New York State Psychiatric Institute

Institutional Review Board

September 29, 2020

To: Dr. Ronit Kishon

From: Dr. Edward Nunes, Co-Chair
Dr. Agnes Whitaker, Co-Chair

Subject: Approval Notice: Continuation*

Your protocol # **6806R** entitled: **PSYCHOLOGICAL MINDEDNESS AS A PREDICTOR OF COGNITIVE BEHAVIOR THERAPY OUTCOME (FORMERLY #5768)** Protocol version date 09/29/2020 and consent forms have been approved by the New York State Psychiatric Institute - Columbia University Department of Psychiatry Institutional Review Board from **September 29, 2020 to September 8, 2021.** (Reviewed at the Full Board meeting on September 14, 2020.)

Consent requirements:
☐ Not applicable:
☐ 45CFR46.116 (f)(3) waiver of consent
√ Signature by the person(s) obtaining consent is required to document the consent process
☐ Documentation of an independent assessment of the participant's capacity to consent is also required.

Approved for recruitment of subjects who lack capacity to consent: √ No ☐ Yes

Field Monitoring Requirements: √ Routine ☐ Special: _____

✓ Only copies of consent documents that are currently approved by the IRB may be used to obtain consent for participation in this study.
✓ A progress report and application for continuing review is required 2 months prior to the expiration date of IRB approval.
✓ Changes to this research may not be initiated without the review and approval of the IRB except when necessary to eliminate immediate hazards to participants.
✓ All serious and/or unanticipated problems or events involving risks to subjects or others must be reported immediately to the IRB. Please refer to the PI-IRB website at http://irb.nyspi.org for Adverse Event Reporting Procedures and additional reporting requirements.

*(*noting approved under 45CFR46.204)*

Cc: RFMH Business Office (NIMH 1R21MH121915-01A1)

Encl: CF, HIPAA, recruitment materials

EN/AHW/alw

Signed copy on file at IRB

Protocol Title:
Psychological Mindedness as a Predictor of Cognitive Behavior Therapy Outcome (formerly #5768)

Version Date:
09/29/2020

Protocol Number:
6806R

Clinic:
Depression Evaluation Service

First Approval:
09/10/2013

Expiration Date:
09/08/2021

Contact Principal Investigator:
Ronit Kishon, PHD
Email: kishonr@nyspi.columbia.edu
Telephone: 646 774 8030

Co-Investigator(s):
Jurgen Kayser, PHD
Maren Westphal, PHD

Research Chief:
B. Timothy Walsh, MD

Cover Sheet

Choose ONE option from the following that is applicable to your study
If you are creating a new protocol, select "I am submitting a new protocol." As 5 Year Renewals are no longer required, this option remains for historical purposes.
I am submitting an annual continuation without modifications

Division & Personnel

Division

What Area Group does the PI belong to?
What Division/Department does the PI belong to?
Clinical Therapeutics
Within the division/department, what Center or group are you affiliated with, if any?
Depression Evaluation Services

Unaffiliated Personnel

List investigators, if any, who will be participating in this protocol but are not affiliated with New York

State Psychiatric Institute or Columbia University. Provide: Full Name, Degrees and Affiliation.
None

Application for Continuation of Research

Status

Current Status of Study:
Subject enrollment is ongoing.

Summary of Experiences to Date

Please provide a summary of scientific progress of the study and the experience of research participants, to date. This requirement is designed to allow for the investigator and the IRB to reassess the study's risks and benefits in terms of developments in the field, changing practice patterns, and new IRB policies and procedures.
We transitioned from a pilot study to an R21 funded grant by NIMH. All changes were made in the PSF and were approved by the IRB in former months this year.

Funding

Have there been any changes in funding status since the prior approval?
No
Have the principal investigator and other investigators made all required disclosures of financial interest in the study sponsor/product?
Yes

Summary

Have there been any study findings, recent literature, or untoward events occuring here or at other sites in the past year which might affect the analysis of the safety, risks or benefits of study participation?
No
Have there been any serious adverse events (serious and/or unanticipated problems involving risks to subjects or others at this site which occured in the past year)?
Yes
Please describe them and indicate resultant protocol modifications made.

The patient entered our study on 2/24/20 for 12 sessions of CBT for depression. On 3/16/2020 (session 4), we needed to move into virtual sessions due too COVID -19. The patient was very motivated in sessions and continued to use the CBT skills between the sessions. On 4/2/2020, our evaluator called her to administer the Hamilton Rating Scale for Depression. We administer this scale at baseline and every three weeks to assess depressive symptoms. The patient seemed on the phone in a fragile state. She was very weepy and distressed. The evaluator asked her about any suicidal ideation, and the patient said she was very hopeless and would like to end her life but has no plans and no intention to act on it. The evaluator asked if

there was someone at home with the patient, and indeed the father was at home. The evaluator called the study's PI, Dr. Ronit Kishon, who immediately called the patient. The patient admitted to smoking pot in the last few days. She reported passive suicidal ideation with no plan or intent but feeling hopeless about the future. Dr. Kishon advised her not to self-medicate or smoke since it was not safe for her mental wellbeing. Dr. Kishon followed up that night and got verbal permission from the patient to speak to both parents of the patient. Both parents expressed concern and showed interest in enrolling the patient in a residential program in AZ that focuses on medication, treatment, and reintegration in daily life. Dr. Kishon advised the first immediate step is to see a psychiatrist for medications, as recommended by the study protocol. Dr. Kishon recommended Dr. Jeff Miller, who has a private practice and could see her the next day. The patient was scheduled to meet Dr. Miller and was treated with medications. She reported feeling better with no suicidal ideation. She continued to be in the study, and on 4/6/20, she met a study therapist for CBT session #7 virtually. She denied any suicidal thoughts. However, at 4/7, she became very hopeless, and in a conversation with Dr. Kishon, she said she has suicidal thoughts but will not act on them. Dr. Kishon spoke with the patient, her parents, and Dr. Miller regarding a treatment plan that would be more rigorous than what the study can offer. There were two options: the Columbia day program at Columbia University Psychiatry or Meadows trauma and addiction treatment at AZ, which a private inpatient treatment. The patient and her family decided she will attend the Meadows treatment at AZ. Dr. Kishon was in daily contact with the patient until 4/14, when she flew with her brother, who escorted her to AZ. She was admitted to the program. Therefore, the patient terminated our study on 4/14/20. Dr. Kishon contacted the patient's father a few days later, and he said she seemed very satisfied with the program.
An SAE was sent to the IRB and Cynthia Desmond. We made all needed adjustments in PSF on how to handle similar situations virtually.

Have all study staff with a significant role in the design or implementation of the human subject components of this study received required training in human research subject protections?
Yes
Is the study covered by a certificate of confidentiality?
No

Overall Progress

Approved sample size
180
Total number of participants enrolled to date
109
Number of participants who have completed the study to date
107
Have there been any significant deviations from the anticipated study recruitment, retention or completion estimates?
No
Comments / additional information

Sample Demographics

Specify population
adults with MDD
Total number of participants enrolled from this population to date
110
Gender, Racial and Ethnic Breakdown

Adults	White (not Hispanic origin	Black (not Hispanic origin)	Hispanic	Asian or Pacific Islander	American Indian/Alaskan Native	Other	Total
Female	51	2	5	4	0	2	64
Male	29	6	5	5	0	0	45
Total	80	8	10	9	0	2	109

Summary of Current Year's Enrollment and Drop-out

Number of participants who signed consent in the past year
4
Number of participants currently enrolled
0
Did the investigator withdraw participants from the study?
No
Did participants decide to discontinue study involvement?
Yes
Circumstances of discontinuation:
On 3/16/2020, we needed to move into virtual CBT sessions due to COVID-19. The patient did two virtual sessions but then decided can't have enough privacy when her husband and three children are at home. We helped her think it through and advised her to ask the husband if he can spend some time with the children

during the session in a remote room in the house. However, the patient did not feel comfortable with all this. It was impossible during COVID to give her a referral to a place that sees patients in person. We did suggest to refer her to a psychiatrist and receive medication for her symptoms. She refused. She had on 3/24 her 4th and last session.

