Positive System Valence Function and Reward Exposure Therapy for Late-Life Depression

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WEILL CORNELL MEDICAL COLLEGE – STUDY PROTOCOL

Project Title: Positive Valence System Function and Reward Exposure Therapy for Late-Life Depression

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Overview

Depression is associated with a host of negative outcomes including compromised quality of life, economic burden, and high risk for suicide (Blazer, 2003; Pearson & Conwell, 1995; Unützer, Bruce, & NIMH Affective Disorders Workgroup, 2002; Verma & Silverman, 2009). Existing evidence-based psychotherapies have response rates of only 60% (Hollon et al., 2005; Solomon & Taylor, 2014) and are rarely used with fidelity in the community due to their complexity. Focused psychotherapies using simple techniques to target neurobiological systems impaired in depression may have greater efficacy in treating core dysfunctions of depression, be easier to implement accurately, and have greater potential for broad use in the community.

A promising target for psychotherapy is neural processing of rewards. Reward processing is impaired in depression (Henriques & Davidson, 2000; Henriques, Glowacki, & Davidson, 1994; Nestler & Carlezon, 2006; Pizzagalli, Iosifescu, Hallett, Ratner, & Fava, 2008; Robinson, Cools, Carlisi, Sahakian, & Drevets, 2012; Wacker, Dillon, & Pizzagalli, 2009), and anhedonia, a cardinal symptom of depression (American Psychiatric Association, 2013), is a clinical expression of reward system dysfunction. Reward system function declines with age (Eppinger, Hämmerer, & Li, 2011), conferring vulnerability to depression in older adults (Alexopoulos, 2005).

Engage is a streamlined therapy for late-life depression that aims to improve reward system function through repeated “reward exposure” (Alexopoulos et al., 2016; Alexopoulos & Arean, 2014). However, the neural mediators of Engage are unknown. In this study, we will compare depressed older adults receiving Engage (n = 35) or supportive therapy (ST; n = 35), a therapy whose presumed mechanism of action is not directly related to the reward system. We will use event-related potentials (ERPs) to examine whether Engage enhances reward processing to a greater degree than ST, and whether change in reward processing is associated with subsequent change in anhedonia during treatment. ERPs will be collected at baseline, mid-treatment (weeks 3 and 6), and end of treatment (week 9).

Three ERPs will be measured: 1) the late positive potential (LPP), 2) the reward positivity (RewP), and 3) the P1. The LPP is a measure of sustained attention to affective stimuli generated by a network of brain areas involved in emotional processing and is larger for positive than neutral stimuli (Y. Liu, Huang, McGinnis-Deweese, Keil, & Ding, 2012; Schupp et al., 2000). It is blunted in depression (MacNamara, Kotov, & Hajcak, 2016; Weinberg, Perlman, Kotov, & Hajcak, 2016) but increases with behavioral therapies (Garland, Froeliger, & Howard, 2015; Leutgeb, Schäfer, & Schienle, 2009), suggesting that it indexes a state-related abnormality. The RewP is a measure of initial responsiveness to reward generated by the ventral striatum in response to feedback indicating desirable outcomes (Carlson, Foti, Mujica-Parodi, Harmon-Jones, & Hajcak, 2011; Foti, Weinberg, Bernat, & Proudfit, 2015; Holroyd, Krigolson, & Lee, 2011; Proudfit, 2014). It is blunted during episodes of depression (Foti, Carlson, Sauder, & Proudfit, 2014; W. Liu et al., 2014) and remission (Weinberg & Shankman, 2016; Whitton et al., 2016) and prior to first-onset depression (Bress, Foti, Kotov, Klein, & Hajcak, 2013; Nelson, Perlman, Klein, Kotov, & Hajcak, 2016), suggesting that it is a trait marker of reward system vulnerability. The P1 is an index of early visual attention generated in the extrastriate cortex (Di Russo, Martínez, Sereno, Pitzalis, & Hillyard, 2002). The P1 for affectively neutral stimuli is not influenced by depression (Dai & Feng, 2011; Dai, Wei, Shu, & Feng, 2016; Zhao et al., 2015). It is included to assess whether the effects of Engage are *specific* to reward systems. Behavioral activation will be assessed with the Behavioral Activation for Depression Scale (BADS) (Kanter, Mulick, Busch, Berlin, & Martell, 2007), and additional behavioral and self-report measures of reward processing are included for hypothesis generation.

