sheehan Disability Scale subscale to represent clinically significant impairment[93] and (6) willingness to refrain from initiating psychosocial/pharmacological treatment until study completion.

Exclusion criteria will consist of (1) Patient report of serious medical conditions - such as history of serious, uncontrolled medical illness, or instability (including significant cardio-pulmonary disease, organic brain syndrome, seizure disorder, cerebrovascular disease, thyroid dysfunction, and diabetes), (2) active suicidal ideation, (3) lifetime bipolar disorder, psychosis, mental retardation, or organic brain damage (4) substance abuse in last 6 months or dependence

in the last 12 months (5) 11 or more cigarettes per week or nicotine equivalent (6) history of marijuana, cocaine, or stimulant use 5-7 times per week or more before 15 years old (e.g., amphetamine, cocaine, methamphetamine) (7) pregnancy (8) bupropion, dopaminergic or neuroleptic medication use in the past 6 months, (9) Heterocyclics and SSRIs are permitted if stabilized (3 months), and PRN benzodiazepines and beta-blockers are permitted but discouraged on laboratory assessment visits, (10) refusal to be video/audio taped.

Interventions

Positive Affect Treatment

Positive Affect Treatment (or PAT) includes three core elements. The first is behavioral activation to rewarding experiences augmented by imaginal recounting and reinforcement of positive mood effects. The second is cognitive exercise focusing on identifying positive

aspects of experience, taking responsibility for positive outcomes, and imagining future positive events. The third is the cultivation and savoring of positive experiences through exercises of appreciative joy, gratitude, generosity, and loving-kindness. The behavioral activation with imaginal recounting is continuous throughout the fifteen weekly therapy sessions, while cognitive exercises are the focus of sessions 8-11, and cultivating positive emotions is the focus of sessions 12-14. Session 15 is relapse prevention.

Behavioral activation with imaginal recounting. Behavioral activation targets the anticipation and motivation for reward by designing rewarding activities and response to attainment of reward through engagement in rewarding activities. Detailed labeling of positive emotions experienced during the activities facilitates reward attainment. Changes in mood are closely monitored from before to after each activity to reinforce the positive mood-inducing effects, and in so doing, targets reward learning (i.e., instrumental learning by which engaging in a specific activity increases positive mood). To deepen and savor the rewarding aspects of the experience each behavioral activity is followed by intensive, first-person perspective and present tense imaginal recounting through visualization and reimagining of assigned activities, including specific sensations, thoughts, emotions, and situational details. Other processes are likely taking place as well since the guided memory recounting involves shifting attention away from negative portions and toward positive portions of the behavioral experience. To that degree, it serves as a type of attentional control (shifting attention from one aspect of a situation to another). Such attentional control has been shown to be effective as a form of emotion regulation.[94] The imaginal recounting resembles other memory specificity interventions for emotional disorders that have led to short-term significant improvements in overgeneral memory, depression, hopelessness, problem solving, anticipatory pleasure, and behavioral intention to engage in activities.[95-99] In Positive Affect Treatment, the primary goal of imaginal recounting is to enhance the hedonic impact of reward and to improve the skill of appreciating and liking a rewarding event. Additionally, imaginal recounting involves sustained attention to positive stimuli, which has shown to lead to subsequent preferences for positive stimuli, albeit in nonclinical samples.[100] Increased preference for positive material is posited to, in turn, decrease interest in negative information.[101] Furthermore, training positive attentional preferences may enhance attentional vigilance for and orienting toward positive information that eventually shifts more elaborate attention mechanisms toward positive meanings and facilitates encoding of positive information in daily experiences.

Cognitive Exercises. PAT involves a set of cognitive training skills for attending to positive stimuli. Unlike cognitive therapy for depression which challenges negative cognitions, cognitive techniques in PAT aim to identify and savor positive aspects of experiences such as taking responsibility for positive outcomes or imagining and appreciating future positive events. Hence, the PAT cognitive skill set does not address negative thoughts or errors in thinking that may have contributed to negative assumptions and beliefs. Instead, all discussion focuses on attending to positive features of situations in the past, present, and future. Targeting attention is expected to impact mood as described with respect to the attentional mechanisms involved in imaginal

recounting (i.e., increases in positive affect, increases in preference for positive stimuli, decreased interest in negative stimuli, and eventual shift toward more positive meanings[101]). Hence, even though there is little direct attempt to change appraisals, underlying meanings and appraisals may shift in a more positive direction indirectly as a function of the cognitive training exercises.

The first cognitive skill, *Finding the Silver Linings*, trains clients to recognize and appreciate the positive features in everyday situations, even situations with a partly negative valence. The repeated practice of identifying multiple positive elements in everyday situations is presumed to enhance preference for, attentional vigilance to, and encoding of positive information.[101] The second skill, *Taking Ownership*, involves repeated practice identifying one's own behavioral contributions to positive outcomes in daily lives (reward learning) and savoring positive emotions of pride, mastery, and excitement (anticipating reward). Accomplishments can be read out loud in front of a mirror to deepen the experience. Taking ownership counters the depressive attributional bias to attribute positive outcomes to external factors and is consistent with experimental evidence for training a positive attributional bias.[102] By asking clients to consider ways in which they may have contributed to a positive outcome, this skill may influence self-appraisals. The third skill, *Imagining the Positive,* is based on evidence for repeated practice imagining positive events to increase positive mood and positive interpretation bias.[103-105] Clients are guided to repeatedly imagine as many positive aspects as possible about an upcoming event, including positive emotions such as excitement, joy, and curiosity, to facilitate the wanting of reward.

Cultivate and Savor Positive Experiences Exercises. The final set of skills is designed to cultivate and savor positive experiences and include daily practices of the mental and physical act of giving. Practices in *Loving-Kindness* (i.e., mentally sending happiness, health, peace, and freedom from suffering) is described as an act of training one's emotional experience toward warmth and tenderness[106]. It encourages the focus of awareness on loving and kind concern of other living beings, oneself, and the world.[107] Even brief practices of Loving-Kindness[108] have been shown to increase positivity toward self and others, improvements in positive affect and personal resources (e.g., personal relationship with others, physical health, self-acceptance, satisfaction).[109] Preliminary evidence from proof-of-concept clinical trials in individuals with schizophrenia,[110] post-traumatic stress disorder[111,] and more recently dysthymia[112] show increases in positive emotions and an improved sense of self and others. Acts of *Generosity* (i.e., engaging in an act of generosity without expecting return) have been linked to improvements in positive mood.[113,114] In a reciprocal cycle, prosocial behaviors have been shown to increase positive mood, which in turn, increases prosocial behaviors[115]. Furthermore, there is some evidence that the positive mood effects of prosocial behavior toward others are greatest for those with depression, at least in adolescent samples[116].

Other skills involve daily practices of the mental act of wishing good to self and others through *Appreciative Joy* (i.e., wishing happiness, joy, and fortune) and of generating a sense of gratefulness through the practice of *Gratitude*. Cultivating *Gratitude* (by creating gratitude lists, gratitude contemplation, or the behavioral expression of gratitude) leads to changes in positive mood, greater resourcefulness, and general well-beingin studies with nonclinical participants[117-120]. It is speculated that practicing *Gratitude* leads to an increased value of help from others,[120,121] which leads to seeking more social support and strengthening social bonds.[122] This "broaden and build" approach[123] is thought to add to resiliency.[124] *Appreciative Joy* is a practice that involves feeling happiness for people with success, good fortune, or happiness. Similar to practices of *Loving-Kindness*, *Appreciative Joy* has been associated with increases in positive mood, positive thinking, interpersonal relations, empathic accuracy, and improvements in psychological distress, although study quality is often problematic.[125,126] In a small study, *Appreciative Joy* alone was found to increase positive mood in a healthy sample.[127]

Positive mood is rated before and after each exercise to assessand understand the mood-inducing effects. In so doing, the exersises across the three treatment modules also target the learning of reward (i.e., by engaging in this practice, mood improves).