Procedures

To create the protocol summary form, first indicate if this research will include any of the following procedures

✓ Psychiatric Assessment
✓ Neuropsychological Evaluation
✓ Psychotherapy Trial
✓ Audio or Videotaping
✓ Internet-based Data Collection or Transmission

Population

Indicate which of the following populations will be included in this research

✓ Pregnant Woman
✓ Adults
✓ Adults over 50

Research Support/Funding

Will an existing internal account be used to support the project?
No
Is the project externally funded or is external funding planned?
Yes
Select the number of external sources of funding that will be applicable to this study

Funding Source #1

Is the PI of the grant/contract the same as the PI of the IRB protocol?
Yes
Select one of the following
The grant/contract is currently funded
Source of Funding
Federal
Institute/Agency
NIMH

Grant Name
R21
Grant Number
1R21MH121915 - 01A1
Select one of the following
Single Site
Business Office
RFMH
Does the grant/contract involve a subcontract?
No

Study Location

Indicate if the research is/will be conducted at any of the following
✓ NYSPI
This protocol describes research conducted by the PI at other facilities/locations
No

Lay Summary of Proposed Research

Lay Summary of Proposed Research

Psychological Mindedness (PM) is viewed as the ability and motivation to achieve a psychological understanding of the self. A person is considered to be psychologically minded if she or he can access their feelings, is willing to try and understand oneself and others, and has an interest in the meaning and motivation of his or her own and others' behavior. Historically, interest in PM grew out of attempts to identify patients best suited for psychoanalytically oriented psychotherapy. There has been limited attention regarding its potential impact on other therapeutic approaches. In recent years different theorists (Conte, Ratto, and Karusa, 1996; Grant, 2001) have noted that PM may have particular relevance for cognitive behavioral therapy (CBT) because PM includes self-monitoring and self-evaluation of one's cognitions, emotions, and behaviors which are central to the successful practice of CBT. This study aims to see if PM is a component in the mechanism of change that is activated in CBT treatment for depression. As such, it may be related to change of symptoms during CBT, and at post-treatment. Mindfulness is another construct of self-awareness that is related to PM and yet distinct. We are studying to see its role in CBT for depression, and its relationship with PM. We will be administrating a few self-report measures of PM that have been used in other studies. We will also begin validating a structured interview of PM that we created in our lab. We also measure other concepts found to be related to PM and mindfulness, rumination, alexithymia, and self-compassion.

Our studies and those of other researchers have found evidence that pretreatment resting EEG, event-related brain potentials (ERPs), and performance on neurocognitive tests show promise of being predictors of subsequent clinical response to antidepressants or CBT. However, the extent to which these tests predict response to specific treatments for depression or the mechanisms underlying

successful response to CBT is not known. We propose to test depressed patients before they begin a treatment study as well as after treatment (pre-post design) to confirm the value of resting EEG, ERPs, dichotic listening, and neuropsychological tests for predicting treatment response in MDD. Patients will be randomized between 12 sessions of CBT and a control condition of non-specific supportive therapy for 12 weeks so to match the experimental condition of CBT with respect to receiving support by a professional, creating an alliance with therapist, length of sessions, and duration of treatment.

Background, Significance and Rationale

Background, Significance and Rationale

Depression is one of the most common psychiatric conditions in the United States. It is a chronic and disabling disorder associated with substantial impairment, decreased quality of life, and psychiatric comorbidity. The two standard treatments for depression are pharmacotherapy and cognitive behavior therapy (CBT). Both treatment modalities are similar in that they are only moderately effective, with a large proportion of patients remaining symptomatic after the initial intervention. Possibly the primary reason for the substantial individual differences in treatment responsiveness is heterogeneity within current psychiatric disease categories, which are present at all levels (i.e.genetic, neurobiological, and psychological levels) (Hollon et al., 2006). In the present study, we measure the changes in self-awareness and specific biomarkers through 12 weeks of CBT for depression and a control condition of 12 weeks of psychoeducation for depression. Psychological mindedness (PM), an aspect of self-awareness, has long been considered to be an essential psychological mediator for therapy outcome. Through the history of clinical psychology, PM was mostly used intuitively by clinicians to evaluate the psychotherapy process, and more specifically, in predicting a patient's ability and motivation in psychotherapy (Farber & Golden, 1977). However, most definitions and measures of PM have approached the task from a psychodynamic perspective, thus limiting the use of this construct by clinicians and researchers from evidence-based psychological perspectives, such as CBT (Grant 2001). Two measures presently being used in studies, the Psychological Mindedness Scale (PMS) (Conte, Ratto, & Karasu 1996), and the more recent measure, Balanced Index of Psychological Mindedness (BIPM) (Nyklíček & Denollet, 2009), have shown some predictive value in different studies of treatment in mentally ill patients. They have not though been

thoroughly investigated as predictors in evidence-based psychotherapies such as CBT for depression. A third measure, the Self-Reflection Index Scale (SRIS; Grant, Franklin, & Langfirm) is an evolved form of the Private Self- Consciousness Scale (PrSCS; Fenigstein, Scheier, & Buss, 1975) which is another method to assess PM, and also recommended in RDoC as a measure of self- knowledge. SRIS is compromised of two separate factors labeled Self-Reflection (SRIS-SR) and Insight (SRIS-IN) which are parts of self-awareness but differently correlate with depression: in studies, the SRIS-SR correlated positively with anxiety and stress, but not with depression and alexithymia. The SRISIN was negatively correlated with depression, anxiety, stress, and alexithymia, and positively correlated with cognitive flexibility and self-regulation (Grant at el. 2002). In addition to PM we examine other concepts that relate to self-awareness so to capture the whole spectrum of one's ability and will to observe oneself. Mindfulness has been found to relate to the construct of PM in a nonclinical sample (Beitel, Ferrer, & Cecero, 2005), yet no study has examined its relationship with PM in a clinical sample despite a growing body of research supporting the role of mindfulness in facilitating clinical improvement in CBT. We measure facets of mindfulness that are particularly relevant to PM and examine their interactions and relative contribution to predicting CBT outcomes in depressed patients. We added a rumination measure because it is a core process in the development and maintenance of depression. Consistent with research indicating a distinction between rumination as a maladaptive form of self-attentiveness, and reflection as an adaptive intellectual form of self-attentiveness thought to underlie PM (Trapnell & Campbell, 1999), we examine the added value of the level of rumination in predicting CBT outcome and its longitudinal relationship with PM through the CBT. Another important construct that has been lately related to different forms of self-awareness and self-observation is self-compassion (Neff, 2003). This is a third construct that may be important for understanding the proposed relationship between increases in PM and symptomatic improvement in depression throughout treatment. There is increasing evidence that self-compassion is a robust predictor of lower psychopathology (for reviews, see Barnard & Curry, 2011; MacBeth & Gumley, 2012). A recent controlled treatment study suggests that self-compassion is a particularly salutary form of emotion regulation in individuals with high levels of depressed mood (Diedrich, Grant, Hofmann, Hiller, &Berking, 2014). To our knowledge, no published research has yet examined the relation between PM and self-compassion. Individuals high in PM may be more likely to develop greater self-compassion throughout CBT treatment as PM taps qualities that may be essential to developing self-compassion. We examine potential interaction effects for self-compassion and PM in the prediction of depression levels pre and post CBT treatment, for example, PM-related symptomatic improvement in depression may be more pronounced for individuals scoring high in self-compassion. Studies have found evidence that pre-treatment resting EEG, event-related brain potentials (ERPs), and performance on neurocognitive tests show promise of being predictors of subsequent clinical response to antidepressants or CBT (Bruder, Kayser, & Tenke, 2012). However, the extent to which these tests predict response to specific treatments for depression or the mechanisms underlying successful response to CBT are not known. We propose to test depressed patients, under Dr. Kayser's protocol (#6559) before they begin a treatment study, both in the CBT condition and control condition, as well as after treatment (pre-post design) to confirm the value of resting EEG, ERPs, dichotic listening, and neuropsychological tests for predicting treatment response in MDD. Patients are retested after the successful completion of CBT, which will take 12 weeks and at the end of psychoeducation treatment (12 weeks). The development of biomarkers for predicting treatment response would be important for personalizing treatment in depression (i.e., determining who will and who will not respond to CBT).

Specific Aims and Hypotheses

Specific Aims and Hypotheses

Study aims: (1) to examine whether pre-treatment PM scores predict the reduction of depressive symptoms at the end of treatments, (2) to determine whether an increase in PM during therapy is associated with a decrease in symptom levels during 12 weeks in both treatments (3) to examine the relationship between PM and conceptually related and distinct concepts: self-reflection, insight, rumination, mindfulness, and self-compassion, and if and how they are related to a reduction of symptoms in CBT and in the control condition, (4) to obtain neurocognitive and electrophysiologic (EEG and ERP) measures so as to further evaluate hypotheses that depressive disorders involve abnormalities of frontal and temporoparietal function (Dr. Jürgen Kayser's protocol (#6559); (5) to evaluate the prediction that treatment with CBT will result in acute and chronic changes in neurocognitive, EEG and ERP measures; (6) measures of left hemisphere processing will be predictive of clinical response to cognitive behavioral therapy; (7) to evaluate any interactions between psychological measures and brain variables in predicting change in symptoms during treatments.

Description of Subject Population

Sample #1

Specify subject population
Adults who suffer from depression
Number of completers required to accomplish study aims
130
Projected number of subjects who will be enrolled to obtain required number of completers
150
Age range of subject population
18 to 70

Gender, Racial and Ethnic Breakdown

Gender breakdown: 60% Female/40% Male

Ethnicity breakdown: The composition of the sample is likely to be 10% non-Hispanic African American, 30% Hispanic/Latino, 5% other minority, and 55% non-Hispanic white.