Aims and Hypotheses

Primary aim: To study target engagement of the reward system in Engage.

H1: Engage-treated participants will have greater increase in LPP and BADS from baseline to week 9, but not in RewP and P1, compared to ST-treated participants.

H2: The course of LPP will be significantly associated with the course of BADS in Engage-treated participants.

Secondary aim: To identify predictors of change in anhedonia with Engage.

SH1: Change in LPP for each assessment interval (baseline-3 weeks, 3-6 weeks) predicts severity of anhedonia at the next assessment time (6, 9 weeks) in Engage, but not in ST participants.

SH2: Change in BADS for each assessment interval predicts severity of anhedonia at the next assessment time in Engage, but not in ST participants.

Analysis Plan

We anticipate that approximately 15% of patients will fail to comply with the treatment protocol. Therefore, we will recruit 85 depressed older adults to meet our goal of 70 participants.

Descriptive Statistics

We will use graphical methods (e.g., box-plot) to examine the distribution and outliers of each clinical and demographic variable. If distribution assumptions are violated, we will use transformations or bootstrapping. In comparisons between Engage- and ST-treated subjects, we will include in regression models any variables (e.g. antidepressant use) that are unbalanced in these groups. We will control the overall Type I error rate at 5% after adjusting for multiple comparisons using Holm's stepdown procedure.

Analyses for Primary Hypotheses

H1. *Engage-treated participants will have greater increase in LPP and BADS from baseline to week 9, but not in RewP and P1, compared to ST-treated participants.* We will use separate mixed-effects regression models for the dependent variables (LPP and BADS assessed at baseline and weeks 3, 6 and 9). Our model will include fixed effects for age, time, sex, antidepressant use, and other variables when they differ between groups. Higher order(s) of the time variable (e.g., quadratic, cubic, etc.) or time as a categorical variable will be investigated. A significant interaction between time and treatment group will confirm our hypotheses. Separate mixed-effects models will be constructed with RewP and P1 assessments at baseline, weeks 3, 6 and 9 as dependent variables; we expect a weak time x group interaction, if any, for these variables because RewP remains blunted even in remitted depression and P1 is unrelated to reward function. While we do not expect to have power to test non-inferiority of RewP and P1 in Engage compared to ST, the proposed analysis will offer preliminary data on lack of change over time during treatment in RewP and P1 in both treatment arms.

H2. *The course of LPP will be significantly associated with the course of BADS in Engage-treated participants.* We will construct a mixed model for LPP as a dependent variable, similar to H1, and include BADS at concurrent assessments as a predictor. A significant effect of BADS will confirm our hypothesis.

Analyses for Secondary Hypotheses

SH1. *Change in LPP for each assessment interval (baseline-3 wks, 3-6 wks) predicts severity of anhedonia at the next assessment time (6, 9 wks) in Engage, but not in ST participants.* ***SH2****. Change in BADS for each assessment interval predicts severity of anhedonia at the next assessment time in Engage, but not in ST participants.* In a linear mixed effects regression, change in LPP from baseline to week 3, week 3-6, and week 6-9 will be used to predict anhedonia severity (SHAPS-C) at 3, 6, and 9 weeks. We will include fixed effects for age, time, gender, and antidepressant use. We will repeat this analysis for BADS (SH2). A significant effect for LPP or BADS will confirm our hypotheses. We chose this correlative analysis rather than a mediation analysis because we are only powered to detect a very large mediation effect.

