**Trial Protocol for
"Reward and Threat Sensitivity as Mediators of Positive and
Negative Affect Treatment"**

Last updated February 5th, 2025

Trial Registration

The trial was officially registered on clinicaltrials.gov on January 10th, 2022. The registry name is "Affect Treatment for Depression and Anxiety" (Clinical Trials ID#: NCT05203861). This study is funded by the National Institute of Health (R33MH115138). 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: "Affect Treatment for Depression and Anxiety"
Scientific Title: "Reward and Threat Sensitivity as Mediators of Positive and Negative Affect Treatment"

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) <u>Attention Bias:</u> 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) <u>Psychophysiology:</u> Anhedonia is associated with reduced cardiac acceleration while viewing pleasant pictorial stimuli[70] or during imagery of pleasant scripts.[71] (4) <u>Neurophysiology:</u> 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]

<u>Reward Learning.</u> (1) <u>Behavior:</u> 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) <u>Neurophysiology:</u> 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, interview-rated anhedonia, and symptoms of depression and anxiety). Targets will be assessed before, twice during, posttreatment, and one-month follow-up, 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.

<u>Aim 1:</u> Treatment Efficacy and Target Engagement. Hypotheses: a) Clinical Outcome (comprised of PANAS-P, DASS Total, and in interview-rated anhedonia) improves more in PAT than in NAT, b) each of the three reward targets show significantly greater target engagement (improvement) in PAT than NAT, and c) threat sensitivity target will improve more in NAT than in PAT.

Aim 2: Specificity of Target Engagement with Respect to Threat versus Reward. Hypotheses: i) PAT leads to significantly greater improvements in reward anticipation-motivation, initial responsiveness to reward attainment, or reward learning than NAT, and ii) PAT leads to significantly greater changes in reward sensitivity than threat sensitivity relative to NAT.

Aim 3: Mediation. Hypothesis: Reward sensitivity targets and the threat sensitivity target will mediate treatment condition (PAT vs. NAT) differences in the improvement in clinical outcomes.

Aim 4: Trimming of Target Measures.

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 $\geq$ 11 for depression, $\geq$ 6 for anxiety or $\geq$ 10 for stress to represent moderate to severe symptom severity,[92] (5) $\geq$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-being in 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 assess and understand the mood- inducing effects. In so doing, the exercises 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 CO_2 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.

<u>Therapist Training, Supervision, and Fidelity</u>

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.

<u>Outcome Measures</u>

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. . .

<u>Primary Outcome Measures.</u>

<u>Self-Rated Positive Affect: Positive Affect Subscale (PANAS-P)</u>[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]

<u>Depression and Anxiety Stress Scales (DASS-21)</u>[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.

<u>Secondary Outcome Measures.</u>

<u>Interviewer-Rated Anhedonia.</u> 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.

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 Scale for Suicidal Ideation. The Beck Scale for Suicidal Ideation will be used to assess suicidal ideation, from baseline to one-month follow-up.

Self-Rated Positive Affect: Basic Positive Emotions Scales and Serenity (PANAS-X)

Measures of Reward Sensitivity and Threat Sensitivity (Target engagement measures)

Target measures of 1) reward anticipation-motivation, 2) response to reward attainment, 3) reward learning, and 4) threat sensitivity 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, posttreatment-assessment, and one-month follow-up.

	Baseline						Post	1MFU
Week	**0**	**1-4**	**5**	**6-9**	**10**	**11-15**	**16**	**20**
Reward Sensitivity (Target)								
Reward Anticipation-Motivation								
B: Effort Expenditure for Rewards Task (EEfRT)	X		X		X		X	X
P: Monetary Incentive Task (MIT)	X		X		X		X	X
S: Behavioral Inhibition and Activation Scale-Reward-Drive Subscale (BAS-RD)	X		X		X		X	X
S: Dimensional Anhedonia Rating Scale (DARS-A-M)	X		X		X		X	X
Response to Reward Attainment								
C: Modified Attentional Dot Probe Task [positive cues]	X		X		X		X	X
P: International Affective Picture System (IAPS) Task [positive stimuli]	X		X		X		X	X
S: Temporal Experience of Pleasure Scale-Consummatory Subscale (TEPS-C)	X		X		X		X	X
S: Dimensional Anhedonia Rating Scale (DARS-C)	X		X		X		X	X
Reward Learning								
B: Probabilistic Reward Task (PRT)	X		X		X		X	X
Threat Sensitivity (Target)								
S: Anxiety Sensitivity Index (ASI)	X		X		X		X	X
S: Probability and Cost Questionnaire	X		X		X		X	X
S: Behavioral Inhibition Scale (BIS)	X		X		X		X	X
P: Mental Arithmetic Task	X		X		X		X	X
P: International Affective Picture System (IAPS) Task [negative stimuli]	X		X		X		X	X
C: Modified Attentional Dot Probe Task [negative cues]	X		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 quarters 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 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] While there are likely to be multiple explanations, including reward devaluation, the end result is less time attending to positive stimuli, which can be considered a weaker response to attainment of reward. 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 <u>engagement</u> 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 <u>disengagement</u> 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).

<u>Physiological Index: Heart rate acceleration to International Affective Picture Systems (IAPS) positive stimuli.</u> 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.

<u>Self-report Index: Temporal Experience of Pleasure Scale-Consummatory Subscale (TEPS-C)</u>[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]

<u>Self-report Index: Dimensional Anhedonia Rating Scale-Consummatory Pleasure (DARS- C).</u> 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).

<u>Reward Learning</u>

<u>Behavioral Index: Probabilistic Reward Task (PRT)</u>[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.

Threat Sensitivity

      Self-report Index: Anxiety Sensitivity Index (ASI)[183] The 16-item ASI is designed to assess the beliefs that unexplained somatic sensations are dangerous and may cause deleterious physical, psychological, or social consequences beyond any immediate physical discomfort. The index has shown good internal consistency (α=.82)[184], test–retest reliability (r=.71–.75)[183], and criterion validity by significantly discriminating between patients with anxiety disorders and college students, as well as patients with agoraphobia and patients with other anxiety disorders[183].

      Self-report Index: Probability and Cost Questionnaire[185] The Probability and Cost Questionnaire was derived from that described by Foa, Franklin, Perry & Herbert (1996)[185]. The survey contains 20 items, each consisting of an example of a negative social event. Half of these items directly involved their own social performance (e.g., "During a job interview or evaluation, you will freeze") and half did not (e.g., "You will be ignored by someone you know"). Participants first rated each item based on how likely they believed it was to occur to them within the next year. They then rated each item based on how bad or distressing the outcomes would be for them if it did occur. All ratings were done on a likert scale ranging from 0 (not at all likely) to 8 (extremely likely).

      Self-report Index: Behavioral Inhibition Scale (BIS)[153] The 7-item BIS measures self-reported threat sensitivity via reactions to anticipation of punishment. Test-retest reliability after 8-weeks in college students was r=.66[153]. BIS correlates positively with PANAS-Negative and neuroticism[177] and improves following CBT for depression[178] and anxiety[179].

      Physiological Index: Mental Arithmetic Task[186] A standard mental arithmetic task was used that had been used previously in cardiovascular reactivity research and has shown to elicit stress and anxiety[186]. The task was preceded by a 3-min baseline and followed by a 3-min recovery period. Participants were asked to add and subtract 12 lines of 12 single or double-digit numbers on a computer screen while listening to background noises (voices of people having indistinguishable conversations in a large room) through in-ear headphones. Four of the lines were highlighted in blue, four in yellow, and four in red. At the end of the task, the experimenter asked the participants the final number and solution. To increase social evaluate threat, participants were told that most people made it towards the end of the red zone of lines.

      Physiological Index: Heart rate acceleration to International Affective Picture Systems (IAPS) negative stimuli. Maximum heart rate acceleration during the 6 seconds of negative image presentation relative to the last 2 seconds before picture onset will be assessed and compared to acceleration to neutral images.

      Cognitive Index: Modified Probe Detection Task (DOTPROBE) negative cues. This task measures attention bias to negative as well as positive cues. Preferential allocation of attention to negative stimuli is associated with negative affect[155], predicts outcomes from CBT for anxiety disorders[180] and changes significantly with CBT for anxiety disorders[181-182].