Negative Affect Treatment

NAT will target elements of elevated threat responding as well as loss and frustrative nonreward, using cognitive behavioral therapeutic strategies.

Augmented Exposure. The first module involves designing, planning, and practicing exposures to feared or stressful situations, sensations, or objects to reduce threat responding. Inhibitory learning and consolidation are optimized by implicit and explicit violation of expectancies, practices for enhanced generalization, and post-exposure analysis.[128,129] Augmented exposure included the part of behavioral activation for depression that directly targets avoidance of stressful situations.[130] Note that behavioral activation toward rewarding or pleasurable activities was excluded to retain a focus upon reducing negative affect.

Cognitive Restructuring. The second module targeted threat as well as loss and frustrative nonreward, and involves exercises for reducing threat appraisal by identifying overestimations of probability and cost for negative outcomes (relevant to depression and anxiety), excessive self-attribution for negative outcomes (i.e., self-criticism, particularly relevant to depression), and by developing evidence-based estimations, problem-solving and alternative interpretations for negative outcomes.[131,132]

Respiratory Training. The third module uses a handheld capnometer to reduce hypocapnia and excessive arousal by means of shallower and slower breathing combined with feedback of partial pressure of end-tidal carbon dioxide levels.[133-135] Although respiratory training was originally developed for panic disorder, low partial pressure of CO2 have been found to predict poor outcomes from cognitive– behavioral therapy for mixed anxiety disorders.[136] In addition, breathing-based interventions have been shown to be effective for depression[137] and to reduce depressive symptoms in anxious patients.[135]

Session 15 is relapse prevention.

Therapist Training, Supervision, and Fidelity

Therapists will be Ph.D. students in clinical psychology with experience in cognitive-behavioral therapies for depression or anxiety. They will attend an annual 2-day standardized training workshop at UCLA led by Drs. Craske and Meuret, for initial training and to ensure proper recalibrations of therapy applications, troubleshooting, and additional therapist training. They will attend weekly supervision at their respective sites with the study PIs (Craske, Meuret). Supervision will include detailed feedback on videotaped treatment sessions and monthly cross-site supervision video calls with the supervising PIs, Dr. Steve Hollon (study consultant), and all study therapists to facilitate cross-site consistency. Additional consultation from Dr. Hollon will be provided as needed. In the event of symptom worsening throughout treatment, the PIs will consult and seek advice from an independent clinician at the UCLA site (Scott Fears, MD) regarding study withdrawal and referral where appropriate.

Treatment fidelity ratings (using our established adherence scales) will be measured by independent ratings of 15% of all sessions by independent assessors at one site reviewing the treatment sessions from the other site. Inter-rater reliability will be assessed on 10% of the adherence-rated sessions. Disparities across sites in competency and adherence will be addressed via additional joint supervision from Drs. Craske and Meuret. To minimize therapist effects, therapists will be assigned to PAT and NAT.

Outcome Measures

Given our goal of evaluating components of reward sensitivity as targets of treatment outcome (Aims 2 and 3), it is essential that our primary outcome measures are distinct from

measures of reward sensitivity. For this reason, we will not select the Snaith–Hamilton Pleasure Scale [SHAPS][138], the Fawcett-Clark Pleasure Scale [FCPS]),[139] the Chapman Physical and Social Anhedonia Scale [PAS])[140] or the TEPS[141] as outcome measures as they purport to measure the underlying components of reward sensitivity, particularly the attainment of reward (SHAPS, FCPS, PAS, and TEPS) and the approach-motivation for reward (PAS, TEPS). Instead, our three primary outcome measures will include (1) self-reported positive affect, (2) interviewer-rated anhedonia, and (3) symptoms of depression and anxiety. . .

Primary Outcome Measures.

Self-Rated Positive Affect: Positive Affect Subscale (PANAS-P)[89] Positive and Negative Affective Schedule (PANAS) is a widely used measure comprised of 20-items assessing positive affect and negative affect. Self-rated levels of positive affect will be assessed using the Positive Affect Subscale ("during the past week"). The PANAS-P directly measures expressed levels of positive affect without reliance upon constructs of reward sensitivity. We have validated the use of PANAS-Positive in our previous trial.[142] The PANAS has high internal consistency and temporal stability. Correlational data support its convergent and discriminant validity. Confirmatory factor analyses support the construct validity of the PANAS.[90]

Interviewer-Rated Anhedonia. Given the importance of heterogeneous measurements with respect to their error and method variance,[143] independent assessor ratings of our primary outcome are a methodological advantage. We will use a method currently employed in another investigation of threat and reward sensitivity (R01MH100117, PI-Craske). Independent interviewers will rate the three diagnostic screener items from the SCID-5 interview ('loss of interest,' 'loss of pleasure,' and 'low drive') that load most heavily onto the anhedonia" factor.[144] All three items will be rated by an independent assessor using a 4-point rating scale (from "absent" to "severe"). In 294 community participants, the three items showed good internal consistency (alpha = .72). 73% of participants identified by interviewers as high in anhedonia were also high in anhedonia by self-report, $X^2(1) = 60.1$, $p < .001$. Assessors will be certified and trained to acceptable levels of inter-rater reliability.

Depression and Anxiety Stress Scales (DASS-21)[145] The 21-item DASS measures depression, anxiety (e.g., difficulty breathing, heart palpitations), and stress (e.g., difficulty relaxing, irritability). The DASS has strong construct validity[146-147] and good-to-excellent internal consistency[147]. It has clinical severity ranges from normal to extremely severe. Significant changes on the DASS were observed in our pilot trial of PAT.[87] The DASS total score will be analyzed.

Secondary Outcome Measures.

Sheehan Disability Scale (SDS)[148] The SDS will be used to assess the degree of impairment in daily functioning in (a) work activities, (b) social life and leisure activities, and (c) family life and home responsibilities (0-10 point scales).

Beck Depression Inventory (BDI). The BDI-item 9 will be used to assess suicidal ideation, from baseline to post-treatment.

Daily Activity/Social Interaction (Actigraphy). Participants will be asked to wear an Actigraph (Actigraph, LLC, Florida, USA) tri-axial accelerometer on their nondominant wrist for 7 consecutive days at baseline, week 5, week 10 and week 16. Raw acceleration data will be collected and used to measure energy expenditure, physical activity, and sleep patterns. Patients with depression show reduced daytime activity that increases following symptom improvement. Low positive affect (a core feature of anhedonia) is associated with reduced physical activity. Sleep disturbances are a core feature of depression.

Measures of Reward Sensitivity (Target engagement measures)

Target measures of 1) reward anticipation-motivation, 2) response to reward attainment, and 3) reward learning are depicted in Table 1.