Missing Data

The proposed mixed-model analysis provides valid inferences when data are missing at random (Hedeker & Gibbons, 2006). To assess the sensitivity of the missing-at-random assumption, we will refit these models with pattern mixture models(Little, 1993), which entails fitting separate models for different drop-out patterns, and then assessing if intervention differences are sensitive to these patterns. To determine whether overall treatment effects, adjusting for study completer status, differ from the analogous control group's estimated differences, we will also employ the pattern-mixture methodology that provides for a way of taking weighted averages of these differences. In the event that we use generalized estimating equations due to untenable distributional assumptions in mixed effect models, we will use Robins's inverse probability weighted estimator (Robins, Rotnitzky, & Zhao, 1995).

Comment on Mixed-Model Analyses

Mixed-effects models will include an age-group level random intercept to account for correlation among Engage- and ST- treated participants matched by age groups. In models where repeated measures are analyzed, we will include another subject-level random intercept nested within age-group to account for correlations among repeated measures and will include a random slope parameter.

Correction for Multiple Comparisons

We will control the study-wide false discovery rate for all hypotheses using the Benjamini-Hochberg method (Benjamini & Hochberg, 1995).

Power

H1. With 35 participants in each group, we will have 80% power at an alpha=2.5% to detect a difference of greater than or equal to 0.8 standard deviations in LPP and BADS change from baseline to 9 weeks, assuming a range of intra-class correlation coefficients for repeated measures (rho=0.2 to 0.5) and an attrition rate of 10%. Our estimate of power is conservative as it is based on a pre-post test of mean difference between two treatment groups, whereas our analytic plan will use repeated measures to detect difference in slopes of LPP or BADS change over time. This study is not powered to detect non-inferiority of RewP and P1 in Engage vs. ST.

H2. With 35 participants in the Engage group, we will be able to estimate the correlation between LPP and BADS with a 95% confidence interval width of 0.15-0.47 for a range of correlations (0.6-0.9).

Patient Study Participants

Subject Population

There are two treatment arms to this study. Arm 1 patient participants will be 70 older adults (age ≥ 60) with MDD, 35 per treatment group. Diagnosis will be determined by the Structured Clinical Interview for DSM-5 (SCID) (First, Williams, Karg, & Spitzer, 2015). Participants will be free of major medical comorbidities and either free of antidepressants or on a stable dose for at least 12 weeks with a plan to continue on the same dose for the duration of the study.

Arm 2 patient participants will be older adults who report significant symptoms of depression but do not meet study criteria due to insufficient symptoms and/or severity, a recent change in medication, or past psychiatric comorbidity that does not contribute significantly to the current clinical presentation. These individuals will be "practice case" participants and will receive therapy from therapists undergoing training to administer therapy for the study.

Recruitment

Participants will be recruited from the outpatient clinic of the Weill Cornell Institute of Geriatric Psychiatry, community-based mental health services, community-based medical practices, and other community organizations. Participants may also be recruited online (e.g., through Facebook ads and on Patch.com

community page posts) and by sending letters to individuals from the target demographic who are included on commercial mailing lists.

The Weill Cornell Institute of Geriatric Psychiatry also maintains a depression screening hotline for older adults. Community partners provide their clients with this number if they are interested in learning about our studies. This hotline is specifically for individuals interested in research protocols, and is not for individuals interested in clinical care. Research Assistants (RAs) will administer a brief phone screen to hotline callers. Potential patient subjects determined to be at high risk for depression are invited to our outpatient clinic for an in-person evaluation to determine study eligibility, conducted by WCMC physicians and clinicians. This screening protocol is titled “Mood Assessment for Adults,” protocol #1809019604.

Additionally, participants may be recruited through the Epic MyChart subject pool, protocol #18120119822 ("Collecting Patient Consent to be Contacted for Research"). Patients in this subject pool have given consent to be contacted about research studies based on the information in their electronic medical record. Volunteers may also be recruited through the ResearchMatch registry. An initial contact message will be sent to potential participants in the registry. Only individuals who respond “yes” to this message to indicate their interest will be contacted further.

Eligible individuals will be invited to participate in the study after providing written or digital informed consent. Individuals who do not meet criteria may be offered participation for other research studies or given referrals for treatment in the community if desired.