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 = 100.

We will use PinT 2.12 (Power in Two-Level Models[170]) 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,[171] 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, 2021. 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 use intent-to-treat multilevel models (MLM) to analyze our longitudinal data. Multivariate multilevel models (MMLM) will be used when there are multiple measures for the outcome being analyzed (i.e., for the clinical outcomes, the three reward targets, and the threat

sensitivity target). We will investigate various growth curve models for our MLMs (e.g., linear, quadratic, logarithmic, square root) and use the best fitting model (lowest BIC) for our analyses. For purposes of this data analysis, the word "target" refers to a conceptual group of potential mediators (i.e., the Reward Anticipation/Motivation, Reward Attainment, and Reward Learning targets, and the Threat Sensitivity target), while the individual measures which comprise a target are referred to simply as "measures". Whenever an MMLM shows a significant difference between PAT and NAT, we will follow the MMLM analysis with univariate MLM analyses of each of the measures comprising the target of that MMLM to determine which individual measures are engaged more by PAT than by NAT.

Aim 1: Treatment Efficacy and Target Engagement.
1a. We will first use MMLM to determine whether our multivariate Clinical Outcome (comprised of PANAS-P, DASS Total, and interviewer-rated anhedonia) improves more in PAT than in NAT. 1b. Using MMLM, we will determine if each of the three reward targets show significantly greater target engagement (improvement) in PAT than NAT. 1c. We will use MMLM to evaluate the hypothesis that the threat sensitivity target will be engaged more in NAT than in PAT.

Aim 2: Specificity of Target Engagement with Respect to Threat versus Reward.
The relative effects of PAT vs. NAT on reward sensitivity vis-à-vis threat sensitivity will be directly tested using an MMLM in which the measures of the threat sensitivity target and the measures of each of the three reward targets (in a separate analysis for each of the 3 targets in turn) are nested within assessments. We will code a dummy variable to contrast the threat sensitivity measures to the reward sensitivity measures. A significant 3-way interaction between the contrast dummy variable, treatment condition, and time will indicate that the effect of PAT vs. NAT is different for the reward sensitivity measures compared to the threat sensitivity measures. This analysis will be performed three times, each comparing the measures of one of the three reward targets to the measures of the threat sensitivity target.

Aim 3: Mediation.
We expect that our reward sensitivity targets and the threat sensitivity target will mediate treatment condition (PAT vs. NAT) differences in the improvement in clinical outcomes. We will evaluate each of the three reward sensitivity targets, and the threat sensitivity target, as a mediator of treatment group differences, with each target analyzed in a separate set of analyses.

For the analysis of each target as a mediator, we will first investigate each individual measure of the target as a single mediator of treatment group differences in clinical outcome improvements using our MMLM model from Aim 1. We will follow those analyses with a multimediator analysis for each target in which all of the individual measures of the respective target are included as simultaneous mediators (e.g., for the reward anticipation/motivation target, we have 4 individual measures of treatment condition differences in clinical outcome: BAS-drive, DARS anticipation/motivation, EEfRT task, Monetary Incentive Task). This analysis will tell us which individual measures are significant mediators of group differences in clinical outcome improvement over and above the other measures in the analysis. We expect that the reward sensitivity measures will be more engaged in PAT vs. NAT (these are the "a" paths in the longitudinal mediation analysis). On the other hand, we expect the threat sensitivity measures to be more engaged in NAT than in PAT. We will use the distribution of products test RMediation to test for significant mediation.

We will first test cross-lag mediation in which the individual measures of the target at each assessment ("t") will be used to predict the multivariate clinical outcome at the next assessment ("t+1"), controlling for clinical outcome at the previous assessment ("t"), in a longitudinal mediation analysis (these will be the "b" paths in the mediation analysis).

If the cross-lag mediation analysis fails to detect any significant cross-lag mediation, we will repeat the analyses using a concurrent mediation analysis, in which the individual measures of the target at assessment "t" are used as predictors of clinical outcomes at assessment "t".

In all mediation analyses, the time-varying mediators (the individual measures of the target) will be disaggregated into their between-subjects components and their within-subjects components. Since the relations among the between-subjects components and clinical outcome

are confounded by potential individual differences between participants, we will only examine mediation by the within-subjects components of the individual mediators.

Aim 4: Trimming of Target Measurement.

To create an optimized mediation model, we will investigate a model in which all the significant individual measures of each target in Aim 3 are included in a single multi-mediator analysis. Models will be optimized by dropping non-significant mediator measures.

This multi-mediator model will first be evaluated as a cross-lag mediation analysis (each measure at time "t" predicting outcome at time "t+1", controlling for outcome at time "t"), as in Aim 3. If the cross-lag mediation analysis fails to detect any significant cross-lag mediation, we will repeat the analyses using a concurrent mediation analysis (as in Aim 3).

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 TO PARTICIPATE IN RESEARCH
for Treatment Participants

Affect Treatment for Depression and Anhedonia

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.

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 and modifying behaviors

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 may ask you to sign a release of information (optional) so that we can contact the other provider regarding your care. 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.

Treatments

During participation in the study, you will receive 15 weekly treatment sessions and one pre-therapy session 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. Video data will also be analyzed to investigate markers of behavioral activation. Remote sessions will be offered through an encrypted video-conferencing platform via Zoom. When appropriate in-person therapy sessions may be offered.

Individuals taking dopaminergic medications (e.g., Ritalin, Wellbutrin, amphetamines, methylphenidate, L-dopa) or Bupropion cannot participate in the study while still on medication. Heterocyclics and SSRIs need to be stabilized (3 months), as does fluoxetine (3 months) – that means that your dose should be the same, or that you should be medication-free, for that number 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 remain on a consistent dose/ regimen of your medication until after completion of the 15-week treatment, post-treatment assessment, and follow-up assessment. You should always consult with your primary provider before making changes to medication, dose, or discontinuation of current medication 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.

Remote Assessments:

You will be asked to complete a set of online questionnaires during weeks 0, 5, 10, post-treatment and at one-month follow-up. In addition, you will be asked to complete a brief interview during these time-points.

In-person Assessments

You will be asked to complete laboratory assessments with our research staff. You will be asked to come into the laboratory to complete a 3-hour laboratory assessment, which is split into two days. The first portion will be a 2-hour appointment (day 1), and the second portion will be 1-hour appointment (day 2). 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. Your weight will also be collected to analyze these physiological responses. We will also analyze inflammatory markers such as C-reactive protein via your saliva.

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, at the completion of treatment, and at a one-month follow-up.

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 will also be a one-month follow up assessment that will mirror the pre and post treatment assessments.

There is an additional, **optional** procedure in which you can elect to participate as a participant in this study. This optional procedure is to provide two blood samples—one at pre and one and post-intervention. You will receive a $25 Amazon gift card at each timepoint if you choose to undergo this procedure. If you choose to complete this procedure, 1/8th of a teaspoon of blood drawn by a self-administered device (i.e. TASSO-M20). The TASSO device sticks to your skin with a light adhesive and forms a vacuum while a lancet pricks the surface of the skin. You have an option to complete the blood draw at your home or at UCLA. If you decide to complete the blood draw procedure at your home, we will collect your home address. 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.

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, a post-treatment assessment approximately one week after the completion of treatment), and a follow-up assessment (approximately one month 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. During one of the laboratory tasks you will see some images that can be disturbing and make you upset. You may ask to stop the task at any time. 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.

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 are 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 the second laboratory session (day 2), 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 five laboratory assessments is $560. You will be reimbursed for parking or Uber/Lyft. If you choose to undergo the optional blood draw procedure, you will be paid $25 at the completion of each blood draw procedure.

Are there any costs for taking part in this study?

You will receive diagnostic evaluations and treatment for free. If in-person therapy sessions are offered, you will be responsible for paying 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 Disorders 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.

Emergency contact: We ask you to provide us with your emergency contact. We will contact your emergency contact only if we have consistently failed to reach you using a variety of channels (phone, email) and if we are concerned about your safety. We will disclose to your emergency contact only that you are participating in a UCLA research study and that we have been trying to reach you but failed to do so. We will disclose that we are concerned about your safety if that is the case. We will not disclose the nature of the study or any other information you have provided to us.