Description of subject population
This pilot study will enroll 150 subjects between the ages of 18 and 70 with primary DSM-V-TR diagnosis of major depression.

Recruitment Procedures

Describe settings where recruitment will occur

Recruitment will occur via referral from other mental health care professionals and physicians, and via self-referral prompted by advertising.

How and by whom will subjects be approached and/or recruited?

A DES research assistant will conduct a 20-minute telephone screening interview, performed under the DES'#6669R to determine likely diagnostic suitability. It includes subject's name, address, demographic information, source of referral, presenting problem, psychiatric history, past treatment, social history, family history, medical history, mental status, provisional diagnosis, and disposition. Potentially eligible participants will be invited to the DES Clinic at NYSPI for a psychiatric intake evaluation and structured clinical interview, which will be performed under the DES's Consent # 6669R. Informed consent will be obtained prior to any procedure after a subject has been found qualified both medically and diagnostically to participate. A full explanation of all research procedures, risks, benefits, and rights of the subject will be given before proceeding. **Recruitment to this protocol will be restricted to those who enroll in protocol #6559. Participansts in this study will need need to have EEG measures (#6559) before 12 sessions of CBT and control group, and at the end of of the 12 weeks.**

How will the study be advertised/publicized?

Online advertisements will be placed on websites that may include RecruitMe (recruit.cumc.columbia.edu, a CU research site aimed at aiding recruitment of study participant), Craigslist, in sections including volunteers, gigs, and jobs, Google AdWords, Facebook, Research Match, and others. We will advertise this study to Columbia-affiliated clinicians on the Columbia University PsychoPharmacology (CUPP) list-serve. We will approve through the IRB any future advertisement material.

Do you have ads/recruitment material requiring review at this time?
Yes
Does this study involve a clinical trial?
Yes
Please provide the NCT Registration Number

NCT01868711,

Concurrent Research Studies

Will subjects in this study participate in or be recruited from other studies?
Yes
Describe concurrent research involvement
Patients recruited for current protocol will also participate in protocol # 6559R.

Inclusion/Exclusion Criteria

Name the subject group/sub sample
Depressed adults
Create or insert table to describe the inclusion criteria and methods to ascertain them

Males or females between ages 18-70 (inclusive)	Screening interview
Primary diagnosis of Major Depression	SCID and clinical review
Beck Depression Inventory	BDI ≥13 BDI
Hamilton Rating Scale for Depression	HRSD ≥ 14
No psychotropic medication or over the counter antidepressant for at least one month prior to recruitment and three months for fluoxetine.	Clinical interview
Ability to give inform consent	Interview, the capacity to consent
Fluent in English Intake interview	Self-Report

Create or insert table to describe the exclusion criteria and methods to ascertain them

Disorder or organic mental disease	Clinical interview
DSM-V substance abuse or dependence within 6 months (except nicotine or caffeine).	Toxicology, screen, intake
Currently taking psychotropic medication.	Clinical interview
Currently receiving another type of psychotherapy or any other therapeutic intervention.	Clinical interview

Participants who have used any of the psychedelic drugs

(Ketamine, Psilocybin, LSD, MDMA)
for the current episode of depression. Clinical interview

Waiver of Consent/Authorization

Indicate if you are requesting any of the following consent waivers
Waiver of consent for use of records that include protected health information (a HIPAA waiver of Authorization)
No
Waiver or alteration of consent
No
Waiver of documentation of consent
No
Waiver of parental consent
No

Consent Procedures

Is eligibility screening for this study conducted under a different IRB protocol?
Yes
Indicate NYSPI IRB #
6669R
Describe Study Consent Procedures

Consent procedures are the following:

When subjects that are eligible for the study, he or **she will be scheduled to meet Dr. Kishon via Webex (HIPAA-compliant teleconference) before signing *a study consent form***. A copy of the consent form will be provided to the participant, before consent is obtained, via encrypted email. Subjects will be accessible to an electronic consent form via REDCap and will join a HIPAA-compliant teleconference with Dr. Kishon to discuss consent. Afterward, they will digitally sign the consent form with the e-signature function in REDCap.

Indicate which of the following are employed as a part of screening or main study consent procedures
✓ Consent Form

Persons designated to discuss and document consent

Select the names of persons designated to obtain consent/assent
Kayser, Jurgen, PHD
Kishon Ph.D., Ronit
Type in the name(s) not found in the above list

Study Procedures

Describe the procedures required for this study

Baseline visits

Subjects will be briefed on the newly-implemented COVID-19 safety protocol to reassure them precautions are being taken. This protocol is based on NYSPI COVID19 Amendment guidelines for research April.20 and NYSPI Remote communication guidelines for clinical care and research 3.30.20). In the current study, all procedures will be done remotely.

Subjects who sign the DES screening consent will be contacted within two weeks after the screening call; they received the diagnoses of major depressive disorder. The DES psychiatrist will approve their medical tests. An evaluator will rate the HRSD-17, CGI-Severity, and Beck Depression Inventory. If still eligible, subjects will be presented with the study consent form **via REDCap** and have their questions answered by Dr. Kishon **via Webex**. **Once they signed the study consent form via REDCap, subjects will complete a battery of self-report measures in REDCap. Patients will also take part in EEG and cognitive tests administered under Jurgen Kayser's protocol #6559R.** The patients will be randomized to the experimental condition of 12 sessions of CBT for depression and 12 sessions of control condition of nonspecific supportive treatment. CBT and supportive therapy provided by Ph.D. student psychologists who are screened and interviewed by Dr. Kishon and approved and credentialed by Dr. Laura Mufson. **All sessions will be administered via Webex**. Dr. Kishon will supervise all therapists every week **via Webex**. All CBT sessions will be audiotaped unless the subject does not consent. The audio recording will not include the subject's full name and will be reviewed by Dr. Kishon, who will evaluate the treatments provided by therapists in this study. The audio recordings will be kept for no more than ten years, after which they will be destroyed.

If the patient withdraws his or her consent, audio recordings can be destroyed during or after the procedure. The patient reserves the right to withdraw this consent at any time before or during the audiotaping. Ph.D. students in psychology supervised by Dr. Kishon will provide nonspecific treatment. Sessions in the control group will be audio recorded

CBT Treatment Protocol

CBT protocol represents incorporation and integration from several sources. These include (a) prior experience of the therapist with the treatment of depression and (b) published cognitive therapy (CBT) manual published by Emery (2000). The present protocol encourages therapist flexibility in approach, yet

during the treatment, specific tools and methods of coping with depression are given to each subject. The subject will learn to use the following basic cognitive-behavioral techniques for the treatment of depression: constructing an 'Action Schedule', setting goals, doing 'behavioral experiments,' and creating a Distorted Thought Record (DTR). The patient is expected to experiment with the tools between sessions.

A nonspecific treatment control condition

Therapists will provide 12 sessions of support focused on the three facilitative conditions (warmth, genuine, and empathy). They will provide support and will assess the patients for levels of depression and suicidality in each session. Approved DES evaluators will administer to all patients in both groups the Hamilton Rating Scale for Depression (HRSD-17) **via Webex**, and the CGI Severity and Improvement Scales at baseline **via REDCap**. The HRSD-17 will be administered every three weeks and at post-treatment **via Webex**. The CGI will be filled every week and at posttreatment. If there is no improvement in depressive symptoms at week 6, the study PI will conduct an informal interview in which she will discuss with the participant alternative treatments. The discussion will be documented in the participant's chart.

Post-Treatment Assessment Visit

Post-treatment assessment visits will occur within 12 days of the subject's last therapy session. All baseline rating scales will be administered (HRSD-17, CGI) **via Webex and REDCap**, as well as all self-report measures (BDI-II, Work and Social Adjustment, TAS-20, PM, BIPM, SRIS, Treatment Credibility and The Expectancy of Improvement Scale, Reasons for Living, Ruminative Response Scale (RRS), The Mindful Attention Awareness Attention Scale(MAAS), Five-Facet Mindfulness Questionnaire (FFMQ), and Self-Compassion Scale (SCS) **via REDCap**. The SCIP -M will be done **via Webex**. Patients will also take part in EEG and cognitive tests administered under Jurgen Kayser's protocol #6559R. If a patient terminates before completing the entire 12-session protocol, in each of the groups, this visit will be conducted as close as possible to the last session. Study participants who do not remit (end treatment HDRS-17 > 7, BDI-II>13) at the end of the trial will be offered a referral for psychotherapy or medications per subject's preference, or if in the control group will be offered CBT based on the availability of therapists.

I attest to follow the COVID-19 Safety Guidelines for Columbia Psychiatry and NYSPI Re-Entry outlined in the NYSPI Director's June 1st memo, which includes but are not limited to:
• Infection Control/PPE – Guidelines
• Research participants will only come on-site if absolutely necessary for the study procedures.
• No volunteers/externs on-site during Stage 1.
• Clinical research teams will screen their participants for COVID symptoms (night before and day of the onsite visit, documenting this in the chart), and escort them in and out of the building.
• COVID/COVID-like symptoms in participants will be reported to the IRB via PRISM as an SAE.