For remote consenting, the consent form will be discussed over Zoom or a phone call, with the consent form being emailed beforehand. The person obtaining consent will explain all content and answer any questions the individual may have, making sure they fully understand the study. If the individual decides to participate, they can sign the consent form digitally through Redcap. If the individual does not have email or internet access, we may mail the consent form along with a pre-stamped envelope to return it to us after the consent form has been reviewed and signed.

In the case of remote evaluations, eligibility for study participation will be determined based on the same criteria used for in-person evaluations. Once an eligibility determination has been made, the individual will be contacted again and given additional information as appropriate (e.g. referrals for community therapists if ineligible, scheduling information for baseline study assessments if eligible).

Inclusion Criteria – Arm 1

1. Age greater than or equal to 60 years.
2. Primary diagnosis of unipolar major depressive disorder without psychotic features, determined by SCID.
3. Montgomery-Asberg Depression Rating Scale (MADRS) score greater than or equal to 20.
4. Mini Mental State Exam (MMSE) score greater than or equal to 24.
5. Off antidepressants or on a stable dose of an antidepressant for 12 weeks and do not intend to change the dose in the next 10 weeks.
6. Capacity to provide written or digital consent for both research assessment and treatment.

Inclusion Criteria – Arm 2

1. Age greater than or equal to 60 years.
2. Two or more clinically significant symptoms of unipolar major depression without psychotic features (including depressed mood and/or anhedonia), at least 2 weeks in duration, determined by SCID.
3. Montgomery-Asberg Depression Rating Scale (MADRS) score greater than or equal to 15.
4. Mini Mental State Exam (MMSE) score greater than or equal to 24.
5. Capacity to provide written or digital consent for both research assessment and treatment.

Exclusion Criteria – Arm 1

1. Intent or plan to attempt suicide in the near future.

2. Presence of current psychiatric diagnoses other than major depressive disorder without psychotic features, persistent depressive disorder, unspecified depressive disorder, or anxiety disorders (e.g., separation anxiety disorder, specific phobia, social phobia, panic disorder, agoraphobia, generalized anxiety disorder, or other anxiety disorder).
3. History of past psychotic disorders, bipolar or related disorders, or attention deficit/hyperactivity disorder.
4. Use of psychotropic drugs or cholinesterase inhibitors other than 1) use of a stable dose of an antidepressant or 2) use of mild doses of benzodiazepines, defined as less than or equal to 1 mg of lorazepam, 0.5 mg of clonazepam, 0.5 mg of alprazolam, or 10 mg of diazepam daily.
5. Neurological disorders (dementias, history of stroke, multiple sclerosis, Parkinson's disease, epilepsy, etc.); cardiac, renal, or respiratory failure; severe chronic obstructive pulmonary disease; metastatic cancer; or debilitated states or less common medical illnesses that may either influence neural systems of interest or ability to participate in the study.

Exclusion Criteria – Arm 2

1. Intent or plan to attempt suicide in the near future.
2. Presence of current psychiatric diagnoses other than major depressive disorder without psychotic features, persistent depressive disorder, unspecified depressive disorder, or anxiety disorders (e.g., separation anxiety disorder, specific phobia, social phobia, panic disorder, agoraphobia, generalized anxiety disorder, or other anxiety disorder).
3. Use of psychotropic drugs or cholinesterase inhibitors other than 1) use of a stable dose of an antidepressant or 2) use of mild doses of benzodiazepines, defined as less than or equal to 1 mg of lorazepam, 0.5 mg of clonazepam, 0.5 mg of alprazolam, or 10 mg of diazepam daily.
4. Neurological disorders (dementias, history of stroke, multiple sclerosis, Parkinson's disease, epilepsy, etc.); cardiac, renal, or respiratory failure; severe chronic obstructive pulmonary disease; metastatic cancer; or debilitated states or less common medical illnesses that may either influence neural systems of interest or ability to participate in the study.

Medication

Taking antidepressant medication does not exclude a subject from participating in this study. Arm 1 participants must either be off antidepressants or on a stable dose of an antidepressant for 12 weeks (without intending to change the dose in the next 10 weeks). The antidepressant type and dosage must be determined by the subject's own physician, as it is unrelated to the research study and participation. Antidepressant type, dosage, and compliance are recorded during assessments, and are considered as a variable during analysis.