Use of data and specimens for future research

Data sharing can benefit science by allowing researchers with a broad set of perspectives to analyze the same data, and by allowing the analysis of large datasets that are combined across many smaller studies. Because we believe that the data being collected from you are valuable, they may be shared with other researchers or included in national or international efforts to create large databases of scientific information.

Identifying information will be removed from the study data, so no identifying information is included in the data that are shared with other investigators. When we share this data, you will not be asked for additional informed consent. You will not be informed of any information learned from the collected data, either by us or by any other group that utilizes shared data.

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 were 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 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 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

Emergency Contact:

Name: _____ Relationship: _____

Phone Number: _____

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

References

1. Villanueva, C. M., Silton, R. L., Heller, W., Barch, D. M., & Gruber, J. (2021). Change is on the horizon: call to action for the study of positive emotion and reward in psychopathology. *Current Opinion in Behavioral Sciences*, 39, 34-40. https://doi.org/10.1016/j.cobeha.2020.11.008

2. Trøstheim M, Eikemo M, Meir R, et al. Assessment of Anhedonia in Adults With and Without Mental Illness: A Systematic Review and Meta-analysis. *JAMA Netw Open*. 2020;3(8):e2013233. doi:10.1001/jamanetworkopen.2020.13233

3. Kendall, A. D., Zinbarg, R. E., Mineka, S., Bobova, L., Prenoveau, J. M., Revelle, W., & Craske, M. G. (2015). Prospective associations of low positive emotionality with first onsets of depressive and anxiety disorders: Results from a 10-wave latent trait-state modeling study. *Journal of abnormal psychology*, 124(4), 933–943. https://doi.org/10.1037/abn0000105

4. Sewart AR, Zbozinek TD, Hammen C, Zinbarg RE, Mineka S, Craske MG. Positive Affect as a Buffer Between Chronic Stress and Symptom Severity of Emotional Disorders. *Clinical Psychological Science*. 2019;7(5):914-927. doi:10.1177/2167702619834576

5. Prenoveau, J. M., Zinbarg, R. E., Craske, M. G., Mineka, S., Griffith, J. W., & Epstein, A. M. (2010). Testing a hierarchical model of anxiety and depression in adolescents: a tri-level model. *Journal of anxiety disorders*, 24(3), 334–344. https://doi.org/10.1016/j.janxdis.2010.01.006

6. Naragon-Gainey, K., Prenoveau, J. M., Brown, T. A. & Zinbarg, R. E. A comparison and integration of structural models of depression and anxiety in a clinical sample: Support for and validation of the tri-level model. *J. Abnorm. Psychol*. 125, 853–867 (2016).

7. Khazanov, G. K., & Ruscio, A. M. (2016). Is low positive emotionality a specific risk factor for depression? A meta-analysis of longitudinal studies. *Psychological Bulletin*, 142, 991–1015. http://dx.doi.org/10 .1037/bul0000059

8. Morris, B. H., Bylsma, L. M., & Rottenberg, J. (2009). Does emotion predict the course of major depressive disorder? A review of prospective studies. *The British Journal of Clinical Psychology*. 48(Pt 3), 255–273. https://doi.org/10.1348/014466508X396549

9. Ducasse, D., Loas, G., Dassa, D., Gramaglia, C., Zeppegno, P., Guillaume, S., Olié, E., & Courtet, P. (2018). Anhedonia is associated with suicidal ideation independently of depression: A meta-analysis. *Depression and Anxiety*. 35(5), 382–392. https://doi.org/10.1002/da.22709

10. Winer, E. S., Nadorff, M. R., Ellis, T. E., Allen, J. G., Herrera, S., & Salem, T. (2014). Anhedonia predicts suicidal ideation in a large psychiatric inpatient sample. *Psychiatry Research*. 218(1-2), 124–128. https://doi.org/10.1016/j.psychres.2014.04.016

11. Fawcett, J., Scheftner, W. A., Fogg, L., Clark, D. C., Young, M. A., Hedeker, D., & Gibbons, R. (1990). Time-related predictors of suicide in major affective disorder. The *American Journal of Psychiatry*. 147(9), 1189–1194. https://doi.org/10.1176/ajp.147.9.1189

12. Ballard, E. D., Wills, K., Lally, N., Richards, E. M., Luckenbaugh, D. A., Walls, T., Ameli, R., Niciu, M. J., Brutsche, N. E., Park, L., & Zarate, C. A., Jr (2017). Anhedonia as a clinical correlate of suicidal thoughts in clinical ketamine trials. *Journal of Affective Disorders*. 218, 195–200. https://doi.org/10.1016/j.jad.2017.04.057

13. Demyttenaere, K., Donneau, A. F., Albert, A., Ansseau, M., Constant, E., & van Heeringen, K. (2015). What is important in being cured from depression? Discordance between physicians and patients (1). *Journal of Affective Disorders*. 174, 390–396. https://doi.org/10.1016/j.jad.2014.12.004

14. Boumparis, N., Karyotaki, E., Kleiboer, A., Hofmann, S. G. & Cuijpers, P. The effect of psychotherapeutic interventions on positive and negative affect in depression: A systematic review and meta-analysis. *Journal of Affective Disorders*. 202, 153–162 (2016).

15. DeRubeis, R. J., Hollon, S. D., Amsterdam, J. D., Shelton, R. C., Young, P. R., Salomon, R. M., O'Reardon, J. P., Lovett, M. L., Gladis, M. M., Brown, L. L., & Gallop, R. (2005). Cognitive therapy vs medications in the treatment of moderate to severe depression. *Archives of General Psychiatry*. 62(4), 409–416. https://doi.org/10.1001/archpsyc.62.4.409

16. Dunn BD, German RE, Khazanov G, Xu C, Hollon SD, DeRubeis RJ. Changes in Positive and Negative Affect During Pharmacological Treatment and Cognitive Therapy for Major Depressive Disorder: A Secondary Analysis of Two Randomized Controlled Trials. *Clinical Psychological Science.* 2020;8(1):36-51. doi:10.1177/2167702619863427

17. Martell, C., Dimidjian, S. & Herman-Dunn, R. Behavioral activation for depression: A clinician's guide. (2010).

18. Dichter, G. S., Felder, J. N., Petty, C., Bizzell, J., Ernst, M., & Smoski, M. J. (2009). The effects of psychotherapy on neural responses to rewards in major depression. *Biological Psychiatry*. 66(9), 886–897. https://doi.org/10.1016/j.biopsych.2009.06.021

19. Moore, R. C., Chattillion, E. A., Ceglowski, J., Ho, J., von Känel, R., Mills, P. J., Ziegler, M. G., Patterson, T. L., Grant, I., & Mausbach, B. T. (2013). A randomized clinical trial of Behavioral Activation (BA) therapy for improving psychological and physical health in dementia caregivers: results of the Pleasant Events Program (PEP). *Behaviour Research and Therapy*. 51(10), 623–632. https://doi.org/10.1016/j.brat.2013.07.005

20. Forbes, C. N. New directions in behavioral activation: Using findings from basic science and translational neuroscience to inform the exploration of potential mechanisms of change. *Clin. Psychol. Rev.* 79, (2020).

21. Landén, M., Högberg, P. & Thase, M. E. Incidence of sexual side effects in refractory depression during treatment with citalopram or paroxetine. *J. Clin. Psychiatry*. 66, 100–106 (2005).

22. McCabe, C., Mishor, Z., Cowen, P. J. & Harmer, C. J. Diminished Neural Processing of Aversive and Rewarding Stimuli During Selective Serotonin Reuptake Inhibitor Treatment. *Biol. Psychiatry*. 67, 439– 445 (2010). PMCID: PMC2828549

23. Nierenberg, A. A. et al. Residual symptoms in depressed patients who respond acutely to fluoxetine. *Prim. Care Companion J. Clin. Psychiatry*. 1, 124 (1999).

24. Price, J., Cole, V. & Goodwin, G. M. Emotional side-effects of selective serotonin reuptake inhibitors: Qualitative study. *Br. J. Psychiatry*. 195, 211–217 (2009).

25. Thomas, R. K., Baker, G., Lind, J. & Dursun, S. Rapid effectiveness of intravenous ketamine for ultraresistant depression in a clinical setting and evidence for baseline anhedonia and bipolarity as clinical predictors of effectiveness. *J. Psychopharmacol*. 32, 1110–1117 (2018).