You can upload charts or diagrams if any

Criteria for Early Discontinuation

Criteria for Early Discontinuation

Criteria for Early Discontinuation

The subject will be withdrawn and prematurely terminated from the study under any of the following circumstances:

1. The subject requests to withdraw from the study.

2. The subject exhibits a clear-cut worsening of anxiety or mood symptoms, e.g., subject whose CGI Improvement score rating increases to 6 (much worse) or 7 (very much worse).

3. The subject reports suicidal ideation of sufficient concern to require hospitalization. Visit the emergency room without admission will be judged on a case-by-case basis erring on the side of ending study participation.

4. The appearance of a new or undercurrent illness that prevents the patient from complying with the protocol.

5. The subject has missed four sessions or is not responding to repeated attempts to contact him or her. Careful medical and psychiatric screening would be conducted to identify patients with risk for potential adverse events if they were to participate in the study treatments. As examples, patients for whom suicide is considered a significant risk will be excluded from all study participation, and subjects with uncontrolled mental impairment.

Any patient who evidences significant clinical deterioration, such as unusually high levels of distress or suicidality at significant risk during the treatments will be removed from the study and treated with alternative and appropriate clinical care at the DES until referred to another treatment. Signs of deterioration will be monitored weekly by the protocol therapist and PI of the study. At each visit during the 12 weeks of the treatments, the clinician will monitor, via clinical interview and various assessment measures for signs of increased severity of depression or the emergence of a major depressive episode. If in the judgment of the clinician and the PI removal of a participant from the study is indicated due to increased severity of depression, the patient will be removed and treated by the study PI (Ronit Kishon) until appropriate referrals will set in place. The threshold for mandatory removal from the study is a CGI Global Improvement score of 6 or 7 (worse to very much worse). Such ratings at any evaluation would prompt premature termination.

However, clinicians and patients can end the study at any time; i.e. a CGI-GI score > 6 is not required to remove a patient from the study.

Assessment Instruments

Create a table or give a brief description of the instruments that will be used for assessment
Screening Visit:
Structured Clinical Interview for DSM-V (SCID-V) (2 hours) Iowa Personality Disorder Screen (7 minutes)
Global Impressions Index: Severity Scale (CGI) (5 minutes)

Total time = 2 hours 12 minutes

Baseline Visit
HAM-D (15 minutes)
CGI - Severity (1 minute)
Beck Depression Inventory-II (BDI-II) (5 minutes)
Twenty Item Toronto Alexithymia Scale (TAS-20) (5 minutes) Work and Social Adjustment Scale (5 minutes)
Reasons for Living Scale (5 minutes)
Psychological Mindedness Scale (PM Scale) (5 minutes)
The Balanced Index of Psychological Mindedness (5 minutes)
The Self Reflection and Insight Scale (5 minutes)
The Ruminative Response Scale (RRS) (5 minutes)
The Mindful Attention Awareness Scale (MAAS) (5 minutes) Five Facet Mindfulness Questionnaire (FFMQ) (5 minutes) Self Compassion Scale (SCS) (5 minutes)
Self Compassion Scale (SCS) (5 minutes)
Structured Clinical Interview for Psychological Mindedness (SCIP-M). (45 min)
Parental socioeconomic status (SES) (15 min)
Emotional Regulations Questionnaire (ERQ) (15 min)
Brunel Lifestyle Physical Activity Questionnaire (10 min)
The Pittsburgh Sleep Quality Index (10 min)
Social Adjustment Scale (10 min)
EEG and cognitive tests administered under Jurgen Kayser's protocol #6559R (2.5 hrs).

Total time = 4 hours and 30 minutes

During-Session Process Measures (week 2, 6, 12)
Treatment credibility and Expectancy of Improvement Scale (3 minutes)
The Working Alliance Inventory (7 minutes)

Total time =10 minutes

Evaluation of depressive symptoms every 3 weeks:
HAM-D (10 minutes)

Mid and Post-treatment Assessments (week 6, 12)
HAM-D (10 minutes) CGI - Severity (2 minutes)
Beck Depression Inventory-II (BDI-II) (5 minutes)
Twenty Item Toronto Alexithymia Scale (TAS-20) (5 minutes)
Work and Social Adjustment Scale (5 minutes)
Reasons for Living Scale (5 minutes)
Psychological Mindedness Scale (PM Scale) (5 minutes)
The Balanced Index of Psychological Mindedness (5 minutes) The Self-reflection and Insight Scale (5 minutes)
The Ruminative Response Scale (RRS) (5 minutes)
The Mindful Attention Awareness Scale (MAAS) (5 minutes) Five Facet Mindfulness Questionnaire (FFMQ) (5 minutes)
Self-Compassion Scale (5 minutes)
Structured Clinical Interview for Psychological Mindedness (SCIP-M). (45 min)
Parental socioeconomic status (SES) (15 min)
Emotional Regulations Questionnaire (ERQ) (15 min)
Brunel Lifestyle Physical Activity Questionnaire (10 min)
The Pittsburgh Sleep Quality Index (10 min)
Social Adjustment Scale (10 min)
EEG and cognitive tests administered under Jurgen Kayser's protocol #6559R (2.5 hrs).

Total time = 4 hour 30 minutes

Please attach copies, unless standard instruments are used

Research Related Delay to Treatment

Will research procedures result in a delay to treatment?
No
Treatment to be provided at the end of the study
At the end of study participation, non-remitters will be offered appropriate referrals as clinically indicated. They will discuss it with their therapist, and after the end of sessions will continue to meet Dr. Kishon as needed, until an appropriate referral will put in place.
Remitters will discuss potential referrals with the therapist in the last 3 weeks of treatment. During this period, and at the end of treatment, Dr. Kishon will be available to meet with the patient to consult on the nature of the referral. After the subject concludes where to be referred, the project coordinator of the

study will provide a list of referrals to the patient and will remain in contact so as to follow how the patient integrates with the new treatment place.

Clinical Treatment Alternatives

Clinical treatment alternatives
CBT is an accepted and empirically supported form of treatment for depression, and thus is not considered experimental. Non-specific supportive treatment was also found to be effective for depression through in smaller percentages than CBT. Subjects may want to be medicated for their depression in which case they will appropriately be referred to during the screening/evaluation process.

Risks/Discomforts/Inconveniences

Risks that could be encountered during the study period
Assessment procedure: Subjects could develop mild to moderate emotional discomfort or frustration associated with psychiatric interviewing, or filling out questionnaires. Only experienced clinicians will administer these interviews; they are well trained and experienced in recognizing and dealing with emotional discomfort. Also, subjects will be informed that they can end the meeting at any time, or skip uncomfortable questions. Unless such skipped questions prevent a diagnosis or other clinical issues from being adequately assessed, the subject will remain study eligible. Subjects' mood symptoms may also worsen during treatment. See procedures for minimizing risk in the next section.

CBT and nonspecific supportive treatments: Subjects may exhibit subjective distress during CBT or supportive treatment, which, if it occurs, is likely to be mild and transient. We will closely monitor reactions and address them therapeutically. In the unlikely event that a subject manifests unusually high levels of distress, the PI will withdraw him or her from the study and provide the necessary support until a referral will be in place.
Describe procedures for minimizing risks
Careful medical and psychiatric screening will be conducted to identify subjects with elevated risk for potential adverse effects. As examples, participants for whom suicide is considered a significant risk will be excluded from the study.

Any subject who evidences significant clinical deterioration, such as unusually high level of distress or suicidality at significant risk during CBT or supportive treatment, will be removed from the study and treated with alternative and appropriate clinical care at the DES until referral plan is set in place. Signs of deterioration will be monitored weekly by the protocol therapist, study PI, and a psychiatrist at the DES as needed. At each visit during the 12 weeks of CBT and control group, the treating clinician will monitor, via clinical interview and various assessment measures for signs of increased severity of depression. If in the judgment of the clinician and the PI, removal of a participant from the study is indicated due to increased severity of depression, the patient will be removed and treated until the referral is in place, or clinically indicated. The threshold for mandatory removal from the study is a CGI Global Improvement score of 6 or 7 (worse to very much worse). Such ratings at any evaluation would prompt premature

termination. However, clinicians and subjects can end the study at any time; i.e., a CGI-GI score > 6 is not required to remove a subject from the study.

Precautionary measures will be taken to prevent the transmission of COVID-19 in experimental processes. The changes we proposed in the amendment section will minimize the subjects' infection risk for COVID-19. We are minimizing risks of in person visits by conducting 12 virtual CBT sessions and 12 virtual control group therapy sessions. All self-report measures and interviews measures will be done remotely.