Therapist Study Participants

Subject Population

Approximately 4 doctoral level therapists will be active at any given time, all of whom will be at this site. Participating therapists are not the subjects of the research intervention per se, and we will not collect medical or psychiatric information about them. Rather, we will collect basic data related to their training background (e.g., training history, years of experience, theoretical orientation) and use of study interventions, which will be important information to provide in future publications.

Therapists' involvement is voluntary and in addition to their primary duties. Information regarding the therapists' performance in the study will not be shared with employers outside of the study. Therapist participants will be given the same protections provided to patient participants. Their information will be confidential. Of particular importance is the need to ensure that the therapist participants understand that their decision to participate (or to withdraw participation) will have no job ramifications.

Inclusion Criteria – Therapist Participants

1. Doctoral degree from an accredited graduate or medical program
2. Fluent in English

Exclusion Criteria – Therapist Participants

1. Doctoral degree from an unaccredited graduate or medical program
2. Not fluent in English

Participant Confidentiality

To protect participant confidentiality, study data will be de-identified using a code number. Paper records will be kept in locked file cabinets, and computerized data will be kept in secure databases. Information provided by the subjects will remain confidential; access will be limited to the research staff and, if applicable, state or federal regulatory personnel (e.g., in the case of an audit). Access to the databases will be limited to the appropriate study personnel using password protection. Study identification numbers will be used on all research instruments, and all completed assessments will be kept in locked file cabinets. Only the relevant project staff will have access to the master list linking subject names to study identification numbers. All information obtained will be coded, and the master list will be locked. No records or materials will be released without the participant's express written or digital consent. Publications or presentation of findings will not include information identifying the subjects.

Experimental Procedures

Study Design

Patient participants in **Arm 1** will be randomized to receive a 9-week course of either weekly Engage therapy or ST, and research assessments will be conducted at baseline and weeks 3, 6, and 9.

Week	Baseline	1	2	3	4	5	6	7	8	9
Therapy Session		x	x	x	x	x	x	x	x	x
Research Assessment	x			x			x			x

Patient participants in **Arm 2** will receive either Engage therapy or ST depending on training needs, and research assessments will be conducted at baseline and week 9.

Week	Baseline	1	2	3	4	5	6	7	8	9
Therapy Session		x	x	x	x	x	x	x	x	x
Research Assessment	x									x

Research Instruments

Trained research assistants unaware of study hypotheses will collect weekly clinical and self-report ratings as well as behavioral and psychophysiological measures at each study time point. Measures may be collected in person or remotely, via phone or WCM Zoom technology. Although every effort will be made to collect all measures, EEG or behavioral data collection may be skipped if participants are unable to be seen in person (e.g., due to an unexpected COVID-related change in social distancing policies).

- **Demographics:** Our demographics questionnaire includes age, gender, race, religion, living conditions, marital status, occupation, and education.
- **Medication List and History of Antidepressant Treatment:** The medication list will also help the RA assess medical comorbidity. The Brief Antidepressant Questionnaire (BAQ) is used to evaluate frequency, dosage, and duration of antidepressant treatment for the past 3 months.
- **Intent to Participate:** We will ask participants their intent to attend the next assessment session. At baseline, the participants will be asked about their intent to complete the study. Accounting for participants' intent to attend may reduce attrition (Leon et al., 2007). The item adds little burden and can be used both for data analyses and to identify participants at risk of attrition.
- **Therapeutic Alliance:** The Working Alliance Inventory (WAI) is an assessment of the working relationship (“alliance”) between the patient and the therapist (Tracey & Kokotovic, 1989). The WAI is administered to the patient at baseline and to both the patient and the therapist after each session.
- **Anhedonia:**
    - The Snaith-Hamilton Pleasure Scale (SHAPS-C) is a self-report scale assessing hedonic response over the previous few days (Ameli et al., 2014; Snaith et al., 1995).
- **Behavioral Activation:** The Behavioral Activation for Depression Scale (BADS) is designed to measure behaviors related to rewarding experiences that are targeted in therapies like Engage (Kanter et al., 2007).
- **Depression Severity:** The Montgomery-Asberg Depression Rating Scale (Montgomery & Asberg, 1979), a 10-item severity scale, will be used to measure symptom severity. The MADRS is sensitive to change and is appropriate for depressed elders. It also allows us to assess suicidal ideation and level of risk.
- **Interpersonal Problems:** The Interpersonal Problems Inventory – 32 items (IIP-32) assesses difficulties in interacting with other people (Barkham, Hardy, & Startup, 1996).
- **Reward Function:**
    - The Effort Expenditure for Rewards Task (EEfRT) is a computer task that will be used to assess participants’ willingness to expend greater effort for a higher monetary reward (Treadway et al. 2009).
    - The BIS/BAS scale (Carver & White, 1994) measures behaviors and attitudes related to