26. Krystal AD, Pizzagalli DA, Smoski M, Mathew SJ, Nurnberger J Jr, Lisanby SH, Iosifescu D, Murrough JW, Yang H, Weiner RD, Calabrese JR, Sanacora G, Hermes G, Keefe RSE, Song A, Goodman W, Szabo ST, Whitton AE, Gao K, Potter WZ. A randomized proof-of-mechanism trial applying the 'fast-fail' approach to evaluating κ-opioid antagonism as a treatment for anhedonia. *Nat Med.* 2020 May;26(5):760-768. doi: 10.1038/s41591-020-0806-7. Epub 2020 Mar 30. PMID: 32231295.

27. Dunn BD. (2012). Helping depressed clients reconnect to positive emotion experience: current insights and future directions. *Clinical Psychology & Psychotherapy*, 19(4):326-40. PMID: 22674611

28. Der-Avakian A, Markou A. (2012). The neurobiology of anhedonia and other reward related deficits. *Trends in Neuroscience*, 35: 68–77. PMID: 22177980

29. Miendlarzewska, E.A., Bavelier, D., & Schwartz, S. (2016). Influence of reward motivation on human declarative memory. *Neuroscience and Biobehavioral Reviews*, 61, 156-176.

30. Morris SE, Cuthbert BN. (2012). Research Domain criteria: cognitive systems, neural circuits, and dimensions of behavior. *Dialogues in Clinical Neuroscience*, 14(1):29–37. PMID: 22577302

31. Thomsen KR, Whybrow PC, Kringelbach ML. (2015). Reconceptualizing anhedonia: novel perspectives on balancing the pleasure networks in the human brain. *Frontiers in Behavioral Neuroscience*. PMCID: PMC4356228

32. Treadway MT, Zald DH. (2011). Reconsidering anhedonia in depression: lessons from translational neuroscience. *Neuroscience & Biobehavioral Reviews*. 35(3), 537-55. PMID: 20603146

33. Pizzagalli DA. (2014). Depression, stress, and anhedonia: toward a synthesis and integrated model. *Annual Review of Clinical Psychology*.10, 393-423. PMID: 24471371

34. Henriques JB, Davidson RJ. (2000). Decreased responsiveness to reward in depression. *Cognition & Emotion*, 14, 711-724.

35. Jazbec S, McClure E, Hardin M, Pine DS, Ernst M. (2005). Cognitive control under contingencies in anxious and depressed adolescents: an antisaccade task. *Biological Psychiatry*, 58(8), 632-639. PMID: 16018983

36. Pizzagalli DA, Sherwood RJ, Henriques JB, Davidson RJ. (2005). Frontal brain asymmetry and reward responsiveness: a source-localization study. *Psychological Science.* 16(10), 805-813. PMID: 16181444

37. McFarland BR, Klein DN. (2009). Emotional reactivity in depression: diminished responsiveness to anticipated reward but not to anticipated punishment or to nonreward or avoidance. *Depression and Anxiety*, 26(2), 117-122. PMID: 18972567

38. Yuan JW, Kring AM. (2009). Dysphoria and the prediction and experience of emotion. *Cognition and Emotion*, 23(6), 1221-1232.

39. Hoerger, M., Quirk, S. W., Chapman, B. P., & Duberstein, P. R. (2012). Affective forecasting and self-rated symptoms of depression, anxiety, and hypomania: Evidence for a dysphoric forecasting bias. *Cognition & Emotion*, 26, 1098-1106. PMID: 22397734

40. Knutson B, Bhanji JP, Cooney RE, Atlas LY, Gotlib IH. (2008). Neural responses to monetary incentives in major depression. *Biological Psychiatry*, 63(7), 686-692. PMID: 17916330

41. Treadway MT, Buckholtz JW, Schwartzman AN, Lambert WE, Zald DH. (2009). Worth the 'EEfRT'? The effort expenditure for rewards task as an objective measure of motivation and anhedonia. *PLoS One*, 4(8): e6598. PMID: 19672310

42. Treadway MT, Bossaller NA, Shelton RC, Zald DH. (2012). Effort-based decision-making in major depressive disorder: a translational model of motivational anhedonia. *Journal of Abnormal Psychology*.121, 553–558. PMID: 22775583

43. Yang XH, Huang J, Zhu CY, Wang YF, Cheung EF, Chan RC, Xie GR. (2014). Motivational deficits in effort-based decision making in individuals with subsyndromal depression, first-episode and remitted depression patients. *Psychiatry Research*, 220(3):874-82. PMID: 25262638

44. Brenner SL, Beauchaine TP, Sylvers PD. A comparison of psychophysiological and self-report measures of BAS and BIS activation. *Psychophysiology*. 2005 Jan;42(1):108-15. doi: 10.1111/j.1469-8986.2005.00261.x.

45. Iaboni F, Douglas VI, Ditto B. Psychophysiological response of ADHD children to reward and extinction. *Psychophysiology*. 1997 Jan;34(1):116-23. doi: 10.1111/j.1469-8986.1997.tb02422.x.

46. Richter M, Gendolla GH. Incentive value, unclear task difficulty, and cardiovascular reactivity in active coping. *Int J Psychophysiol*. 2007 Mar;63(3):294-301. doi: 10.1016/j.ijpsycho.2006.12.002.

47. Tranel DT, Fisher AE, Fowles DC. Magnitude of incentive effects on heart rate. *Psychophysiology*. 1982 Sep;19(5):514-9. doi: 10.1111/j.1469-8986.1982.tb02578.x.

48. Brinkmann K, Schüpbach L, Joye IA, Gendolla GH. (2009). Anhedonia and effort mobilization in dysphoria: reduced cardiovascular response to reward and punishment. *International Journal of Psychophysiology*, 74(3):250-8. PMID: 19808061

49. Brinkmann K, Franzen J. (2013). Insensitivity to varying levels of reward in dysphoria. *Biological Psychology*, 94(2):263-71

50. Franzen J, Brinkmann K. (2015) Blunted cardiovascular reactivity in dysphoria during reward and punishment anticipation. *International Journal of Psychophysiology*. 95(3):270-7. PMID: 25462217

51. Smoski MJ, Felder J, Bizzell J, Green SR, Ernst M, Lynch TR, Dichter GS. (2009). fMRI of alterations in reward selection, anticipation, and feedback in major depressive disorder. *Journal of Affective Disorders*, 118(1-3):69-78. PMID: 19261334

52. McCabe C, Cowen PJ, Harmer CJ. (2009). Neural representation of reward in recovered depressed patients. *Psychopharmacology*.205(4):667-77. doi: 10.1007/s00213-009-1573-9. PMID: 19529923

53. Steele JD, Kumar P, Ebmeier KP. (2007). Blunted response to feedback information in depressive illness. *Brain*, 130(9):2367-74. PMID: 17586866

54. Forbes EE, Hariri AR, Martin SL, Silk JS, Moyles DL, Fisher PM, Brown SM, Ryan ND, Birmaher B, Axelson DA, Dahl RE. (2009). Altered striatal activation predicting real-world positive affect in adolescent major depressive disorder. *The American Journal of Psychiatry*, 166(1):64-73. PMID: 19047324

55. Chentsova-Dutton Y, Hanley K. (2010). The effects of anhedonia and depression on hedonic responses. *Psychiatry Research*, 179: 176–180. PMID: 20478624

56. Forbes EE, Christopher May J, Siegle GJ, Ladouceur CD, Ryan ND, Carter CS, Birmaher B, Axelson DA, Dahl RE. (2006). Reward-related decision-making in pediatric major depressive disorder: an fMRI study. *Journal of Child Psychology and Psychiatry*, and allied disciplines, 47(10):1031-40. PMCID: PMC2129133

57. Greenberg T, Chase HW, Almeida JR, Stiffler R, Zevallos CR, Aslam HA, Deckersbach T, Weyandt S, Cooper C, Toups M, Carmody T, Kurian B, Peltier S, Adams P, McInnis MG, Oquendo MA, McGrath PJ, Fava M, Weissman M, Parsey R, Trivedi MH, Phillips ML. (2015). Moderation of the Relationship Between Reward Expectancy and Prediction Error-Related Ventral Striatal Reactivity by Anhedonia in Unmedicated Major Depressive Disorder: Findings From the EMBARC Study. *The American Journal of Psychiatry*, 172(9):881–91. PMID: 26183698