Methods to Protect Confidentiality

Describe methods to protect confidentiality

All collected data will be kept confidential and used for research purposes only. Patient charts and hard copy data will be held in locked file cabinets and identifiable only by number and a naming code of initials. Access to research records is restricted to research staff and regulatory authorities. No research participant's identifying data will be published. All electronic records will be kept confidential to the extent permitted by law. Participant's names and other personal identifying information will be stored in an electronically secure database at the New York State Psychiatric Institute on a registered password-protected computer. The information may be accessed only by the PI and the research coordinator. The study Data Manager will manage a data file on SPSS that has all study data without identifying information. Patients' names will not be entered into the study database, and each will be uniquely identified only by the ID number. All data will be entered once, but checked and audited by two different staff members. When data entry is complete, all data will be cleaned and rechecked for accuracy before being backed up on an encrypted flash drive. Any data that is transmitted electronically will be fully encrypted and password protected.

Due to remote administration of intake evaluation procedure, therapy sessions, clinical interviews through sessions, and self-report measures at pretreatment, mid-treatment, and post-treatment, confidentiality is protected through HIPAA-compliant videoconferencing and web-based platforms, and encrypted email communication.

Will the study be conducted under a certificate of confidentiality?
No

Direct Benefits to Subjects

Direct Benefits to Subjects
All participants will receive a complete medical and psychiatric evaluation, and the PI will share the necessary information with the participant.
Benefits to participants are direct (i.e., treatment of depression; amelioration of symptoms). Also, some participants may experience relief of their depressive symptoms.

Compensation and/or Reimbursement

Will compensation or reimbursement for expenses be offered to subjects?
No

References

References

Baer, R. A., Smith, G. T., Hopkins, J., Krietemeyer, J., & Toney, L. (2006). Using Self-Report Assessment Methods to Explore Facets of Mindfulness. Assessment, 13(1), 27-45. doi: 10.1177/1073191105283504

Barnard, L. K., & Curry, J. F. (2011). Self-compassion: Conceptualizations, correlates, & interventions. Review of General Psychology, 15(4), 289-303. doi: 10.1037/a0025754

Beitel, M., Ferrer, E., & Cecero, J. J. (2005). Psychological mindedness and awareness of self and others. Journal of Clinical Psychology, 61(6), 739-750. doi: 10.1002/jclp.20095

Brown, K. W., & Ryan, R. M. (2003). The benefits of being present: Mindfulness and its role in psychological well-being. Journal of personality and social psychology, 84(4), 822-848. doi: 10.1037/0022-3514.84.4.822

Bruder, Kayser, J., Tenke, C.E. (2012). Event-related brain potentials in depression: Clinical, cognitive and neurophysiologic implications. In S.J. Luck & E.S. Kappenman (Eds.), The Oxford Handbook of EventRelated Potential Components (pp. 563-592). New York: Oxford University Press.

Conte, H. R., Ratto, R., & Karasu, T. B. (1996). The Psychological Mindedness Scale: Factor structure and relationship to outcome of psychotherapy. Journal of Psychotherapy Practice and Research, 5, 250–259.

Diedrich, A., Grant, M., Hofmann, S. G., Hiller, W., & Berking, M. (2014). Self-compassion as an emotion regulation strategy in major depressive disorder. Behaviour Research and Therapy, 58, 43-51. doi: http://dx.doi.org/10.1016/j.brat.2014.05.006

Farber, B. A., & Golden, V. (1997). Psychological-mindedness in psychotherapists.
In M. McCaUum & W. Piper (Eds.), Psychological- mindedness. Hillsdale, NJ: Erlbaum.

Fenigstein, A., Scheier, M.F., & Buss, A.H. (1975). Public and private self- consciousness: Assessment and theory. Journal of counseling and Clinical Psychology, 43, 522-527.

Grant, A. M. (2001). Rethinking psychological mindedness: Metacognition self-reflection and insight. Behavior Change, 18(1), 8-17.

Grant, A. M., Franklin, J., & Langford, P. (2002). The self-reflection and insight scale: A new measure of private self-consciousness. Social Behavior and Personality: an international journal, 30(8), 821-835.

Hollon, S.D., Shelton, R. C., Wisniewski, S. et al. (2006). Presenting characteristics of depressed outpatients as a function of recurrence: preliminary findings from the STAR*D clinical trial. Journal of Psychiatric Research, February 40 (1), 59-69

Kayser, J., Tenke, C.E., Abraham, K.S., Alschuler, D.M., Alvarenga, J.E., Skipper, J., Warner, V., Bruder, G.E., & Weissman, M.M. (2017). Motivated attention and family risk for depression: Neuronal generator patterns at scalp elicited by lateralized aversive pictures reveal blunted emotional responsivity. NeuroImage: Clinical, 14, 692-707.

MacBeth, A., & Gumley, A. (2012). Exploring compassion: A meta-analysis of the association between self-compassion and psychopathology. Clinical Psychology Review, 32(6), 545-552. doi: http://dx.doi.org/10.1016/j.cpr.2012.06.003

Neff, K. D. (2003). The development and validation of a scale to measure self-compassion. Self and Identity, 2(3), 223-250.

Nolen-Hoeksema, S. (2000). The role of rumination in depressive disorders and mixed anxiety/depressive symptoms. Journal of Abnormal Psychology, 109(3), 504-511. doi: 10.1037/0021-843x.109.3.504

Nyklíček, I., & Denollet, J. (2009). Development and evaluation of the Balanced Index of Psychological Mindedness. Psychological Assessment, 21, 32–44.

Trapnell, P. D., & Campbell, J. D. (1999). Private self-consciousness and the five-factor model of personality: Distinguishing rumination from reflection. Journal of personality and social psychology, 76(2),284-304. doi: 10.1037/0022-3514.76.2.284

Treynor, W., Gonzalez, R., & Nolen-Hoeksema, S. (2003). Rumination reconsidered: A psychometric analysis. Cognitive Therapy and Research, 27(3), 247-259. doi: 10.1023/a:1023910315561

Watkins, E. R. (2008). Constructive and unconstructive repetitive thought. Psychological Bulletin, 134(2), 163-206. doi: 10.1037/0033-2909.134.2.163

Uploads

Upload the entire grant application(s)
4375306_Egrant_Science4IRB (1).pdf
Upload copy(ies) of unbolded Consent Form(s)
Consent summary and form undbolded 9_27_2020.pdf
Upload copy(ies) of bolded Consent Form(s)
Upload copy(ies) of recruitment materials/ads to be reviewed
RecruitMe text bolded Aug 26 2020 (1).pdf
RecruitMe text unbolded Aug 26 2020 (1).pdf
Upload copy(ies) of the HIPAA form
HIPPA Form October , 2017.pdf
Upload any additional documents that may be related to this study

Twelve Weeks of Cognitive Behavior Therapy (CBT) vs. Supportive Therapy for Depression

Sponsor:	Pilot study
Enrolling:	Male and Female Patients
Study Length:	15 Weeks
Clinic Visits:	12 virtual sessions online, 2 actual visits to New York States Psychiatric Institute
Age Range:	Between 18 and 65 years old
IRB Number:	6806R
U.S. Government ID:	NCT01868711
Contact:	Ronit Kishon Ph.D.: 646 724 4171/ ronit.kishon@nyspi.columbia.edu

Additional Study Information:

This study offers 12 individual free sessions of Cognitive Behavior Therapy (CBT) or Supportive Therapy to people who suffer from depression. All sessions will be administered virtually using HIPAA-compliant video teleconferencing. Participants must have access to a device on which they can access internet and video conferencing capabilities to participate. **Besides the virtual, sessions participants will need to come in person once for a urine and blood test as part of the evaluation (protocol #6669) and two times for an electroencephalogram (EEG) test (protocol #6559) before and after the 12 virtual sessions.** You should exercise caution when traveling in public and follow public health guidelines, such as wearing masks in public and avoiding crowds. It is important for you to stay informed about public health recommendations and guidelines regarding COVID-19, such as those issued by the Centers for Disease Control (CDC.gov) and local government guidelines and directives. If you have questions about how you will travel for appointments or do not feel safe traveling, please let us know, and know that you can call to reschedule visits

CBT is a well-established psychotherapy for depression. The primary goal of CBT is to provide specific tools and methods of depression management. The primary goal of supportive psychotherapy is to strengthen the patient's ability to cope effectively with various life stressors.

The purpose of this research study is to learn which psychophysiological and psychological variables predict who will benefit from each treatment and how these variables may change throughout therapy.

Participants are randomized to one of these groups and are required to fill out measures that assess various psychological variables at three-time points through 12 weeks of treatment in

addition to smaller measures throughout the treatment. These measures will be filled out online using HIPPA-compliant platforms. We will assist you in accessing and filling out those measures online.

We plan to recruit 60 participants with depression who will complete the psychotherapy, study forms, and EEG. This research is funded by the National Institute of Mental Health.