Table 1. Self-report, behavioral, cognitive, and physiological measures of reward anticipation-motivation, response to reward attainment and reward learning at baseline, week 5, week 10, and posttreatment-assessment

	Baseline						Post
Week	**0**	**1-4**	**5**	**6-9**	**10**	**11-15**	**16**
Reward Anticipation-Motivation							
B: Effort Expenditure for Rewards Task (EEfRT)	X		X		X		X
P: Monetary Incentive Task (MIT)	X		X		X		X
S: Behavioral Inhibition and Activation Scale-Reward-Drive Subscale (BAS-RD)	X		X		X		X
S: Dimensional Anhedonia Rating Scale (DARS-A-M)	X		X		X		X
Response to Reward Attainment							
C: Modified Attentional Dot Probe Task (DOTPROBE)	X		X		X		X
P: International Affective Picture System (IAPS) Task	X		X		X		X
S: Temporal Experience of Pleasure Scale-Consummatory Subscale (TEPS-C);	X		X		X		X
S: Dimensional Anhedonia Rating Scale (DARS-C)	X		X		X		X
Reward Learning							
B: Probabilistic Reward Task (PRT)	X		X		X		X
B: Pavlovian Instrumental Transfer Task – force (PIT-FORCE)	X		X		X		X
S: Change in valence for stimuli associated with reward (PIT-VALENCE)	X		X		X		X

B=behavioral, C=cognitive, P=physiological, S=subjective/experiential

Reward Anticipation-Motivation

Behavioral Index: Effort Expenditure for Rewards Task (EEfRT)[41] The EEfRT is a behavioral measure for reward motivation (i.e., willingness to work for reward). Trait anhedonia[140] correlates with choosing easy tasks for small rewards over harder tasks for larger rewards in healthy controls[41] and the effort individuals with depression expend to obtain rewards correlates negatively with anhedonia.[42,43,149] Dopamine agonists produce a dose-dependent increase in willingness to work for EEfRT rewards, and depressed individuals showed reduced striatal response (caudate nucleus) using EEfRT, relative to healthy controls.[150] The task is a computer game with monetary incentive which varies effort (hard vs easy), probability (12%, 50%, 88%) and amount of reward ($1.00 for easy trials, $1.24-$4.30 for hard tasks), for maximum earning of $16. The dependent variable is ratio of hard-effort choices for each probability of reward.

Physiological Index: Heart rate acceleration during Monetary Incentive Task (MIT) Heart rate normally accelerates in tasks that require effort to obtain monetary rewards.[44-47] Dysphoric individuals show less heart rate acceleration to the prospect of reward in MIT tasks[48-50] and striatal hyporesponsiveness during MIT is linked to deficits of reward anticipation in various conditions, including depression.[151,152] In this forced-choice reaction time task, participants react to a target stimulus presented after an incentive cue but before the reward is given. The incentive cue comprises an image of two quartes which indicate the maximum reward that can be earned on a trial. The target stimulus consists of a series of five arrows. The participant must indicate whether

the middle arrow is pointing to the right or the left. Participants receive a maximum reward ($0.50) for a correct and fast response. Total maximum earning is $16. The dependent variable is heart rate acceleration from initial practice trial to initial reward trial, as the initial reward trial of this task has been shown to generate the strongest cardiac acceleration in non-dysphoric individuals.[44,45] The unrewarded practice trial serves as a baseline that holds constant for nonspecific factors (such as physical activity, visual processing) except for the prospect of reward.

Self-report Index: Behavioral Activation Scale (Reward Drive Subscale; BAS-RD). The Behavioral Inhibition and Activation Scale (BIS/BAS)[153] is a 24-item self-rated measure of habitual behavioral inhibition and activation sensitivities (i.e., avoidance and approach motives), which are hypothesized to reflect the negative and positive valence systems, respectively. The BAS Reward Drive subscale is a measure of effort valuation/willingness to work. Significant correlations have been established between the BAS-Reward Drive subscale and measures of positive affect.[153] BAS-Reward Drive is purported to reflect individual differences in ventral–striatal-related circuitry.[153]

Self-report Index: Dimensional Anhedonia Rating Scale-Reward Anticipation-Motivation (DARS-A-M). DARS is a 17-item self-report questionnaire designed to assess anhedonia in MDD. Respondents provide their own examples of rewarding experiences across the domains of hobbies, social activities, food/drink, and sensory experience. They subsequently answer a set of standardized questions with the timeframe of “right now” to evaluate four domains of reward sensitivity within each domain: interest, motivation, effort, and enjoyment of reward. DARS shows good convergent and divergent validity and reliability of the subscales are high across studies (Cronbach's α = 0.75-0.92).[154] Items related to desire, motivation, and effort will be summed to create an index of reward anticipation-motivation (DARS-A-M). The summation was ad hoc, but ratings showed high internal consistency (alpha=.94).

Response to Reward Attainment

Cognitive Index: Modified Probe Detection Task (DOTPROBE). Attentional biases for emotional information are observed for depression and anxiety.[155,156] Less attention is directed to positive information and more attention is directed at negative information as a function of low positive affect,[69,157] depression,[64,67] and social anxiety. [158] Depressed individuals spend more time gazing at negative stimuli and less time gazing at positive stimuli[159] and meta-analyses indicate greater disengagement from positive stimuli within dot probe attention tasks as a function of depression.[160] There is good evidence for test-retest reliability for positive bias using the dot probe task in healthy controls.[161] Stimuli comprise standardized male and female disgust, sad, happy, and neutral faces.[162] Each emotional face is paired with a neutral face from the same person (e.g., sad–neutral). Neutral trials serve as a baseline to compute engagement bias and disengagement bias scores.[163,164]

The task trials instruct participants to attend to a small line that will appear on the right or left side of the screen, which is either horizontal or vertical. The first line that appears is the “cue.” The cue disappears, and two images appear on the screen. One of them is a random blur, and the other is a sad, happy, or neutral face (presented for 500ms or 1000ms, randomized). The images disappear, and then another line appears on either side of the screen, which is again either horizontal or vertical. This second line that appears is the “target.” The participant must indicate with a keypress whether the cue and target lines were identical or different. The dependent variable is engagement bias for happy and disengagement bias for sad faces. Engagement bias trials are when the cue does not appear on the same side (i.e., distal) as the emotional image. Disengagement bias trials are when the cue appears on the same side (i.e., proximal) as the emotional image. According to Rudaizky et al. [165] the calculation of these indices is as follows:

Reaction time (RT) index for engagement bias: (Cue appears *distal* to the emotional face in the pair of emotional face and random blur image: RT for target *distal* to emotional face minus

RT for target *proximal* to emotional face) minus (Cue appears *distal* to neutral face in the pair of neutral face and random blur image: RT for target *distal* to neutral face minus RT for target *proximal* to neutral face).

Reaction time (RT) index for disengagement bias: (Cue appears *proximal* to emotional face in the pair of emotional face and random blur image: RT for target *distal* to emotional face minus RT for target *proximal* to emotional face) minus (Cue *proximal* to neutral face in pair of neutral face and random blur image: RT for target *distal* to neutral face minus RT for target *proximal* to neutral face).

Physiological Index: Heart rate acceleration to International Affective Picture Systems (IAPS). The IAPS is a well-established paradigm for studying psychophysiology of emotion.[166] Heart rate acceleration within 6 seconds of stimulus presentation is typically stronger with increasing pleasure of pictorial material.[166] Compared to controls, participants with anhedonia showed less heart rate acceleration with increasing pleasantness of images,[166] and positive stimuli elicit greater activation of the vmPFC and less activation of the striatum in individuals with anhedonia.[167] Following the previously used paradigm with anhedonia patients[166], 21 IAPS images (7 positive, 7 neutral, and 7 negative, selected using normative IAPS valence and arousal ratings) will be presented randomly, followed by repeated presentation as participants rate pleasure, arousal, and dominance using the Self-Assessment Manikin.[168] Maximum heart rate acceleration during the 6 seconds of positive image presentation relative to the last 2 seconds before picture onset will be assessed and compared to acceleration to neutral images.