58. Stoy M, Schlagenhauf F, Sterzer P, Bermpohl F, Hägele C, Suchotzki K, Schmack K, Wrase J, Ricken R, Knutson B, Adli M, Bauer M, Heinz A, Ströhle A. (2011). Hyporeactivity of ventral striatum towards incentive stimuli in unmedicated depressed patients normalizes after treatment with escitalopram. *Journal of Psychopharmacology*. 26(5), 677-688. PMID: 21926423

59. Ubl B, Kuehner C, Kirsch P, Ruttorf M, Diener C, Flor H. (2015). Altered neural reward and loss processing and prediction error signalling in depression. *Social Cognitive and Affective Neuroscience*, pii: nsu158. PMID: 25567763

60. Berlin I, Givry-Steiner L, Lecrubier Y, Puech AJ. (1998). Measures of anhedonia and hedonic responses to sucrose in depressive and schizophrenic patients in comparison with healthy subjects. *European Psychiatry*. 1998;13:303–309. PMID: 19698645

61. Dichter, G.S., Felder, J.N., Smoski, M. (2010). The Effects of Brief Behavioral Activation Therapy for Depression on Cognitive Control in Affective Contexts: an fMRI investigation; *Journal of Affective Disorders*, 126(1-2):236-244. PMID: 20421135

62. Swiecicki L, Zatorski P, Bzinkowska D, Sienkiewicz-Jarosz H, Szyndler J, Scinska A. (2009). Gustatory and olfactory function in patients with unipolar and bipolar depression. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. 33(5), 827-834. PMID: 19345708

63. Bylsma LM, Morris BH, Rottenberg J. (2008). A meta-analysis of emotional reactivity in major depressive disorder. *Clinical Psychology Review*, 28(4), 676-691. PMID: 18006196

64. Peckham AD, McHugh RK, Otto MW. (2010). A meta-analysis of the magnitude of biased attention in depression. *Depression and Anxiety*, 27(12), 1135-1142. PMID: 21049527

65. Clepce M, Gossler A, Reich K, Kornhuber J, Thuerauf N. (2010). The relation between depression, anhedonia and olfactory hedonic estimates--a pilot study in major depression. *Neuroscience Letters*, 471(3):139-43. PMID: 20097263

66. Armstrong, T., Olatunji, B. O. (2009). What they see is what you get: Eye tracking of attention in the anxiety disorders. *Psychological Science Agenda*, 23, 3.

67. Fritzsche A, Dahme B, Gotlib IH, Joormann J, Magnussen H, Watz H, Nutzinger DO, von Leupoldt A. (2010). Specificity of cognitive biases in patients with current depression and remitted depression and in patients with asthma. *Psychological Medicine*. 40(5), 815-826.

68. Soltani S, Newman K, Quigley L, Fernandez A, Dobson K, Sears C. (2015). Temporal changes in attention to sad and happy faces distinguish currently and remitted depressed individuals from never depressed individuals. *Psychiatry Research*. 230(2), 454-463.

69. Tamir M, Robinson MD. (2007). The happy spotlight: positive mood and selective attention to rewarding information. *Personality and Social Psychology Bulletin*. 33(8),1124-1136.

70. Fitzgibbons L, Simons RF. (1992). Affective response to color-slide stimuli in subjects with physical anhedonia: a three-systems analysis. *Psychophysiology*, 29(6):613-20. PMID: 1461952

71. Fiorito ER, Simons RF. (1994). Emotional imagery and physical anhedonia. *Psychophysiology*, 31(5):513-21. PMID: 7972606

72. Epstein J, Pan H, Kocsis JH, Yang Y, Butler T, Chusid J, Hochberg H, Murrough J, Strohmayer E, Stern E, Silbersweig DA. (2006). Lack of ventral striatal response to positive stimuli in depressed versus normal subjects. *The American Journal of Psychiatry*, 163(10), 1784-1790. PMID: 17012690

73. Tremblay LK, Naranjo CA, Graham SJ, Herrmann N, Mayberg HS, Hevenor S, Busto UE. (2005). Functional neuroanatomical substrates of altered reward processing in major depressive disorder revealed by a dopaminergic probe. *Archives of General Psychiatry*, 62(11), 1228-36. PMID: 16275810

74. Pizzagalli DA, Holmes AJ, Dillon DG Goetz EL, Birk JL, Bogdan R, Dougherty DD, Iosifescu DV, Rauch SL, Fava M. (2009). Reduced caudate and nucleus accumbens response to rewards in unmedicated subjects with Major Depressive Disorder. American *Journal of Psychiatry*, 166, 702–710. PMID: 19411368

75. Keedwell PA, Andrew C, Williams SC, Brammer MJ, Phillips ML. (2005) The neural correlates of anhedonia in major depressive disorder. *Biological Psychiatry*, 58(11), 843-853. PMID: 16043128

76. Wacker J, Dillon DG, Pizzagalli DA. (2009). The role of the nucleus accumbens and rostral anterior cingulate cortex in anhedonia: integration of resting EEG, fMRI, and volumetric techniques. *NeuroImage*, 46(1), 327-337. PMID: 19457367

77. Chung YS, Barch D. (2015). Anhedonia is associated with reduced incentive cue related activation in the basal ganglia. *Cognitive, Affective & Behavioral Neuroscienc*e, 15(4): 749–767. PMCID: 5141384

78. Keedwell PA, Andrew C, Williams SC, Brammer MJ, Phillips ML. (2005) The neural correlates of anhedonia in major depressive disorder. *Biological Psychiatry*, 58(11), 843-853. PMID: 16043128

79. Wacker J, Dillon DG, Pizzagalli DA. (2009). The role of the nucleus accumbens and rostral anterior cingulate cortex in anhedonia: integration of resting EEG, fMRI, and volumetric techniques. *NeuroImage*, 46(1), 327-337. PMID: 19457367

80. Brailean AM, Koster EH, Hoorelbeke K, De Raedt R. (2014). Attentional modulation by reward and punishment cues in relation to depressive symptoms. *Journal of Behavior Therapy and Experimental Psychiatry*. 45(3), 351-359.

81. Pizzagalli DA, Iosifescu D, Hallett LA, Ratner KG, Fava M. (2008). Reduced hedonic capacity in major depressive disorder: evidence from a probabilistic reward task. *Journal of Psychiatric Research*, 43, 76–87. PMID: 18433774

82. Whitton AE, Treadway MT, Pizzagalli DA. (2015). Reward processing dysfunction in major depression, bipolar disorder and schizophrenia. *Current Opinion in Psychiatry*, 28(1):7-12. PMCID: PMC4277233

83. Kumar P, Waiter G, Ahearn T, Milders M, Reid I, Steele JD. (2008). Abnormal temporal difference reward-learning signals in major depression. *Brain*, 131: 2084–2093. PMID: 18579575

84. Robinson OJ, Cools R, Carlisi CO, Sahakian BJ, Drevets WC. (2012). Ventral striatum response during reward and punishment reversal learning in unmedicated major depressive disorder. *American Journal of Psychiatry*, 169: 152–159. PMID: 22420038

85. Gradin, V. B., Kumar, P., Waiter, G., Ahearn, T., Stickle, C., Milders, M., Reid I, Hall J, Steele, J. D. (2011). Expected value and prediction error abnormalities in depression and schizophrenia. *Brain*, 134(6), 1751-1764. PMID: 21482548

86. Taylor CT, Lyubomirsky S, Stein, MB. (2016) Upregulating the positive affect system in anxiety and depression: Outcomes of a positive activity intervention. *Depression and Anxiety*, 00:1–14. PMID: 28060463

87. Craske, M.G., Meuret, A.E., Ritz, T., Treanor, M., & Dour, H. (2016). Treatment for anhedonia: neuroscience driven approach. *Depression and Anxiety*, 33, 927-938.

88. Craske, M. G., Meuret, A. E., Ritz, T., Treanor, M., Dour, H., & Rosenfield, D. (2019). Positive affect treatment for depression and anxiety: A randomized clinical trial for a core feature of anhedonia. *Journal of Consulting and Clinical Psychology*, 87(5), 457–471.