behavioral inhibition and behavioral activation. It includes subscales measuring behavioral inhibition, drive, fun seeking, and reward responsiveness.
    - The Positive and Negative Affect Scale (PANAS) (Watson, Clark, & Tellegen, 1988) includes 20 items assessing state positive or negative affect. The positive affect subscale will be used as a measure of initial responsiveness to reward attainment.
    - The Temporary Experience of Pleasure Scale (TEPS) is an 18-item self-report scale assessing anticipatory and consummatory pleasure (Gard et al. 2006).
    - The Probabilistic Reversal Learning (PRL) task measures reward-related learning and behavior. In this task, subjects repeatedly choose between a blue or yellow triangle and are given positive feedback when correct and negative feedback when incorrect. Subjects learn correct responses through trial and error, and contingencies switch periodically throughout the task.
    - The Doors task (Hajcak, Holroyd, Moser, & Simons, 2005) will be used during EEG recording to elicit the RewP. This task is a guessing paradigm in which participants repeatedly choose between images of two doors displayed simultaneously, and receive feedback on each trial indicating that they have won or lost money.
    - A passive picture-viewing task (Cuthbert, Schupp, Bradley, Birbaumer, & Lang, 2000) will be used during EEG recording to elicit the LPP. In this task, participants view a series of positive and neutral images.
- **Handedness**: The Edinburgh Handedness Inventory (EHI)—short form (Veale, 2014), a 4-item inventory, will be used to assess the consistency and direction of hand use.**Suicidal Ideation**: The Beck Scale for Suicidal Ideation (BSSI) (Beck, Kovacs, & Weissman, 1979) evaluates suicidal ideation in the patient currently and during their most severe time of crisis. It asks about attitudes toward suicide, suicidal ideation, and thoughts of an actual attempt.

Exploratory Measures: Additional EEG tasks may be administered to a subset of participants to for the purpose of exploratory analyses. These tasks may include the Monetary Incentive Delay (MID) task (Knutson, Westdorp, Kaiser, & Hommer, 2000), which uses monetary rewards and measures neural activity related to reward anticipation and receipt, and the Social Incentive Delay (SID) task, which is structured identically to the MID task but uses images of people as feedback in place of monetary rewards. An additional 6-minute recording of resting EEG, recorded while participants are sitting quietly, may also be collected. Resting EEG can be used to assess alpha power asymmetry between the two brain hemispheres which is known to be associated with reward responsiveness and depression.

Selected administrations of diagnostic and other interview measures will be audio-recorded for the purposes of evaluation of inter-rater reliability. These recordings will not be labeled with information such as participants' name, date of birth, or other identifying information.