Self-report Index: Temporal Experience of Pleasure Scale-Consummatory Subscale (TEPS-C)[141] The TEPS Consummatory subscale measures initial response to reward attainment, with high test-retest reliability in college students.[141] Scores on the consummatory subscale correlate with measures of positive affect[141] and Met carriers of the COMT gene had higher TEPS-consummatory scores and greater left PFC activation following reward consumption.[169]

Self-report Index: Dimensional Anhedonia Rating Scale-Consumatory Pleasure (DARS-C). DARS is a 17-item self-report questionnaire designed to assess anhedonia in MDD. Respondents provide their own examples of rewarding experiences across the domains of hobbies, social activities, food/drink, and sensory experience. They subsequently answer a set of standardized questions with the timeframe of “right now” to evaluate four domains of reward sensitivity within each domain: interest, motivation, effort, and consummatory pleasure of reward. DARS shows good convergent and divergent validity and reliability of the subscales are high across studies (Cronbach's α=0.75-0.92)[154]. Items related to enjoyment will be summed to create an index of response to reward consumption (DARS-C).

Reward Learning

Behavioral Index: Probabilistic Reward Task (PRT)[78] This task measures propensity to modulate behavior as a function of prior reinforcements, with good test-retest reliability in college students.[78] Poor learning in Reward Tasks is associated with deficits in the ventral striatum.[84] Reduced reward learning in MDD correlated with self-reported anhedonia,[79,81] and predicted poor antidepressant response two months later.[79] Participants determine, via button press, whether a short (11.5 mm) or a long (13 mm) “mouth” was presented on a previously mouthless cartoon face. Correct identification is rewarded with money on 40% of trials. Total maximum earning is $16. The dependent variable is response bias (measured as accuracy) toward the more frequently rewarded stimulus.

Behavioral Index: Pavlovian Instrumental Transfer (PIT-FORCE) The PIT tests the extent to which a conditional stimulus (CS) paired with reward (Pavlovian) enhances instrumental responding to gain rewards[170]. Handgrip strength to the CS+ (as a measure of instrumental responding) is related to activation in nucleus accumbens.[170] Aversive PIT (but not appetitive PIT) has been shown to be negatively associated with anhedonia.[171] The PIT task begins with a baseline measure of handgrip strength, during which the participant holds the handgrip without

exerting any pressure. A calibration trial followed to determine individual maximum handgrip strength. Throughout the rest of the experiment, required handgrip strength randomly oscillates between 50% and 70% of the participant's maximum handgrip strength. For the *instrumental conditioning phase*, the instrumental response of squeezing the handgrip will be followed by monetary reward. Participants will be told that they should perform quick squeezes and use their judgment to decide when to squeeze to obtain the reward to maximize their profit. The phase includes 24, 12-second trials of the handgrip strength indicator overlaid atop a fractal cue, both centered on the screen. Participants will receive a reward (cued with $ symbol) if the exerted handgrip strength reached the maximum required handgrip strength for the trial during two, one-second randomly selected windows when reward is available. The one-second reward windows are not signaled in any way. Each trial is followed by a 4-12 second intertrial interval (ITI), during which a fixation cross is presented.

For the *Pavlovian phase*, participants will be presented with 36, 12-second trials, during which either the CS+ or the CS- is presented, with the CS+ paired with a reward symbol and the CS- presented with a "no reward" symbol. The reinforcement rate during Pavlovian conditioning is 100%. A baseline stimulus will be presented during ITIs, during which neither the "reward" nor the "no reward" symbol is presented. CS+, CS- and baseline stimuli appeared in one of four randomly selected orders of stimuli, which will be counterbalanced. Participants will not use the handgrip during this phase. Over each CS, a gray "patch" image obscures the outcome (i.e., reward or no reward). It disappears to reveal whether the reward was obtained during the Pavlovian phase. Participants will be asked to press as quickly as possible the "1" key with their non-dominant index finger to reveal the outcome but will be informed that this response simply monitors their attention to the task and has no bearing on the outcome. The patch will be removed automatically to reveal the outcome regardless of participants' pressing. There are three equal monetary rewards for each CS+ trial which will be presented at random times equally distributed throughout the stimulus presentation. After each trial comes a 4-second ITI, during which the baseline stimulus is presented. At the end of this phase, valence and arousal ratings of each fractal image will be collected to assess evaluative learning.

Next, participants completed *forced choice ratings* on preference for the CS+, CS-, and baseline stimuli. Participants are presented with each possible combination of two stimuli at a time (six trials total) in one of two randomly selected orders. The two stimuli are centered on the left and the right side of the screen. Participants select a stimulus by pressing the right or left arrow key on the keyboard to indicate their preferred stimulus (i.e., CS+, CS-, or baseline fractal image). Each trial is followed by a 1-second ITI with a fixation cross. Choice scores per stimulus will be computed as the number of times each stimulus was preferred.

Next is a *second instrumental phase with partial extinction* which is identical to the first instrumental phase followed by 12 partial extinction trials. Each instrumental trial includes three reward windows, while each partial extinction trial includes one reward window. Partial extinction is included to increase the potential transfer effect.[172] During the final *PIT test phase*, participants undergo 18 full-extinction trials (six trials per cue), during which the three Pavlovian stimuli are presented with the thermometer to assess the Pavlovian-Instrumental interaction. Participants view one of four randomly selected orders of stimuli, which are counterbalanced. Participants respond by squeezing the handgrip during these trials. The PIT test trials are 12 seconds in duration and are followed by 4-12 second (mean of 8 seconds) ITIs. The durations of ITIs are randomized across the phase. The dependent variable is handgrip force exerted during each CS+ versus CS- in the PIT test phase.

<u>Self-report Index: Pavlovian Instrumental Transfer (PIT-VALENCE)</u> Within PIT, participants rate preference and pleasantness (0-4) for the three CS's, to indicate the value of reward. Typically, the CS+ yields higher preference and pleasantness ratings than CS- or baseline CS.[170] The dependent variable is pleasantness or valence for the CS+ versus CS-.

Reliability of Target Measurement

Cross-site consistency in procedures for the behavioral and physiological measurement of the anticipation, motivation, attainment, and learning of reward sensitivity will be maintained in the following ways. First, detailed protocol manuals outline the procedures, including verbatim instructions to experimenters and participants. Second, experimenters will undergo standardized training involving: (a) use of physiological equipment, experimental procedures, data collection, and (b) implementation of the laboratory paradigms. Training will include one full protocol rehearsal per experimenter and an observation certification check, in which experimenters will be observed by Dr. Ritz, who will rate adherence to procedures at both sites (SMU and UCLA). Experimenters will have to pass the adherence check before being certified. Adherence checks will be repeated annually to minimize site or experimenter drift, combined with annual joint 1-day laboratory protocol adherence meetings. Dr. Ritz will be primarily responsible for overseeing and maintaining within and cross-site consistency in these paradigms and measures and will address disparities across sites as they arise. In addition, Dr. Pizzagalli (study consultant) will review methods, procedures, and ongoing data collection for the Probabilistic Reward Task and will be available as needed for troubleshooting.

We will complete cross-site quality checks of behavioral and physiological data, including consultation from Dr. Diego Pizzagalli for the PRT annually.

Sample Size

Our target sample size is n = 68.