89. Watson, D., Clark, L. A., & Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: the PANAS scales. *Journal of Personality and Social Psychology*, 54(6), 1063.

90. Crawford JR, Henry JD. (2004). The positive and negative affect schedule (PANAS): construct validity, measurement properties and normative data in a large non-clinical sample. *British Journal of Clinical Psychology*, 43, 245-265.

91. Lovibond, S. H., & Lovibond, P. F. (1995). Manual for the Depression Anxiety Stress Scales (2nd ed.). Sydney, Australia: Psychology Foundation of Australia.

92. Brown TA, Chorpita BF, Barlow DH. (1998). Structural relationships among dimensions of the DSM-IV anxiety and mood disorders and dimensions of negative affect, positive affect, and autonomic arousal. *Journal of Abnormal Psychology*, 107(2):179-92. PMID: 9604548

93. Willams, J.B.W. (2000) Mental health status, functioning, and disabilities measures. American Psychiatric Association (Eds), *Handbook of Psychiatric Measures* (93-100). Washington, DC: American Psychiatric Association.

94. Gross JJ. The emerging field of emotion regulation: An integrative review. *Review of General Psychology*. 1998;2(3):271–299. https://doi.org/10.1037/1089-2680.2.3.271

95. Barry TJ, Sze WY, & Raes F. A meta-analysis and systematic review of Memory Specificity Training (MeST) in the treatment of emotional disorders. *Behaviour Research and Therapy*. 2019; 116:36–51. https://doi.org/10.1016/j.brat.2019.02.001

96. Hallford DJ, Sharma MK, & Austin DW. Increasing anticipatory pleasure in major depression through enhancing episodic future thinking: a randomized single-case series trial. *Journal of Psychopathology and Behavioral Assessment*. 2020. https://doi.org/10.1007/s10862-020-09820-9

97. Hallford DJ, Farrell H, & Lynch E. Increasing anticipated and anticipatory pleasure through episodic thinking. *Emotion*. 2020. https://doi.org/10.1037/emo0000765

98. McMakin DL, Siegle GJ, & Shirk SR. Positive Affect Stimulation and Sustainment (PASS) module for depressed mood: A preliminary investigation of treatment-related effects. *Cognitive Therapy and Research*. 2011; 35(3), 217–226. https://doi.org/10.1007/s10608-010-9311-5

99. Pictet A, Jermann, F, & Ceschi, G. When less could be more: Investigating the effects of a brief internet-based imagery cognitive bias modification intervention in depression.

Behaviour Research and Therapy. 2016; 84, 45–51.
https://doi.org/10.1016/j.brat.2016.07.008

100. Wadlinger HA, & Isaacowitz DM. Looking happy: The experimental manipulation of a positive visual attention bias. *Emotion*. 2008; 8(1):121–126. https://doi.org/10.1037/1528-3542.8.1.121

101. Wadlinger HA., & Isaacowitz DM. Fixing our focus: training attention to regulate emotion. Personality and Social Psychology Review : *An Official Journal of the Society for Personality and Social Psychology*, Inc. 2011; 15(1): 75–102. https://doi.org/10.1177/1088868310365565

102. Peters KD, Constans JI, Mathews A. Experimental modification of attribution processes. *Journal of Abnormal Psychology*. 2011; 120(1):168–173. https://doi.org/10.1037/a0021899

103. Holmes D, Murray SJ, Perron A & Rail G. Deconstructing the evidence-based discourse in health sciences: truth, power and fascism. *International Journal of Evidence-Based Healthcare*. 2006;4(3): 180–186. https://doi.org/10.1111/j.1479-6988.2006.00041.x

104. Holmes EA, Mathews A, Mackintosh B, Dalgleish T. (2008). The causal effect of mental imagery on emotion assessed using picture-word cues. *Emotion*, 8(3), 395-409. PMID: 18540755

105. Pictet, Arnaud, Coughtrey, A. E., Mathews, A., & Holmes, E. A. (2011). Fishing for happiness: the effects of generating positive imagery on mood and behaviour. *Behaviour Research and Therapy*, 49(12), 885–891. https://doi.org/10.1016/j.brat.2011.10.003

106. Garland EL., Fredrickson B, Kring AM., Johnson DP, Meyer PS, & Penn DL. Upward spirals of positive emotions counter downward spirals of negativity: insights from the broaden-and-build theory and affective neuroscience on the treatment of emotion dysfunctions and deficits in psychopathology. *Clinical Psychology Review*. 2010;30(7):849–864. https://doi.org/10.1016/j.cpr.2010.03.002

107. Hofmann SG, Grossman P, & Hinton DE. Loving-kindness and compassion meditation: potential for psychological interventions. *Clinical Psychology Review*. 2011; 31(7):1126–1132. https://doi.org/10.1016/j.cpr.2011.07.003

108. Hutcherson CA, Seppala EM, Gross, JJ. Loving-kindness meditation increases social connectedness. *In Emotion*. 2008;8(5):720–724. https://doi.org/10.1037/a0013237

109. Fredrickson BL, Cohn MA, Coffey KA, Pek J, Finkel, SM. (2008). Open hearts build lives: positive emotions, induced through loving- kindness meditation, build consequential personal resources. *Journal of Personality and Social Psychology*, 95:1045-1062. PMID: 18954193

110. Mayhew, SL, Gilbert P. Compassionate mind training with people who hear malevolent voices: a case series report. *Clinical Psychology & Psychotherapy*,. 2008;15(2):113–138. https://doi.org/10.1002/cpp.566

111. Kearney DJ., Malte, CA, McManus C, Martinez ME, Felleman B, Simpson TL. Loving-kindness meditation for posttraumatic stress disorder: a pilot study. *Journal of Traumatic Stress*. 2013;26(4):426–434. https://doi.org/10.1002/jts.21832

112. Hofmann SG., Petrocchi N, Steinberg J, Lin M, Arimitsu K, Kind S, Mendes A, Stangier U. Loving-Kindness Meditation to Target Affect in Mood Disorders: A Proof-of-Concept Study. *Evidence-Based Complementary and Alternative Medicine*. 2015. https://doi.org/10.1155/2015/269126

113. Nelson, SK, Layous K, Cole SW, Lyubomirsky S. Do unto others or treat yourself? The effects of prosocial and self-focused behavior on psychological flourishing. *Emotion* (Washington, D.C.). 2016;16(6):850–861. https://doi.org/10.1037/emo0000178

114. Rowland L, Curry OS. A range of kindness activities boost happiness. *The Journal of Social Psychology*. 2019;159(3):340–343. https://doi.org/10.1080/00224545.2018.1469461

115. Snippe E, Jeronimus BF, Aan Het Rot M, Bos EH, de Jonge P, Wichers M. The Reciprocity of Prosocial Behavior and Positive Affect in Daily Life. *Journal of Personality*. 2018;86(2):139–146. https://doi.org/10.1111/jopy.12299

116. Schacter HL, Margolin G. When it feels good to give: Depressive symptoms, daily prosocial behavior, and adolescent mood. *Emotion* (Washington, D.C.). 2019;19(5):923–927. https://doi.org/10.1037/emo0000494

117. Froh, JJ, Kashdan TB, Ozimkowski KM, & Miller N. Who benefits the most from a gratitude intervention in children and adolescents? Examining positive affect as a moderator. *The Journal of Positive Psychology*. 2009;4(5):408–422. https://doi.org/10.1080/17439760902992464

118. Geraghty, AWA, Wood AM, Hyland ME. Dissociating the facets of hope: Agency and pathways predict dropout from unguided self-help therapy in opposite directions. *Journal of Research in Personality*. 2010a;44(1):155–158. https://doi.org/https://doi.org/10.1016/j.jrp.2009.12.003

119. Geraghty AWA., Wood AM, Hyland ME. Attrition from self-directed interventions: investigating the relationship between psychological predictors, intervention content and dropout from a body dissatisfaction intervention. *Social Science & Medicine*. 2010b;71(1):30–37. https://doi.org/10.1016/j.socscimed.2010.03.007

120. Wood, AM, Froh JJ, Geraghty, AWA. Gratitude and well-being: a review and theoretical integration. *Clinical Psychology Review*. 2010;30(7):890–905. https://doi.org/10.1016/j.cpr.2010.03.005

121. Maltby J, Wood AM, Day L, Kon TWH, Colley A, Linley PA. Personality predictors of levels of forgiveness two and a half years after the transgression. *Journal of Research in Personality*. 2008;42(4): 1088–1094.