Schedule of Assessments

Arm 1:

Instrument	Baseline	Week 3	Week 6	Week 9
Behavioral Activation for Depression (BADS)	x	x	x	x
Beck Scale for Suicidal Ideation (BSSI)	x	x	x	x
BIS/BAS	x	x	x	x
Brief Antidepressant Questionnaire (BAQ)	x			
Demographic questionnaire	x			
Doors Task	x	x	x	x
Edinburgh Handedness Inventory (EHI)	x			
Effort Expenditure for Rewards (EEfRT) task	x	x	x	x
Intent to Attend Next Assessment	x	x	x	
Intent to Complete	x			
Interpersonal Problems Inventory – 32 items (IIP-32)	x	x	x	x
Montgomery Åsberg Depression Rating Scale (MADRS)	x	x	x	x

Passive Picture-Viewing Task	x	x	x	x
Positive and Negative Affect Schedule (PANAS)	x	x	x	x
Probabilistic Reversal Learning task	x	x	x	x
Snaith-Hamilton Pleasure Scale (SHAPS-C)	x	x	x	x
Temporary Experience of Pleasure Scale (TEPS)	x	x	x	x

Arm 2:

Instrument	**Baseline**	**Week 9**
Behavioral Activation for Depression (BADS)	x	x
Beck Scale for Suicidal Ideation (BSSI)	x	x
BIS/BAS	x	x
Brief Antidepressant Questionnaire (BAQ)	x	
Demographic questionnaire	x	
Doors Task	x	x
Edinburgh Handedness Inventory (EHI)	x	
Effort Expenditure for Rewards (EEfRT) task	x	x
Intent to Attend Next Assessment	x	
Intent to Complete	x	
Interpersonal Problems Inventory – 32 items (IIP-32)	x	x
Montgomery Åsberg Depression Rating Scale (MADRS)	x	x
Passive Picture-Viewing Task	x	x
Positive and Negative Affect Schedule (PANAS)	x	x
Probabilistic Reversal Learning task	x	x
Snaith-Hamilton Pleasure Scale (SHAPS-C)	x	x
Temporary Experience of Pleasure Scale (TEPS)	x	x

Cost and Reimbursement

Participants in Arm 1 will be compensated approximately $260 for completion of the study:

- $50 for the baseline session
- $30 each for the week 3, 6, and 9 sessions ($90 total)
- Up to $30 won during computer tasks at each of the four sessions ($120 total)

Participants in Arm 2 will be compensated approximately $120 for completion of the study:

- $50 for the baseline session
- $30 for the week 9 session
- Up to $30 won during computer tasks at each of the two sessions ($60 total)

For remote assessments, a compensation check will be mailed to the participant's home.

Participants may be eligible to have travel expenses for study visits paid for by the study

Participants will not be compensated for the study psychotherapy treatment.

Interventions

Engage Therapy

Engage is a stepped care psychotherapy based on what is known about how older adults respond to depression interventions. Stepped care is a model of treatment that starts with the minimum effective

therapeutic techniques first, and then based on how well people respond to treatment, additional therapeutic techniques are added until people are recovered from their depression. The steps of ENGAGE are:

- Basic social and physical engagement, which has been found to be a very effective depression strategy for most older adults
- The addition of strategies to address clinical features of depression interfering with treatment engagement, namely affect regulation, pessimism, and disorganization

Not all subjects will need these additional strategies; in fact, we anticipate that about one third to one half of subjects will respond well to re-engagement in rewarding activities alone. One of the biggest problems with existing psychotherapies is that while very effective, they are difficult to implement well into regular practice, and often difficult for older people, particularly those who have extensive care-giving demands, medical illnesses or hectic schedules to use on a consistent basis. Our research into the treatment of late-life depression has found that simple support around engagement in social activities, volunteerism, physical activities, and basic problems can result in significant improvements in mood and disability.

The treatment components we selected for ENGAGE are evidence-based and selected to match the most common problems we see in older adults with depression. Underlying the therapeutic process is basic problem solving. Regardless of the step or strategy used, subjects will do the following:

1. Identify a goal
2. Develop a list of strategies to meet the goal
3. Select a strategy
4. Create an action plan, which also address any obstacles that could interfere with successful action plan implementation

Supportive Therapy

Supportive therapy is efficacious but focuses more on providing emotional support than changing thoughts or behaviors. Supportive therapy treats depression using common factors (e.g., therapist concern, facilitation of affect expression, therapeutic optimism) in the context of a supportive therapeutic relationship. During earlier sessions, therapists obtain patients' history and discuss the approach of ST and patients' expectations for therapy. As ST continues, therapists help patients identify themes that emerge, provide reassurance, normalize patients' experience, emphasize coping skills, and provide guidance as needed. We will use the same ST manual that has been used in our prior studies (Alexopoulos, Raue, & Arean, 2003; Areán et al., 2010).