We will use PinT 2.12 (Power in Two-Level Models[173]) to calculate the minimum effect size (ES) detectable with power >.80 unless otherwise noted. We assume a conservative estimate of 25% missing data. Data from our pilot study provided estimates for covariances and error variances that are needed by PinT. Since the Benjamini-Hochberg correction cannot be directly implemented in power analysis calculations, we will use the more conservative Bonferroni correction for our power analyses. Since MMLM analyses have greater power than the single outcome MLM analyses,[174] for each Aim, we will calculate the power for the more conservative univariate MLM analysis. For hypotheses regarding clinical outcomes, we have greater than .80 power to detect an ES difference between PAT and NAT as small as d = .35. For hypotheses regarding target engagement, we have greater than .80 power to detect an ES difference between PAT and NAT as small as d = .39. For hypotheses regarding covariation between target measures and clinical outcome measures, we have .80 power to detect covariation between a target and PANAS-P as small as d = .44.

Ethics and Dissemination

Trial conduct will be overseen by a data and safety monitoring board comprised of four researchers from three universities with extensive experience in treatments for depression and anxiety. The trial was approved by internal review boards of the respective data collection sites (UCLA and SMU) December, 2018. Written informed consent will be obtained from all participants by research personnel at UCLA and SMU. Any potential changes to the protocol will be submitted as amendments to the IRB and discussed with the data monitoring board at meetings. This study will follow the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Individuals will be assigned a subject number upon entering the study. The study staff will place the participant's name and contact information on a code sheet next to their subject number. This code sheet will be stored on a password-protected computer in a locked laboratory with restricted access. Paperwork with identifying information will be shredded. Only coded identifiers will be used for data archiving. Personally identifying information will be kept in a secure location, password-protected, and stored completely separate from any subject data that will be processed or analyzed for the research.

Results will be communicated and disseminated through publication in scientific journals, conferences, and other common research outlets. Any use of the study data would require strong contributions in the conceptualization of the paper to constitute authorship.

Randomization and Masking

Participants will be randomized 1:1 to PAT vs. NAT via centralized, computer-generated allocation sequences with variable-sized permuted block sizes, stratified by medication status (2 strata; y/n). Randomization will be managed by the study statistician (D.R.). Because of the nature of the study, only outcome assessors were masked to group allocation. Study coordinators enrolled participants and assigned them to interventions according to the randomization table.

Statistical Methods

We will examine the distributional properties of all measures and use transformations to improve distributions when necessary. We will use Multilevel Modeling (MLM) because it is an intent-to-treat analysis that includes all participants, regardless of missing data, thus increasing power and generalizability.[175] When targets (i.e., reward approach-motivation, attainment, and learning) have multiple measures, we will use multivariate MLM (MMLM). For the model for the outcome variables which are assessed weekly, we will examine various alternative covariance matrices (e.g., unstructured, Toeplitz, Auto-regressive) and decide among them using AIC and BIC.[176] All models will include relevant control variables (e.g., gender, age, initial severity, medication use) if significant. Further, site will be investigated as an additional independent variable so that site differences can be controlled. To determine the effects of missing data, we will use pattern mixture modeling. Following Enders[177], we will rerun our analyses coding for various missing data patterns (e.g., no missing data, sporadic missing, dropouts) to determine: 1) if missingness impacts our findings and 2) how differences between treatment conditions depend on the missing data pattern. When multiple tests are performed, we will correct for inflation of Type I error using the Benjamini-Hochberg correction for false discovery rate.[178] We chose Benjamini-Hochberg rather than the conservative Bonferroni correction that can inflate Type II error. Following recent advances concerning time-varying predictors (TVPs) in longitudinal data analysis[179], we will disaggregate between-and within-subjects components of the TVPs in all analyses. R61 analyses will be limited to measures that demonstrate adequate test-retest reliability (rtt >.70119) in our sample.

Aim 1: Test of Replicability of Efficacy. We will conduct an MMLM to determine if the level of outcome on our 3 primary outcome variables (PANAS-P, interviewer-rated anhedonia, and DASS) is different for PAT vs. NAT at post-treatment. Because outcome is measured weekly, we will use a growth curve to model change in the multivariate outcome over time. We will compare various possible growth curve models (e.g., linear, quadratic, logarithmic, or hyperbolic), choosing the best model based on standard AIC and BIC information criteria.

Aim 2: Target Engagement. Three MMLM analyses will be conducted to compare the efficacy of PAT vs. NAT, one for each reward target (reward approach-motivation, initial reward responsiveness, reward learning). These analyses will be modeled as the MMLM equivalent of a 2 x 4 ANOVA (treatment condition x Time (baseline, weeks 5, 10, 15). To determine if PAT is superior to NAT, we will test the difference between treatment conditions at post-treatment. If the MMLM analysis indicates significant differences between condition, we will perform these same 2 x 4 ANOVAs for each individual measure of each reward target for the Go/No-Go criteria below. We will also analyze the PANAS-P for the Go/No-Go criteria. Because the PANAS-P is measured weekly, we will use a growth curve to model change in PANAS-P over time. We will compare various possible growth curve models (e.g., linear, quadratic, logarithmic, or hyperbolic), choosing the best model based on standard AIC and BIC information criteria.

Aim 3: Target and Outcome Covariation. We will use SEM to model the covariation of within-subjects change in targets to within-subjects change in the outcome. Each target will be

represented as a latent variable (representing the individual measures of that reward target) that covaries with a latent variable representing our 3 primary outcomes. Each will be examined separately as a disaggregated TVP of outcome. We will analyze each measure individually in order to be more inclusive in identifying potential mediators for further testing in our R33 phase. Using the MMLM approach, we will retain for the R33 those targets that show significantly greater improvement in PAT than NAT in the MMLM, with an effect size of d>.5 (p-levels were corrected for multiple tests using Benjamini-Hochberg). All individual measures of such "engaged" targets will be retained for the R33 for that target.

Safety Monitoring

Study staff will be available 24 hours to respond to urgent issues. All staff will be able to provide information about local emergency facilities. The therapist or Ph.D. level project coordinator will generally be the first person to respond to a participant with a problem. They will handle some events immediately. If they are not able to manage the emergency event, they will contact the PIs, who will also be available 24 hours by cell phone to assist with participant management or crisis intervention. In addition, a DSMB will oversee safety and other related issues pertinent to the ongoing study (see Data Safety Monitoring Plan).

A Data Safety and Monitoring Board (DSMB) will be a committee of four members that oversee clinical and ethical issues pertaining to the clinical trial. Dr. Bruce L. Kagan, M.D., Ph.D., who will serve as the chair, is a Professor of Clinical Psychiatry at the UCLA Semel Institute for Neuroscience and Human Behavior Brain Research Institute. Dr. Robert DeRubeis, Ph.D., is a Professor of Psychology at the University of Pennsylvania. Drs. Sherwood Brown, M.D., Ph.D., and Robin Jarret, Ph.D., are Professors of Psychiatry at the UT Southwestern Medical Center in Dallas. All members have extensive research and clinical expertise in mood disorders. All members are independent of the sponsor and do not hold competing interests.

Regarding our data sharing efforts, we will submit the Data Monitoring Agreement and complete annual enrollment and submission of raw data to the NIMH Data Sharing repository.

According to the NIMH definition, an adverse event is "Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign, symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research." The following adverse events will be monitored: deaths, suicide attempts, study dropout, psychiatric hospitalizations, and clinical deterioration, defined as emergent suicidal ideation or suicidal plan, development of serious substance abuse, or the emergence of a new psychiatric or medical diagnosis or behavior posing a significant risk to the subjects of others. Adverse events will be presented at the annual DSMB meeting. DSMB committee members will independently evaluate whether each event qualified as a serious adverse event using the following criteria: 1) Serious/Not serious: Is the event serious or places subjects or others at greater risk than previously known or recognized? 2) Expected/Unexpected: Is the event unexpected (not described in the protocol or consent or exceeds severity/frequency of expected event) 3) Causality: Is the event-related or possibly related to research procedures? If an event qualifies as a serious adverse event, then the serious adverse event will be reported to IRB.