122. Wood AM, Joseph S, Maltby J. Gratitude uniquely predicts satisfaction with life: Incremental validity above the domains and facets of the five factor model. *Personality and Individual Differences*. 2008; 45(1):49–54. https://doi.org/https://doi.org/10.1016/j.paid.2008.02.019

123. Fredrickson BL. The role of positive emotions in positive psychology. The broaden-and-build theory of positive emotions. *The American Psychologist*, 2001;56(3):218–226. https://doi.org/10.1037//0003-066x.56.3.218

124. Emmons, R. A., & McCullough, M. E. (2003). Counting blessings versus burdens: an experimental investigation of gratitude and subjective well-being in daily life. *Journal of Personality and Social Psychology*, 84(2), 377–389. https://doi.org/10.1037//0022-3514.84.2.377

125. Shonin E, Van Gordon W, Compare A, Zangeneh M, Griffiths MD. Buddhist-derived loving-kindness and compassion meditation for the treatment of psychopathology: A systematic review. *Mindfulness*. 2015;6(5);1161–1180. https://doi.org/10.1007/s12671-014-0368-1

126. Zeng X, Chiu CPK, Wang R, Oei TPS, Leung, FYK. The effect of loving-kindness meditation on positive emotions: a meta-analytic review. *Frontiers in Psychology*. 2015; 6:169. https://www.frontiersin.org/article/10.3389/fpsyg.2015.01693

127. Zeng X, Wang R, Oei TPS, Leung FYK. Heart of joy: a randomized controlled trial evaluating the effect of an appreciative joy meditation training on subjective well-being and attitudes. *Mindfulness*. 2019;10(3):506–515.

128. Craske, M.G., Hermans, D., & Vervliet, B. (2018). State of the art and future directions for extinction as a translational model for fear and anxiety. *Philosophical Transactions B: Biological Sciences*, 373(1742), 20170025. doi: 10.1098/rstb.2017.0025

129. Craske, Treanor, Zbozinek & Vervliet (in press)

130. Martell, C. R., Dimidjian, S., & Herman-Dunn, R. (2010). Behavioral activation for depression: A clinician's guide . The Guilford Press, New York, NY.

131. Beck, A. T. (1972). Cognition, anxiety, and psychophysiological disorders. In C. Spielberger (Ed.), Anxiety: Current trends in theory and research (pp. 343–354). New York, NY: Academic Press. http://dx.doi.org/10 .1016/B978-0-12-657402-9.50008-9

132. Disner, S. G., Beevers, C. G., Haigh, E. A. P., & Beck, A. T. (2011). Neural mechanisms of the cognitive model of depression. *Nature Reviews Neuroscience*, 12, 467– 477. http://dx.doi.org/10.1038/nrn3027

133. Meuret, A. E., Ritz, T., Wilhelm, F. H., Roth, W. T., & Rosenfield, D. (2018). Hypoventilation therapy alleviates panic by repeated induction of dyspnea. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, 3, 539 –545. http://dx.doi.org/10.1016/j.bpsc.2018.01.010

134. Meuret, A. E., Rosenfield, D., Seidel, A., Bhaskara, L., & Hofmann, S. G. (2010). Respiratory and cognitive mediators of treatment change in panic disorder: Evidence for intervention specificity. *Journal of Consulting and Clinical Psychology*, 78, 691–704. http://dx.doi.org/10.1037/ a0019552

135. Meuret, A. E., Wilhelm, F. H., Ritz, T., & Roth, W. T. (2008). Feedback of end-tidal pCO_2 as a therapeutic approach for panic disorder. *Journal of Psychiatric Research*, 42, 560 – 568. http://dx.doi.org/10.1016/j .jpsychires.2007.06.005

136. Davies, C. D., & Craske, M. G. (2014). Low baseline pCO_2 predicts poorer outcome from cognitive behavioral therapy: Evidence from a mixed anxiety disorders sample. *Psychiatry Research*, 219, 311–315. http://dx .doi.org/10.1016/j.psychres.2014.06.003

137. Sharma, A., Barrett, M. S., Cucchiara, A. J., Gooneratne, N. S., & Thase, M. E. (2017). A Breathing-based meditation intervention for patients with major depressive disorder following inadequate response to antidepressants: A randomized pilot study. *The Journal of Clinical Psychiatry*, 78, e59 – e63. http://dx.doi.org/10.4088/JCP.16m10819

138. Snaith RP, Hamilton M, Morley S, Humayan A, Hargreaves D, Trigwell P (1995). A scale for the assessment of hedonic tone the Snaith- Hamilton Pleasure Scale. *The British Journal of Psychiatry*, 167, 99–103.

139. Fawcett, J., Clark, D. C., Scheftner, W. A., and Gibbons, R. D. (1983). Assessing anhedonia in psychiatric patients. The pleasure scale. *Archives of General Psychiatry*, 40, 79–84. PMID: 6849623

140. Chapman LJ, Chapman JP, Raulin ML. (1976). Scales for physical and social anhedonia; *Journal of Abnormal Psychology*, 85: 374–382. PMID: 956504

141. Gard, D.E., Germans Gard, M.K., Kring, A.M., & John, O.P. (2006). Anticipatory and consummatory experience of pleasure: A scale development study. *Journal of Research in Personality*, 40, 1086-1102.

142. Craske MG, Meuret AE, Ritz T, Treanor M, Dour H, Rosenfield D. Positive affect treatment for depression and anxiety: A randomized clinical trial for a core feature of anhedonia. *J Consult Clin Psychol*. 2019 May;87(5):457-471. doi: 10.1037/ccp0000396. PMID: 30998048.

143. Campbell, D. T., & Fiske, D. W. (1959). Convergent and discriminant validation by the multitrait-multimethod matrix. *Psychological Bulletin*, 56(2), 81-105. PMID: 13634291

144. Prenoveau, J.M., Zinbarg, R.E., Craske, M.G., Mineka, S., Griffith, J.W., & Epstein, A. (2010). Testing a hierarchical model of anxiety and depression in adolescents: a trilevel model. *Journal of Anxiety Disorders*, 24, 334-344. PMID: 20171054

145. Lovinbond P.F. & Lovindbond S.H. (1995). The structure of negative emotional states: Comparison of the depression anxiety stress scales (DASS) with the Beck Depression and Anxiety Inventories. *Behaviour Research and Therapy*, 33(3), 335-343.

146. Shea TL, Tennant A, Pallant JF. (2009). Rasch model analysis of the Depression, Anxiety and Stress Scales (DASS). *BMC Psychiatry*, 9(1), 21. PMID: 19426512

147. Antony M, Bieling PJ, Cox BJ, Enns MW, Swinson RP. (1998). Psychometric properties of the 42-item and 21-item versions of the Depression Anxiety Stress Scales in clinical groups and community a sample. *Psychological Assessment*; 10:176–181. PMCID: PMC2709995

148. Sheehan DV, Harnett-Sheehan K, Raj BA. The measurement of disability. International *Clinical Psychopharmacology* 1996;11:89–95

149. Sherdell L, Waugh CE, Gotlib IH. (2012). Anticipatory pleasure predicts motivation for reward in major depression. *Journal of Abnormal Psychology*. 121, 51–60. PMID: 21842963

150. Borsini, A., Wallis, A.S.J., Zunszain, P. et al. Characterizing anhedonia: A systematic review of neuroimaging across the subtypes of reward processing deficits in depression. *Cogn Affect Behav Neurosci* 20, 816–841 (2020). https://doi.org/10.3758/s13415-020-00804-6

151. Knutson, B., Bhanji, J.P., Cooney, R.E., Atlas, L.Y., Gotlib, I.H. (2008). Neural responses to monetary incentives in major depression. *Biol. Psychiatry*. 63, 686–692.