The intervention can occur in person or remotely, via phone or WCM Zoom technology.

Therapists

Therapy will be provided by doctoral level therapists working as clinical postdoctoral fellows at Weill Cornell or by other qualified clinicians with doctoral degrees. Fellows are recruited based on strong clinical experience with evidence-based therapies and are licensed by year 2 of fellowship. A clinical psychologist in the Institute of Geriatric Psychiatry will provide weekly supervision to the therapists to ensure adherence to treatment protocols and address clinical issues.

Therapist Training

Training will be conducted as follows.

Step 1: Therapists read the manual, and an instructor holds a 2-hour session describing the intervention.

Step 2: Therapists participate in a 2-3 hour training session. The instructor role-plays a therapy session. Therapists role-play sessions, and the instructor evaluates trainees' fidelity to the manual using the Engage Adherence Scale (EAS) or Supportive Therapy Adherence Scale (STAS). Therapists may only continue to Step 3 if they earn a score of ≥ 4 (very good) on at least one simulated case after 12 chances.

Step 3: Therapists must conduct therapy with "practice cases" and earn scores of ≥ 4 on at least three consecutive sessions with these cases within the first 2.5 months in order to be certified. Treatment fidelity will be rated by experienced therapists, Rebecca Shermer, PhD and Rebecca Crabb, PhD, who are not members of the research team.

Selected therapy sessions will be audio-recorded for the purposes of supervision and evaluation of therapist adherence to the therapy protocol using the EAS or STAS. These recordings will not be labeled with information such as participants' name, date of birth, or other identifying information. Therapists will meet with a supervisor weekly for supervision, during which corrective feedback will be provided to therapists that show "skill drift" (i.e. fidelity scores < 4).

Monitoring of Clinical State

Participants' clinical state will be monitored by their study therapists. Therapists and their supervisor will discuss symptoms that may require treatment other than that provided by the study. The supervisor will also be available for phone calls with therapists between supervision sessions. If a participant requires additional care, the therapist and supervisor will collaborate on a referral.

Therapists will administer the Patient Health Questionnaire (PHQ-9) during each therapy session. If a participant endorses suicidal ideation or behavior on item 9 of the PHQ-9 ("Thoughts that you would be better off dead, or of hurting yourself"), the therapist will conduct a thorough safety evaluation. If the therapist determines that the participant is at risk, the therapist will consult with a supervisor and/or with the director of the Weill Cornell Institute of Geriatric Psychiatry to determine a course of action.

Additionally, research assistants will administer the MADRS during research assessments. If a participant endorses suicidal ideation or behavior on item 10 of the MADRS ("This past week, have you felt like life isn't

worth living?"), the research assistant will complete the Suicide Risk Assessment protocol (see attachments), which has been approved by NIMH for determining an increase in suicidal ideation. The research assistant will then report the results of the Suicide Risk Assessment to the participant's study therapist or another clinician in the Institute of Geriatric Psychiatry, who will conduct a thorough safety evaluation if warranted.

Research assistants also administer the Beck Scale for Suicidal Ideation during research assessments. If participants report any suicidal ideation (a score of 1 or 2 on items 2-5), the research assistant will contact the patient's study therapist or another clinician with the results of the questionnaire, and the clinician will do a safety evaluation if warranted.

Depending on the level of risk, the participant may be encouraged to speak to his/her own clinician; the PI or therapist may call the participant's clinician and/or family member; the participant may be referred for an evaluation by a psychiatrist present in the office at the time; or the participant may be escorted to the on-campus evaluation center for possible hospitalization. Other urgent risks may necessitate calling 911 or having a family member bring the participant to a local emergency room for evaluation (if participant is being interviewed over the phone, for example).

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