Consent Statement (UCLA[1])

Treatment for Affect Dimensions (TAD)

You are invited to complete a web-based online survey for the Treatment of Affect Dimensions (TAD) study. The purpose of this survey is to collect baseline data prior to the completion of any treatment and assessments procedures. Participation in this survey will take approximately 45-60 minutes to complete. This electronic consent is for your participation in this online survey only. You will complete your informed written consent for the study when you come on-site for your initial appointment before completing any further procedures.

The Treatment for Affect Dimensions (TAD) study compares two types of treatment for individuals with elevated symptoms of depression, anxiety, or stress. All of the treatments will be conducted by fully trained clinical psychology doctoral students, with the aid of a senior research staff, and supervised licensed, clinical psychologists with extensive experience. The study will also include a number of assessments before, during, and after treatment. Qualified staff in the Department of Psychology at the University of California, Los Angeles will conduct the assessments. Overall, your involvement in the study will last up to 5 months, including the initial assessments, 15 weekly psychotherapy sessions, and a post-treatment assessment.

Participation

Your participation in this survey is voluntary. You may refuse to take part in the research or exit the survey at any time without penalty.

Confidentiality

Your survey answers will be stored initially on a secure web application for building and managing online surveys and databases in a password protected electronic format. The data will later be downloaded and stored in a secure location five years after the study has been completed and then they will be destroyed.

Any information obtained in connection with this study and that can be identified with you will remain confidential to the extent allowed by law. No identifying information will be revealed in the presentation or publication of any results from the project.

All information obtained from the study will be included in a research data pool, which will be used to add to scientific knowledge about psychological disorders and their treatment. All data with identifying information will be stored in locked files.

Potential Risks & Benefits

There are no known risks associated with the completion of this survey beyond any discomfort you might experience talking about your medical and psychological history.

You will receive no direct benefits from participating in this survey. At the completion of this survey, you will be eligible to enroll into our study and receive 15 treatment sessions at no cost to you. Furthermore, at the completion of each physiological session, you will be compensated monetarily. The laboratory assessments will take place at four time points: prior to treatment, 5 and 10 weeks into treatment, and at post-treatment. Findings from this study may help clinicians provide more effective treatments for psychological disorders. Research has shown that these treatment approaches are likely to be of benefit to those who show symptoms similar to yours. It is important to note that individuals respond differently to therapy, and so it is not possible to know in advance if the treatment will be helpful in your particular case. However, potential benefits may include significant reductions in your symptoms of anxiety, depression, or stress. You will be

[1] Corresponding consent forms were used for the Southern Methodist University site

provided with additional or alternative treatment referrals at any point in time during the study if you make such a request.

You will be compensated $75 at the completion of each laboratory session, and you will also be able to earn up to $70 on certain tasks during the laboratory sessions. The maximum amount that can be earned for the four laboratory assessments is $580. You will be reimbursed for parking during assessments but not for treatment visits.

Your participation in the study is voluntary. Refusal to participate will involve no penalty or loss of benefits to which you would be otherwise entitled. You may discontinue participation at any time without penalty or loss of benefits to which you may be otherwise entitled.

Contact

If you have any questions or concerns regarding your participation in this survey, please feel free to contact Michelle G. Craske, Ph.D., Professor of Psychology, Director of the Anxiety and Depression Research Center at UCLA, Franz Hall 3170, who can be reached at (310) 825-8403.

If you have any questions about your rights while taking part of this study, or you have concerns or suggestions and you want to talk to someone other than the researchers about the study, please call the UCLA Office of the Human Research Protection Program (OHRPP) at (310) 825-7122 or write to:

UCLA Office of the Human Research Protection Program:
11000 Kinross Avenue, Suite 211, Box 951694
Los Angeles, CA 90095-1694

If any problems arise as a result of your participation in this study, including research-related injuries, please call the Principal Investigator, Michelle G. Craske, Ph.D., at (310) 825-8403, immediately. If you are injured as a result of being in the study, UCLA will provide necessary medical treatment. The costs of the treatment may be covered by the University of California, or billed to you and your insurer just like other medical costs, depending on a number of factors. The University does not normally provide any other form of compensation (payment) for injury. For more information about this you may call the UCLA office of the Human Research Protection Program at 310-825-5344 or send an email to mirb@research.ucla.edu.

If you are having thoughts of suicide, please contact the National Suicide Prevention Lifeline
at 1-800-273-8255, or call 911 if you are in immediate danger.

ELECTRONIC CONSENT: Please select your choice below. You may print a copy of this consent form for your records. Clicking on the “Agree” button indicates that

- You have read the above information
- You voluntarily agree to participate in the online survey

☐ Agree

☐ Disagree

CONSENT TO PARTICIPATE IN RESEARCH
for Treatment Participants

Treatment for Affect Dimensions (TAD)

Michelle G. Craske, Ph.D., (Department of Psychology at the University of California, Los Angeles) is conducting a research study. You were selected as a possible participant in this study because of your responses to a preliminary screening, which indicated that you may experience elevated symptoms of anxiety, depression, or stress. If eligible, you will be asked to participate in this study for up to five months.

Your participation in this study is voluntary. You should read all of the information below and ask questions about anything that you do not understand, before deciding whether or not to participate. Research designs often require that the full intent of the study not be explained during participation. Although we have described the general nature of the tasks that you will be asked to perform, there may be some details that are not revealed for the sake of accurate data collection. For scientific reasons, this consent form does not include complete information about the study hypotheses and the research questions being tested. You will be fully debriefed following your participation in the research. Similarly, after the study, we will provide you with an explanation of the study, which will include relevant background information. You will also be given an opportunity to ask any questions you might have about the hypothesis and the procedures used in the study.

Why is this study being done?

The purpose of the study is to examine which individuals with symptoms of anxiety, depression, and stress are more likely to benefit from two different versions of therapy. Each of these therapies includes components and therapeutic strategies that have been demonstrated to be effective for these problem areas. One therapy focuses on enhancing and increasing positive coping and life strategies, whereas the other therapy focuses on decreasing or eradicating negative coping and life strategies. Both versions involve examining thoughts, modifying behaviors, and focusing on breathing.

What will happen if I take part in this research study?

If you volunteer to participate in this study, we would ask you to do the following things:

You already should have gone through two screening procedures, which were designed to determine if the study is appropriate for you. Screening procedures include answering initial eligibility questions, a diagnostic interview dealing with anxiety, depression, and other psychological problems, use of illegal drugs and medical history. This interview can last up to 2 hours. In addition, a medical evaluation will be encouraged if you have not had a full medical examination in the last 12 months, at your cost. If you are seeing another mental health provider (e.g., psychiatrist) we will ask you to sign a release of information (optional) so that we can contact the other provider and inform them of your participation in our treatment study. If it is determined that the study is not appropriate for you, your participation will end at that point, and we can provide you with a list of referrals.

<u>Treatments</u>

During participation in the study, you will receive 15 weekly treatment sessions with a trained therapist. You will be randomly assigned, or by chance, to one of two treatments. One therapy focuses on enhancing and increasing positive coping and life strategies, whereas the other therapy focuses on decreasing or eradicating negative coping and life strategies. Both versions involve examining thoughts, modifying behaviors, and focusing on breathing.

All of the treatments will be conducted by fully trained clinical psychology doctoral students, with the aid of a senior research staff, and supervised by licensed, clinical psychologists with extensive experience. All of the treatment sessions will be audio- and videotaped. This is done in order to monitor reliability and consistency among the therapists. Remote sessions will be offered through an encrypted video-conferencing platform via Zoom. You will have the right to review, edit, or erase the research tapes containing your participation in whole or in part.