152. Stoy M, Schlagenhauf F, Sterzer, P., Bermpohl, F., Hägele, C., Suchotzki, K., Schmack, K., Wrase, J., Ricken, R., Knutson, B., Adli, M., Bauer, M., Heinz, A., & Ströhle A.J. (2012). Hyporeactivity of ventral striatum towards incentive stimuli in unmedicated depressed patients normalizes after treatment with escitalopram. *Journal of Psychopharmacology*. 26(5):677-88. doi: 10.1177/0269881111416686.

153. Carver CS, White TL. (1994). Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: The BIS/BAS scales. *Journal of Personality and Social Psychology*, 67:319-333.

154. Rizvi, S.J., Quilty, L.C., Sproule, B., Cyriac, A., Bagby, R.M. et al. (2015). Development and validation of the Dimensional Anhedonia Rating Scale (DARS) in a community sample and individuals with major depression. *Psychiatry Research*, 229(1-2): 109-119. 10.1016/j.psychres.2015.07.062

155. Taylor CT, Amir N. (2010). Attention and emotion regulation. Guilford Press, New York.

156. Bar-Haim Y, Lamy D, Pergamin L, Bakermans-Kranenburg MJ, van IMH.(2007). Threat-related attentional bias in anxious and nonanxious individuals: a meta-analytic study. *Psychological Bulletin*.;133(1):1-24. PMID: 17201568

157. Joormann J, Talbot L, Gotlib IH. (2007). Biased processing of emotional information in girls at risk for depression. *The Journal of Abnormal Psychology*, 116(1), 135-143. PMID: 17324024

158. Taylor CT, Bomyea J, Amir N. (2010). Attentional bias away from positive social information mediates the link between social anxiety and anxiety vulnerability to a social stressor. *Journal of Anxiety Disorders*. 24(4), 403-408. PMID: 20207102

159. Kellough, J. L., Beevers, C. G., Ellis, A. J., & Wells, T. T. (2008). Time course of selective attention in clinically depressed young adults: an eye tracking study. *Behaviour research and therapy*, 46(11), 1238–1243. https://doi.org/10.1016/j.brat.2008.07.004

160. Winer, E. S., & Salem, T. (2016). Reward devaluation: Dot-probe meta-analytic evidence of avoidance of positive information in depressed persons. *Psychological bulletin*, 142(1), 18–78. https://doi.org/10.1037/bul0000022

161. Britton JC, Bar-Haim Y, Clementi MA, Sankin LS, Chen G, Shechner T, Norcross MA, Spiro CN, Lindstrom KM, Pine DS. (2013). Training-associated changes and stability of attention bias in youth: Implications for Attention Bias Modification Treatment for pediatric anxiety. *Developmental cognitive neuroscience*, 4:52-64. PMCID: PMC3606014

162. Matsumoto D, Ekman P. Japanese and Caucasian facial expressions of emotion (JACFEE) [Slides]. San Francisco, CA: Intercultural and Emotion Research Laboratory, Department of Psychology, San Francisco State University; 1988.

163. Amir N, Taylor CT, Donohue MC. (2011). Predictors of response to an attention modification program in generalized social phobia. *Journal of Consulting and Clinical Psychology*.;79(4):533-541. PMID: 21707134

164. Koster EH, Crombez G, Verschuere B, De Houwer J. (2004). Selective attention to threat in the dot probe paradigm: differentiating vigilance and difficulty to disengage. *Behaviour Research and Therapy*, 42(10), 1183-1192. PMID: 15350857

165. Daniel Rudaizky, Julian Basanovic & Colin MacLeod (2014) Biased attentional engagement with, and disengagement from, negative information: Independent cognitive pathways to anxiety vulnerability?, *Cognition and Emotion*, 28:2, 245-259, DOI: 10.1080/02699931.2013.815154

166. Lang PJ, Greenwald MK, Bradley MM, Hamm AO. (1993). Looking at pictures: affective, facial, visceral, and behavioral reactions. *Psychophysiology*, 30(3):261-73. PMID: 8497555

167. McGuire JT, Kable JW. (2010). Medial prefrontal cortical activity reflects dynamic re-evaluation during voluntary persistence. *Nature Neuroscience*. 18(5),760-6.

168. Bradley MM, Lang PJ. (1994). Measuring emotion: the Self-Assessment Manikin and the Semantic Differential. *Journal of Behavior Therapy and Experimental Psychiatry*, 25(1):49-59. PMID: 7962581

169. Kaz AC, Sarapas C, Bishop JR, Patel SR, Shankman SA. (2015). The mediating effect of prefrontal asymmetry on the relationship between the COMT Val(158)Met SNP and trait consummatory positive affect. *Cognition and Emotion*, 29:867-81. PMID: 25195915158.

170. Snijders, T.A., & Bosker, R. J. (1993). Standard errors and sample sizes for two-level research. *Journal of Educational Statistics*, 18, 237-259.

171. Hox, J. (2010). Multilevel analysis: Techniques and applications (2nd ed.). Lawrence Erlbaum Associates Publishers, Utrecht.

172. Hamer, R.M., & Simpson, P.M. (2009). Last observation carried forward versus mixed models in the analysis of longitudinal psychiatric clinical trials. *American Journal of Psychiatry*, 166, 639-641. PMID: 19487398

173. Heck, R. H., Thomas, S. L., & Tabata, L. N. (2014). Multilevel and Longitudinal Modeling with IBM SPSS. Routledge, New York: NY.

174. Enders, C.K. (2011). Missing not at random models for latent growth curve analyses. *Psychological Methods*, 16, 1-16. PMID: 21381816

175. Benjamini, Y., & Yekutieli, D. (2001). The control of the false discovery rate in multiple testing under dependency. *Annals of Statistics*. 29, 1165-1188.

176. Wang, L., and Maxwell, S. E. (2015). On disaggregating between-person and within-person effects in longitudinal data using multilevel models. *Psychological Methods*, 20, 63-83.

177. Campbell-Sills, L., Liverant, G., & Brown, T.A. (2004). Psychometric evaluation of the Behavioral Inhibition/Behavioral Activation Scales in a large sample of outpatients with anxiety and mood disorders. *Psychological Assessment*, 16, 244-54. PMID: 15456380

178. Tang TZ, DeRubeis RJ, Hollon SD, Amsterdam J, Shelton R, Schalet B. (2009). Personality change during depression treatment: a placebo-controlled trial. *Archives of General Psychiatry*, 66 (12), 1322-1330

179. Hedman E, Andersson G, Lindefors N, Gustavsson P, Lekander M, Ruck C, Andersson E, Ljotsson B. (2014). Personality Change following Internet-Based Cognitive Behavior Therapy for Severe Health Anxiety. *PLoS ONE* 9(12): e113871. doi:10.1371/journal.pone.0113871

180. Barry T J, Vervliet B, Hermans D. (2015) An integrative review of attention biases and their contribution to treatment for anxiety disorders. Frontiers in Psychology, 6, Article 968. doi: 10.3389/fpsyg.2015.00968

181. Niles, A., Mesri, B., Burklund, L., Lieberman, M., & Craske, M.G. (2013). Attentional bias and emotional reactivity as predictors and moderators of behavioral treatment for social phobia. Behaviour Research and Therapy, 51(10), 669-679.

182. Hadwin JA, Richards HJ (2016) Working Memory Training and CBT Reduces Anxiety Symptoms and Attentional Biases to Threat: A Preliminary Study. Frontiers in Psychology, 7, Article 47. doi: 1 O. 3389/fpsyg .2016. 0004 7

183. Reiss, S., Peterson, R., Gursky, D., & McNally, R. (1986). Anxiety sensitivity, anxiety frequency, and the prediction of fearfulness. *Behavior Research and Therapy, 24*, 1–8.

184. Telch, M. J., Shermis, M. D., & Lucas, J. A. (1989). Anxiety sensitivity: Unitary personality trait or domain-specific appraisals? *Journal of Anxiety Disorders, 3*, 25–32.

185. Foa, E. B., Franklin, M. E., Perry, K. J., & Herbert, J. D. (1996). Cognitive biases in generalized social phobia. *Journal of Abnormal Psychology, 105*(3), 433–439. https://doi.org/10.1037/0021-843X.105.3.433

186. Vögele, C., Steptoe, A., 1992. Emotional coping and tonic blood pressure as determinants of cardiovascular responses to mental stress. J. Hypertens. 10 (9). https://doi.org/10.1097/00004872-199209000-00024