Twelve Weeks of Cognitive Behavior Therapy (CBT) vs. Supportive Therapy for Depression

Sponsor:	Pilot study
Enrolling:	Male and Female Patients
Study Length:	15 Weeks
Clinic Visits:	12 virtual sessions online, 2 actual visits to New York States Psychiatric Institute
Age Range:	Between 18 and 65 years old
IRB Number:	6806R
U.S. Government ID:	NCT01868711
Contact:	Ronit Kishon Ph.D.: 646 724 4171/ ronit.kishon@nyspi.columbia.edu

Additional Study Information:

This study offers 12 individual free sessions of Cognitive Behavior Therapy (CBT) or Supportive Therapy to people who suffer from depression. All sessions will be administered virtually using HIPAA-compliant video teleconferencing. Participants must have access to a device on which they can access internet and video conferencing capabilities to participate. Besides the virtual, sessions participants will need to come in person once for a urine and blood test as part of the evaluation (protocol #6669) and two times for an electroencephalogram (EEG) test (protocol #6559) before and after the 12 virtual sessions**.** You should exercise caution when traveling in public and follow public health guidelines, such as wearing masks in public and avoiding crowds. It is important for you to stay informed about public health recommendations and guidelines regarding COVID-19, such as those issued by the Centers for Disease Control (CDC.gov) and local government guidelines and directives. If you have questions about how you will travel for appointments or do not feel safe traveling, please let us know, and know that you can call to reschedule visits

CBT is a well-established psychotherapy for depression. The primary goal of CBT is to provide specific tools and methods of depression management. The primary goal of supportive psychotherapy is to strengthen the patient's ability to cope effectively with various life stressors.

The purpose of this research study is to learn which psychophysiological and psychological variables predict who will benefit from each treatment and how these variables may change throughout therapy.

Participants are randomized to one of these groups and are required to fill out measures that assess various psychological variables at three-time points through 12 weeks of treatment in

addition to smaller measures throughout the treatment. These measures will be filled out online using HIPPA-compliant platforms. We will assist you in accessing and filling out those measures online.

We plan to recruit 60 participants with depression who will complete the psychotherapy, study forms, and EEG. This research is funded by the National Institute of Mental Health.

OMB Number: 4040-0001
Expiration Date: 10/31/2019

APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)

3. DATE RECEIVED BY STATE	State Application Identifier

1. TYPE OF SUBMISSION*

❍ Pre-application ● Application ❍ Changed/Corrected Application

4.a. Federal Identifier
MH121915

b. Agency Routing Number

2. DATE SUBMITTED
2019-11-15

Application Identifier
PD/2019/01214

c. Previous Grants.gov Tracking Number

5. APPLICANT INFORMATION

Organizational DUNS*: 1672049940000

Legal Name*: Research Foundation for Mental Hygiene, Inc.
Department: 110 NYPI Translational Epidemi
Division:
Street1*: NYPI
Street2: 1051 Riverside Dr
City*: New York
County: New York
State*: NY: New York
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 10032-1007

Person to be contacted on matters involving this application
Prefix: Ms. First Name*: Janelle Middle Name: Rene Last Name*: Greenhill Suffix: MPH
Position/Title: Director of Administration
Street1*: NYPI
Street2: 1051 Riverside Dr
City*: New York
County: New York
State*: NY: New York
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 10032-1007
Phone Number*: 646-774-6500 Fax Number: 646-774-6540 Email: nga@nyspi.columbia.edu

6. EMPLOYER IDENTIFICATION NUMBER *(EIN) or (TIN)** 1141410842A2

7. TYPE OF APPLICANT* M: Nonprofit with 501C3 IRS Status (Other than Institution of Higher Education)

Other (Specify):
Small Business Organization Type ❍ Women Owned ❍ Socially and Economically Disadvantaged

8. TYPE OF APPLICATION*

❍ New ● Resubmission
❍ Renewal ❍ Continuation ❍ Revision

If Revision, mark appropriate box(es).
❍ A. Increase Award ❍ B. Decrease Award ❍ C. Increase Duration
❍ D. Decrease Duration ❍ E. Other *(specify)* :

Is this application being submitted to other agencies?* ❍Yes ●No What other Agencies?

9. NAME OF FEDERAL AGENCY*
National Institutes of Health

10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER
TITLE:

11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT*
Combining Electrophysiological, Behavioral and Psychological Measures to Target Mechanisms of Emotion Processing and Regulation During Cognitive Behavior Therapy in Depression

12. PROPOSED PROJECT
Start Date* Ending Date*
07/01/2020 06/30/2022

13. CONGRESSIONAL DISTRICTS OF APPLICANT
NY-013

SF 424 (R&R) APPLICATION FOR FEDERAL ASSISTANCE

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix: First Name*: Ralf Middle Name: J Last Name*: Kayser Suffix: PhD
Position/Title: Research Scientist Level V-NL
Organization Name*: Research Foundation for Mental Hygiene, Inc.
Department: 110 NYPI Translational Epidemi
Division:
Street1*: NYPI
Street2: 1051 Riverside Dr
City*: New York
County: New York
State*: NY: New York
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 10032-1007
Phone Number*: (646) 774-5207 Fax Number: Email*: jurgen.kayser@nyspi.columbia.edu

15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested*	$445,500.00
b. Total Non-Federal Funds*	$0.00
c. Total Federal & Non-Federal Funds*	$445,500.00
d. Estimated Program Income*	$0.00

16.IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?*

a. YES ○ THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:
DATE:

b. NO ● PROGRAM IS NOT COVERED BY E.O. 12372; OR
○ PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

17. By signing this application, I certify (1) to the statements contained in the list of certifications* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances * and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)

● I agree*

** The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.*

18. SFLLL or OTHER EXPLANATORY DOCUMENTATION File Name:

19. AUTHORIZED REPRESENTATIVE

Prefix: Ms. First Name*: Janelle Middle Name: Rene Last Name*: Greenhill Suffix: MPH
Position/Title*: Director of Administration
Organization Name*: Research Foundation for Mental Hygiene, Inc.
Department: 110 NYPI Facilities and Admini
Division:
Street1*: NYPI
Street2: 1051 Riverside Dr
City*: New York
County: New York
State*: NY: New York
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 10032-1007
Phone Number*: 646-774-6500 Fax Number: 646-774-6540 Email*: nga@nyspi.columbia.edu

Signature of Authorized Representative*
Ms. Janelle Rene Greenhill MPH

Date Signed*
11/15/2019

20. PRE-APPLICATION File Name:

21. COVER LETTER ATTACHMENT File Name:R21KayKis-CoverLetter_2019-11-11.pdf

PROJECT SUMMARY

This R21 application aims to clarify the neurobiological mechanisms by which change occurs during cognitive behavior therapy (CBT) for major depressive disorder (MDD). This hypothesis-driven study will explore the association between the psychological constructs of psychological mindedness (PM) and mindfulness (M) during the time course of CBT for MDD, and its relationship to electrophysiological and behavioral measures of automatic (i.e. stimulus-driven or bottom-up) emotion processing. This objective is motivated by the following rationale: PM and M represent *different* meta-cognitive processes of self-knowledge deemed critical for emotion regulation (ER) and CBT success. Event-related potentials (ERPs) to salient affective pictures reflect different *stages of motivated attention*. Using advanced analytic EEG techniques, we have linked these stages to the *hierarchical activation of 'emotional' brain regions* along the occipitotemporal ventral stream, ranging from preconscious stimulus categorization (right secondary visual cortex, right temporoparietal junction) to conscious appraisal (posterior cingulate cortex, ventromedial cortex). Importantly, blunted ERP responses to emotionally-arousing stimuli have been observed in clinical depression, and hypoactivation of right temporoparietal and dorsolateral prefrontal regions normalize after successful antidepressant or electroconvulsive treatment. A dichotic emotion recognition test, which provides an *auditory* measure of bottom-up emotion processing in form of a left ear (right hemisphere) advantage for recognizing the emotional intonation of speech patterns, has revealed behavioral deficits in MDD patients. Moreover, an *increased* right ear advantage for verbal stimuli (left hemisphere) is seen in CBT responders. Employing a sample of 60 MDD patients randomly assigned to CBT or nonspecific supportive therapy (placebo), we will obtain psychological, electrophysiological, behavioral and clinical outcome measures of response to 12 weeks of CBT in a pre-post treatment design to determine: (1) *when* and *where* in the brain automatic emotion processing is altered by CBT; (2) if changes in emotional responding are moderated or mediated by meta-cognitive processes of self-knowledge; and, (3) if these measures, alone or in combination, have promise as markers of CBT treatment response. Existing ERP and behavioral data for healthy adults (HC) obtained using the same experimental protocols will provide normative (yardstick) data. This study brings together experienced clinical psychologists and psychiatrists doing treatment and research in depression with investigators having expertise in affective neuroscience and electrophysiological studies in MDD. It will provide a critical new step for outlining the affective-cognitive and neurophysiological mechanisms of ER by which change through CBT occurs. Apart from their theoretical relevance, the findings of this project will also aid in developing novel and more targeted interventions and in identifying patients who may benefit most from CBT for unipolar depression.