Individuals taking dopaminergic medications (e.g., Ritalin, Wellbutrin, amphetamines, methylphenidate, L-dopa) or Bupropion cannot participate in the study while still on medication. Heterocyclics, SSRIs and fluoxetine need to be stabilized (3 months) – that means that your dose should be the same, or that you should be medication-free, for that amount of weeks (differing by medication) before enrolling in the study. PRN (when required) use of benzodiazepines and beta blockers are permitted, but they should not be used on assessment days, and ideally not within 2 weeks leading up to the assessments. If you are on medications, you will be asked to tell this to the study team at the time of screening and/or informed consent. Also, you will be asked to inform us if you seek other forms of medical or psychological treatment for depression, anxiety, or stress before completion of the 15-week treatment study.

All 15 treatment sessions must be completed within 19 weeks. In addition, you may be removed from the study if you miss more than three treatment sessions without notifying study staff within 24 hours of your scheduled session. Further, we expect all participants to notify study staff within 24 hours before missing a physiological assessment. These assessments often require up to 5 researchers, and cancellations without notice are very inconvenient. We will work hard to schedule your appointments when convenient for you, so please let us know at least 24 hours in advance for any changes or cancellations.

If you delay starting therapy for six or more weeks following your diagnostic interview, you will need to complete the diagnostic assessment and lab tasks again.

Assessments

You will be asked to complete laboratory assessments with our research staff. During these assessments, your behavior and your physical responses (pCO_2, respiration rate, pulse, and heart rate) will be monitored and recorded while you are asked to attempt computer tasks. Your physiological responses will be measured by electrodes that are taped on your skin. We will also analyze inflammatory markers such as C-reactive protein via your saliva.

You will be asked to wear a water resistant wrist band (ActiGraph) at four time-points for 7 consecutive days each to monitor your physical activity levels, general sleep patterns, and overall energy expenditure. This wrist monitors activity only, and does not monitor location data. It also does not record audio or capture images.

The first diagnostic interview, laboratory assessment, behavioral assessment, and questionnaires will be administered at baseline, prior to starting treatment. The laboratory assessment,

behavioral assessment and questionnaires will also be administered after 5 weeks into treatment, 10 weeks into treatment, and at the completion of treatment.

Upon completing the treatment phase of the study, you will be asked to complete one diagnostic evaluation with one of our research staff. The diagnostic evaluation will cover anxiety, depression, and other psychological disorders. This evaluation will be occurring after treatment and is expected to last approximately one hour.

There are two additional, ***optional*** procedures in which you can elect to participate as a participant in this study.

One is to provide two blood samples—one at pre and one and post-intervention. If you choose to complete this procedure, you will have 3-4 tablespoons of blood drawn by a certified phlebotomist. Your sample will be used to look at differences in immune system functioning. The blood draw is for research purposes only, and you will not receive the results. Any leftover study blood samples may be stored for future research studies. Samples will only be released for use in future studies after approval by the Principal Investigator and other regulatory bodies, as appropriate.

Similarly, you can choose to undergo an fMRI scan at the California Institute of Technology. If you elect to receive an fMRI scan, you will come to CalTech from 10am-4pm to take part in two, two hour MRI sessions. A break will be given between sessions.

How long will I be in the research study?

Overall, your involvement in the study will last approximately five months (approximately one month for initial assessment, four months for treatment, and a post-treatment assessment approximately one week after the completion of treatment).

Are there any potential risks or discomforts that I can expect from this study?

There are no known risks associated with the initial diagnostic evaluation or any of the follow-up assessments beyond any discomfort you might experience talking about your medical and psychological history.

During the treatment phase of the study, you may experience anxiety from being asked to face things that cause you distress or from being asked to confront situations and feelings that you find anxiety provoking.

The laboratory sessions can induce symptoms such as discomfort or mild physical symptoms in some people. Furthermore, the paste and collars of the electrodes may cause minor skin irritations in some participants. The assessment of the physiological measures (pCO_2, respiration rate, pulse, heart rate, etc.) is non-invasive and therefore is of minimal risk. All medical supplies (nasal cannulas, electrodes) are sterile to reduce the risk of infection.

Blood draw risks:

While neither the public nor the controlled-access databases developed for this project will contain information that is traditionally used to identify you, such as your name, address, telephone number, or social security number, people may develop ways in the future that would allow someone to link your genetic or medical information in our databases back to you. For example, someone could compare information in our databases with information from you (or a blood relative) in another database and be able to identify you (or your blood relative). It also is possible

that there could be violations to the security of the computer systems used to store the codes linking your genetic and medical information to you.

Because this is a research study, there may be some unknown risks that are currently unforeseeable. You will be informed of any significant new findings.

Please also note: Any specimens (e.g., blood, saliva) obtained for the purpose of this study will become the property of the University of California. Once you provide the specimens you will not have access to them. The University may share your specimens in the future with other researchers or outside institutions. Information that identifies you will not be shared with anyone outside of UCLA. The specimens will be used for research and such use may result in inventions or discoveries that could become the basis for new products or diagnostic or therapeutic agents. In some instances, these inventions and discoveries may be of potential commercial value and may be patented and licensed by the University. You will not receive any money or other benefits derived from any commercial or other products that may be developed from use of the specimen.

MRI Risks:

1. Physical discomfort: you may feel some discomfort, fatigue, and muscular aches from lying on your back for approximately 60 minutes in the scanner. Minimal discomfort may occur from the fingertip cuff.
2. Metal: the MRI machine produces a constant strong magnetic field, so if you have metal implants or clips within your body they may be influenced by the magnetic field and shift in position. This is a risk if you have a history of: a cardiac pacemaker; metal fragments in your eyes, skin, or body; heart valve replacement; brain clips; venous umbrella; being a sheet-metal worker or welder; aneurysm surgery; intracranial bypass; renal or aortic clips; prosthetic devices such as middle ear, eye, joint, or penile implants; joint replacements; hearing aid; neurostimulator; insulin pump; I.U.D.; shunts/stents; metal mesh/coil implants; metal plate/pin/screws/wires, or any other metal implants; permanent eyeliner or eyebrows. Thus, if you have such implants you must inform us and you cannot participate in this study. Metal earrings and necklaces also must be removed prior to the study.
3. Hearing: the MRI scanner produces a loud high frequency tone that can cause hearing damage if appropriate hearing protection is not used. Adequate hearing protection in the form of foam ear-plugs and headphones will be provided and required. Minimal discomfort may occur from the use of this hearing protection.
4. Claustrophobia: the head holder fits closely around your head, so if you feel anxious in confined spaces you may not want to participate. If you decide to participate, and then at a later time decide to discontinue, just let us know and we will stop the experiment.
5. Dizziness: on occasion individuals undergoing MRI might become dizzy. If you become dizzy while in the magnet, use the intercom to inform the scanner operator; do not leave the scanner gurney table without assistance from the scan operator. We will evaluate your dizziness at the scanning site. We may make recommendations about your dizziness, including recommending that you not leave the scanning center until you are no longer dizzy. In more severe cases of dizziness the investigator might recommend that you no longer continue with the study.
6. Muscle twitching and skin sensations: at times individuals undergoing MRI can experience muscle twitching or skin sensations, such as tingling or pain, that are unrelated to any physical contact. If you experience these sensations, please use the intercom to contact the scanner

operator, who will stop the scan. In cases of clear muscle twitching, the research team is likely to recommend that you end participation in the study.