PROJECT NARRATIVE

This research aims to elucidate mechanisms through which change occurs during cognitive behavior therapy (CBT) for depression. Assessing meta-cognitive processes of self-knowledge (top-down), electrophysiological and behavioral correlates of emotion processing (bottom-up), and their relation to treatment outcome will provide new insights into the mechanisms of emotion regulation deficits in depression. It will also contribute toward the clinical goal of identifying patients who may benefit most from CBT for unipolar depression.

INTRODUCTION TO REVISED APPLICATION

Reviewers found our proposal to be "significant," "[very] well designed with few, if any, weaknesses," "innovative," "rigorous," and with "potential impact in developing ... biomarkers [of CBT] response." Addressing their comments (*italics, R1-R3*) has strengthened the proposal (multiple changes noted below). This R21 aims to explore the utility of jointly measuring psychological, behavioral, and ERP predictors of CBT outcome in MDD. Studying these predictors in a pre/post design will foster an understanding of the neurocognitive mechanisms underlying CBT.

1. *R1 did not note any weaknesses* but emphasized strengths for all review criteria, including Significance (clinical relevance, examining neurofunctional mechanisms, efficacy of *M*-based psychotherapies), Investigators (methodological excellence/expertise in EEG/CBT, funding/publication track record), Innovation (first to examine the EEG of two meta-cognitive processes in the context of CBT, bridging with ERPs of motivated attention), Approach (sound, detail-oriented, advanced source localization, detailed functional neuroanatomical model linking stages of motivated attention to hierarchical activation of brain regions involved in *ER*), and Environment (excellent).

2. *Approach: The methodology and stimulus paradigms are somewhat difficult to disseminate (R2)*. Self-report, EEG and behavioral measures are feasible (and cost-effective) in clinical practice. If this R21 is successful, larger (multi-site) studies will need to determine if these measures are useful for personalized medicine applications.

3. *Significance: Metacognitive process of self-observation defined as [M] and [PM] are abstract concepts measured by self-report and it is unclear how they map onto RDoC (R3)*. Self-report metrics are well-established, regularly used in cognitive neuroscience and psychiatry, have explanatory and predictive utility, and are essential for understanding individual differences in disposition, affect, health, and psychopathology. RDoC recognizes *Self-Report* as a reliable and valid research tool, including it as a *Unit of Analysis* for most constructs and domains [167]. Self-knowledge – we now use this term in lieu of self-observation – is a specific construct within the RDoC *Social Processes* domain. *M* and *PM* measure – via validated self-report instruments [199] – different aspects of self-knowledge related to *ER* and CBT [33]. Notably, *M* increases emotional awareness (discrimination, responsivity) [44, 89, 230].

4. *Significance/Approach: The investigators lay out a case for brain regions involved in [ER] yet do not directly assess changes in these areas for target engagement (R3); The biological model of how the proposed tasks would probe a neural circuit of interest for [M] is unclear (R2)*. To the contrary, we outlined our prior findings revealing 3 distinct emotional ERPs that map onto key nodes of emotional brain circuits and known neurofunctional hierarchy (now circled in **Fig. 4E**): N2 sink = extrastriate visual cortex/rTPJ, P3 source = posterior cingulate cortex, CP source = medial-temporal cortex (AI, amygdala). These activations are reflected in the corresponding CSD-tPCA factor scores that yielded the source inverse tomographies, which in turn represent measures of these emotional brain targets (see new **Fig. 5**). We will determine if pre/post CBT activation changes in these target regions are related to treatment success. Further, neural circuits specific to *M* are still not well established and are not a direct focus of this proposal. Rather, we aim to investigate putative neural circuits involved with CBT and CBT response.

5. *Investigators: Dense writing style, many acronyms. PIs could communicate their ideas in a clearer, crisper way (R3)*. Concise writing and use of acronyms is de facto mandated by R21 page limits to outline a complex proposal spanning cognitive psychology, affective neuroscience, human electrophysiology, psychopathology, and clinical practice. To aid comprehensibility, we (i) restructured/simplified the text, (ii) updated the citations, and included (iii) an acronym table (***A2***), (iv) a conceptual model (**Fig. 5**), and (v) a timeline for outcome assessment (**Fig. 6**).

6. *Innovation: Concepts and methods are not novel nor cutting edge and the project seems like an incremental advance to the field (R3)*. The innovation of our proposal lies in the joint consideration of concepts/methods spanning several research disciplines. While ***M*** has been linked to ER and CBT efficacy, ***PM*** has rarely been studied in a clinical sample, let alone together with ***M*** and affective EEG tasks. There have been few studies of emotional ERP modulation in MDD patients receiving CBT but recent ERP [209-210] and fMRI findings [63] underscore the clinical utility of neurobiological assessments for negative valence systems as predictors of treatment outcome. The neural circuits and mechanisms involved with established CBT effects are not well understood; little is known how CBT affects immediate, automatic (bottom-up) detection of salience and its further processing downstream. These early and later processing stages are difficult to disentangle with fMRI. The combined study of these promising measures in a longitudinal design is a major leap forward and not incremental. If successful, a larger R01 application will be the logical next step. Neurobehavioral research has recently been subject to intense scrutiny with respect to its reproducibility. Thus, it is critical to rely on *proven* experimental paradigms that can be creatively utilized in a mechanistic clinical trial. Unlike research applications in which all aspects are new and unproven, we judge our current proposal to be a stronger model for rigor, one that will likely yield substantive advances.

7. *Approach: [M] and [PM] constructs as a proxy for self-observation; the evidence for these measures is not as robust as EEG/ERP or EHT task (R3)*. The ***M*** construct received considerable development over the last 20 years, and ***M*** metrics show adequate or good reliability, validity, and predictive utility. ***PM*** received less attention but shows promise as a construct for predicting CBT response, indexing self-awareness in that differs from ***M***. We also added a robust measure of ***ER*** (ERQ [82]). This will provide new data on their relations to neurocognition and CBT.

Lastly, our preliminary ***PM*** findings (***A3***) have now been accepted for publication in the *Int. J. of Cogn. Ther.* [141].

SPECIFIC AIMS

Dysfunction in emotion regulation (ER) is considered to be at the core of mood disorders. This dysfunction is characterized by deficits in emotion-related processing involving abnormal activations of specific brain regions [81, 243] that overlap with core modules identified by affective neuroscience for emotion processing and self-awareness [180, 181] (see section ***A4*** below). Activity in these brain regions is modulated by prefrontal regions responsible for up- and down-regulation of emotional processes [65, 73, 213]. An improved understanding of these processes would be of great value in the study and treatment of mood disorders.

Cognitive behavior therapy (CBT) is a widely-used and evidence-based set of clinical interventions that focus on the importance of cognitive processes for ER [95]. CBT is designed to alleviate the suffering associated with mood and other psychiatric disorders [163, 206]. In unipolar depression, CBT is effective for 40% to 60% of patients. Still, clinical practice suffers from a lack of specific understanding about who may benefit, which would increase response rates and decrease costs by targeted referrals. Research has focused less on comparative efficacy between different modules of CBT for depression [52, 96, 153, 163] but rather on key components of therapeutic interventions to relieve the suffering of individual patients. Aligning with NIMH initiative for personalized medicine [61, 197, 238], researchers have begun studying moderator variables that target change mechanisms and can be used to characterize patients who may benefit from a specific CBT module [46]. The meta-cognitive process of self-knowledge, as measured by the constructs of *psychological mindedness (PM)* [78] and *mindfulness (M)* [241], is thought to be associated with ER and successful CBT, but the neural basis of these meta-cognitive processes is not well understood [166, 241]. The challenge is to (i) target (and index) a mechanism for depression associated with biomarkers having established reliability and construct validity [142, 197], as recommended by the NIMH RDoC initiative [167], (ii) identify meaningful moderators, and (iii) examine their joint value for predicting clinical response to CBT.

We developed an *emotional hemifield task (EHT)*, in which negative or neutral pictures are briefly presented to the left or the right visual field to target right temporoparietal and occipital cortex (ventral attention network [43]) involved in bottom-up salience detection [123, 129] (***A5***). We found that the late positive potential (LPP), a prominent event-related potential (ERP) over parietal regions that is greater to negative vs. neutral stimuli, is reduced in major depressive disorder (MDD) [123]. We also showed that these emotional ERP effects reflect brain activations of the ventral visual pathway during stages of salience processing, with maximal activations in the right occipitotemporal (212 ms; N2), bilateral posterior cingulate (385 ms; P3) and bilateral inferior temporal cortex (630 ms; LPP) [129]. These emotional effects were reduced in individuals at risk for or with a lifetime diagnosis of MDD [130] (***A7***). Individuals with MDD also had a reduced right hemisphere advantage during a dichotic *emotion recognition test (ERT)* [23] (***C6***). Recent magnetoencephalography (MEG) studies reveal that parietal hypoactivation during emotion processing in MDD patients [123, 164] before electroconvulsive [244] or monopharmacotherapy [60] normalized after successful treatment. This suggests neuronal activation patterns indicative of dysfunctional emotion processing in a fronto-parieto-temporal neural network are a possible biomarker of treatment outcome, including CBT [209]. However, although fMRI evidence links conscious ER to CBT success [191, 192], there are no *longitudinal* studies of whether clinical response to CBT is likewise associated with normalization of ERPs to motivationally salient stimuli.