7. The potential risks to a fetus are unknown, Thus, if you are pregnant, or you think you may be pregnant, you should not participate in this study

You have the right to refuse to answer any question that you do not wish to answer, and to refuse any task that you do not wish to do. You can stop your participation in the study at any time without penalty.

Are there any potential benefits if I participate?

You will receive a diagnostic evaluation and treatment at no cost to you. At the completion of each physiological session, you will be compensated monetarily. Findings from this study may help clinicians provide more effective treatments for psychological disorders. Research has shown that these treatment approaches are likely to be of benefit to those who show symptoms similar to yours. It is important to note that individuals respond differently to therapy, and so it is not possible to know in advance if the treatment will be helpful in your particular case. However, potential benefits may include significant reductions in your symptoms of anxiety, depression, or stress.

Also, you will be provided with additional or alternative treatment referrals at any point in time along the study if you make such a request.

What other choices do I have if I choose not to participate?

Your participation in the study is voluntary. Refusal to participate will involve no penalty or loss of benefits to which you would be otherwise entitled. You may discontinue participation at any time without penalty or loss of benefits to which you may be otherwise entitled.

Medication or therapy (e.g., cognitive-behavioral therapy) from other providers is acceptable alternatives to participating in this study. If you would like, we will provide you with a referral list.

Will I be paid for participating?

You will be compensated $75 at the completion of each laboratory session, and you will also be able to earn up to $70 on certain tasks during the laboratory sessions. The maximum amount that can be earned for the four laboratory assessments is $580. You will be reimbursed for parking during all four assessments but not for treatment visits.

If you elect to receive an fMRI scan, you will be paid $200 for your participation in an fMRI scan plus any winnings from experiments undergone while in the scanner (up to $40 per experiment). Transportation will be reimbursed or arranged as necessary.

Are there any costs for taking part in this study?

You will receive diagnostic evaluations and treatment for free. At the UCLA site only, you will be responsible for paying for parking during your treatment visits.

What happens if I believe I am injured because I took part in this study?

It is important that you promptly tell the researchers if you believe that you have been injured by taking part in this study. You can tell the researcher in person or call her at the number listed below.

Michelle Craske, Ph.D.
UCLA Anxiety and Depression Research Center
Department of Psychology
Franz Hall - Box 951563
Los Angeles, CA 90094-1563
(310) 825-8403

If you are injured as a result of being in this study, UCLA will provide necessary medical treatment. The costs of the treatment may be covered by the University of California, or billed to you and your insurer just like other medical costs, depending on a number of factors. The University does not normally provide any other form of compensation (payment) for injury. For more information about this you may call the UCLA Office of the Human Research Protection Program at 310-825-5344 or send an email to mirb@research.ucla.edu.

If you are having thoughts of suicide, please contact the National Suicide Prevention Lifeline at 1-800-273-8255, or call 911 if you are in immediate danger.

Will information about me and my participation be kept confidential?

The researchers will make every attempt to protect your confidentiality, or privacy, and to make sure that your personal identity does not become known. The investigator has obtained a Confidentiality Certificate from the Department of Health and Human Services to further help us protect your privacy. The Certificate protects us from being forced to disclose or provide information that may identify you in any federal, state, local, criminal, administrative, legislative or any other procedures. However, information will be disclosed upon request of DHHS for purposes of audit or evaluation. You need to be aware that the Confidentiality Certificate does not prevent you from voluntarily releasing information. However, if an employer or insurer finds out about your participation in the study and obtains your consent to receive research information, then we will not be able to withhold the requested information. Accordingly, it is important that you and your family actively protect your own privacy.

Finally, you need to be aware that the investigator will need to disclose information including reporting to authorities to prevent harm to yourself or others. In the event that you tell the research or clinical staff that you are thinking about suicide, or if you answer yes to a question to having thoughts about suicide, the research staff will ask you more questions about the thoughts. Depending on how intense the thoughts are or how much you feel like hurting yourself, the research staff may provide you with referrals for treatment; work with you to contact your personal physician, trusted family member, or therapist to discuss your thoughts of harming yourself; or work with you on a plan that may include getting you to a hospital for safety.

This signed consent form will be stored in a locked file that will be accessible only to a very small number of the authorized people involved in this project. The research will carefully follow the coding, storage, and data sharing plan explained below.

Some identifiable information about you will be replaced with a code. A list linking the code and your identifiable information will be kept separate from the research data. All research data and

records will be maintained in a secure location at the pertaining sites, UCLA and SMU. Only authorized individuals will have access to it. Some research data and records will be stored electronically on a secure network with password protection.

All of the diagnostic evaluations and treatment sessions will be video- and/or audio-taped and later reviewed by research staff for educational purposes (supervision) and to determine whether the assessments and treatment have been delivered appropriately (quality assurance). The data and video/audiotapes will be stored in a secure location for five years after the study has been completed, and then they will be destroyed.

If you are ineligible for the study, we will still need to enter some of your screening information in our database. However, the diagnostic interviews and any other screening information will be shredded, and there will be no personal identifiers between your data that is in the database and yourself.

What are my rights if I take part in this study?

- You can choose whether or not you want to be in this study, and you may withdraw your consent and discontinue participation at any time.
- Whatever decision you make, there will be no penalty to you, and no loss of benefits to which you will be otherwise entitled.
- You may refuse to answer any questions that you do not want to answer and still remain in the study.

The investigator may withdraw you from this research if things happen that make your removal necessary. The decision may be made either to protect your health and safety, or because it is part of the research plan that people who develop certain conditions may not continue to participate.

Who can I contact if I have questions about this study?

If you have any questions or concerns about the research, please feel free to contact Michelle G. Craske, Ph.D., Professor of Psychology, Director of the Anxiety and Depression Research Center at UCLA, Franz Hall 3170, who can be reached at (310) 825-8403.

UCLA Office of the Human Research Protection Program (OHRPP):
If you have questions about your rights while taking part in this study, or you have concerns or suggestions and you want to talk to someone other than the researchers about the study, please call the OHRPP at (310) 825-7122 or write to:

UCLA Office of the Human Research Protection Program:
11000 Kinross Avenue, Suite 211, Box 951694
Los Angeles, CA 90095-1694

SIGNATURE OF RESEARCH SUBJECT

I understand the procedures described above. My questions have been answered to my satisfaction, and I agree to participate in this study. I have been given a copy of this form.

Please initial next to **one** of the following responses. Your decision will not affect your participation in the current study.

_____ I agree to allow my answers from the telephone screener to be part of my research record.

_____ I do not want my answers from the telephone screener to be part of my research record.

Please initial next to **one** of the following responses. Your decision will not affect your participation in the current study.

_____ I agree to provide blood samples at pre and post-intervention.

_____ I do not want to provide blood samples at pre and post-intervention.

Please initial next to **one** of the following responses. Your decision will not affect your participation in the current study.

_____ I agree to participate in the fMRI scan portion of this study.

_____ I do not want to participate in the fMRI scan portion of this study.

Please initial next to **one** of the following responses. Your decision will not affect your participation in the current study.

_____ I agree to be contacted about other research studies conducted by Michelle Craske, Ph.D.

_____ I do not agree to be contacted about other research studies conducted by Michelle Craske, Ph.D.

_____
Name of Subject

_____ _____
Signature of Subject Date

SIGNATURE OF INVESTIGATOR

In my judgment the subject is voluntarily and knowingly giving informed consent and possesses the legal capacity to give informed consent to participate in this research study.

_____ _____
Name of Person Obtaining Consent Contact Number

_____ _____
Signature of Person Obtaining Consent Date

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