The focus of this exploratory/developmental R21 is to begin research aimed at elucidating mechanisms underlying CBT [29] by assessing the association between: (1) *motivated attention/perception* [195], as measured by ERP [123, 129] and behavioral [23] responses to emotional stimuli; (2) the meta-cognitive process of self-knowledge, as differentially reflected by trait PM [15, 78] and M [38, 91]; and (3) the clinical response to CBT vs. no CBT in a pre-post treatment design. Basic elements of CBT focus on metacognitive processes of self-knowledge that affect ER [94, 173]. PM and M (i) entail different aspects of self-knowledge, and (ii) both are linked to processes that enhance ER, but the underlying neurophysiological mechanisms are poorly understood [84, 91, 225, 241]. This mechanistic study is the first to bring together psychological, behavioral and ERP measures to better understand the neurophysiology of emotion processing in MDD and to evaluate the potential of these measures, alone or jointly, as markers of CBT outcome. Our **3 specific aims** and a fourth exploratory aim (and hypotheses [H#]) are to:

1. measure ERPs during the EHT in MDD *before* CBT or nonspecific supportive therapy (referred to here as placebo [PBO] [152]), using existing data of healthy adults as a yardstick: (***H1***) emotional ERP effects (amplitude, asymmetry) [129] will be reduced in MDD [60, 123]; (***H2***) their extent will vary with CBT response [192, 209];
2. also measure ERPs during the EHT in MDD *after* CBT/PBO: (***H3***) blunted emotional ERPs will be persistent (stable) in nonresponders, whereas (***H4***) blunted emotional ERPs will ameliorate with successful CBT [244];
3. use the ERT to provide a behavioral measure of the right hemisphere bias (left ear advantage; LEA) for emotion processing: (***H5***) LEA will be reduced in MDD at baseline [23], particularly in CBT responders; (***H6***) LEA will normalize after successful CBT; (***H7***) LEA will be correlated with asymmetric emotional ERP effects of N2;
4. *[exploratory]* obtain measures of PM/M/ER before, during and after treatment as important mediators of CBT outcome [78, 141]: (***H8***) MDD scoring high in PM/M/ER will be more likely to selectively respond to CBT but not improve with PBO; (***H9***) explore if and how PM/M/ER are associated with emotional ERPs and LEA pre-/post-treatment; (***H10***) PM/M/ER moderate or mediate the association of ERP/LEA measures with CBT outcome.

A. SIGNIFICANCE

A1. Scientific Premise. *Cognitive behavior therapy (CBT)* is an effective [29,62,154] and widely-studied psychotherapy for adult major depressive disorder (MDD) [47]. Meta-analyses even show CBT to be somewhat superior to anti-depressants in adults [29]. However, ~16% of CBT patients prematurely drop-out of treatment [41], and 20-45% fail to show clinical improvement [103, 220]. This emphasizes the need for targeting mechanisms through which the change in CBT occurs to characterize patients who may benefit from CBT. *Emotion regulation* (***ER***) plays an important role in many mental disorders, including MDD [1, 228, 243]. One proposal [68] considers ***ER*** a transdiagnostic factor [207] that maps directly onto the NIMH *Research Domain Criteria (RDoC)* framework [68,167], serving as a unique domain that bridges all others (**Fig. 1**). CBT is believed to consist of basic treatment elements that focus on cognitive processes for ***ER*** [94]. In fact, specifically enhancing ***ER*** skills has been shown to improve the efficacy of CBT for MDD [16]. Therefore, a **joint consideration** of measures from **clinical psychology** and **affective neuroscience** may shed further light on the cognitive processes and neurophysiological mechanisms that underlie successful CBT in MDD.

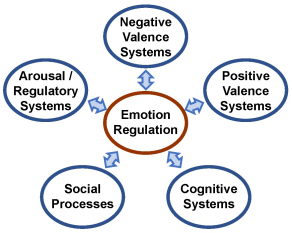


Fig. 1. ***ER*** within RDoC [167].

A2. Self-Knowlege as a Key to ER and CBT. Self-knowledge, a cognitive process presumed to underlie effective ER [11, 187], constitutes an important element of CBT [193]. Dispositional *mindfulness* (***M***) and *psychological mindedness* (***PM***) are two distinct, yet related, constructs reflecting meta-cognitive processes of self-knowledge [15, 78, 79, 98]. ***M*** consists of (I) *attention* directed toward present-moment sensations, emotions, thoughts and actions, and (ii) their non-judgmental, non-reactive *acceptance* [7,45,198]. Over recent decades, ***M***-based interventions have increased exponentially [76], with efficacy in preventing MDD relapse [146, 156, 215] and treating residual symptoms [138]. Separately, ***PM*** has long been studied in psychology as a meta-cognitive process of self-awareness. ***PM*** refers to the motivation of using one's intellectual and affective abilities to gain better self-understanding of the relationship between inner thoughts, feelings, and behaviors [79], ultimately recognizing what causes one's experiences and behaviors [78, 87]. ***M*** *and* ***PM*** overlap with *self-knowledge*, a sub-construct of the RDoC domain *Social Processes*: the ability to make judgments about one's current cognitive or emotional internal states, traits, or abilities [167]. Both ***M*** and ***PM*** were shown to enhance ***ER***, which can occur at any stage during emotion generation [68]. In both clinical and non-clinical samples, ***M*** has been linked to ***ER*** [219, 237]. For instance, non-judgmental awareness of negative states results in increased willingness to experience negative emotions, reduced reactivity to emotional stimuli and situations, increased stability of negative emotions over time, and – critically – deactivation of emotional brain regions (e.g. amygdala) early in the time course of affective processing [145, 213]. ***M*** may enhance ***ER*** by increasing meta-cognitive insight (awareness) in which cognition about life events becomes more accurate [215], thus preventing relapse or reducing symptoms [36, 203, 215]. However, the mechanisms of ***M*** require further study [36, 215]. ***PM*** has been hypothesized to play an important role in the development of adaptive ***ER*** [172] and in sustaining ***ER*** throughout life. Studies with mostly non-clinical samples have linked ***PM*** to emotional awareness, self-regulation, self-monitoring, and cognitive flexibility [15, 35, 71, 78, 90], and enhanced overall insight and behavior adaptation [168]. Although the role of meta-cognition in vulnerability to mood disorders and their alleviation via CBT has been recognized [9, 204], empirical studies have only considered ***M*** but not ***PM***.

ACC	anterior cingulate cortex
AI	anterior insula
BDI	Beck depression inventory
CBT	cognitive behavior therapy
CSD	current source density
CTS	cognitive therapy scale
DL	dichotic listening
EHT	emotional hemifield task
ER	emotion regulation
ERQ	emotion regulation questionnaire
ERT	emotion recognition test
ERP	event-related potential
FFMQ	five-facet mindfulness questionnaire
HC	healthy controls
HRSD	Hamilton rating scale for depression
LEA	left ear advantage
LH	left hemisphere
LPP	late positive potential
M	mindfulness
MAAS	mindful attention awareness scale
MDD	major depressive disorder
MMN	mismatch negativity
tPCA	temporal principal component analysis
PA	perceptual asymmetry
PBO	placebo
PCC	posterior cingulate cortex
PFC	prefrontal cortex
PA	perceptual asymmetry
PM	psychological mindedness
PMS	psychological mindedness
RDoC	research domain criteria
REA	right ear advantage
RH	right hemisphere
rTPJ	right temporo-parietal junction
SCID	structured clinical
SRIS	self-reflection and insight scale
SES	socioeconomic status
TAS	Toronto alexithymia scale
Tx	treatment

A3. PM and CBT Outcome. In the first study in adult MDD, we found that ***PM*** correlated with symptom improvement during treatment (Tx) [140, 141]. 71 patients (32 men; age: 42.5 ±13.7) received 14 CBT sessions and completed the *Beck Depression Inventory (BDI)* [12], the *Hamilton Rating Scale for Depression (HRSD)* [88], *Psychological Mindedness Scale (PMS)* [40], and the *Toronto Alexithymia Scale (TAS)* [5] at baseline, wk 8, and post-Tx [141]. Compared to baseline (BDI: 30.3 ±10.1; HRSD: 14.6 ±4.6), 29% remitted (***C3***). Baseline ***PM*** was associated with remission (generalized linear mixed model, $p = 0.03$) and also post-Tx BDI (ß = -12.2, $p = 0.02$) and HRSD (ß = -8.4, $p = 0.01$, Cohen's f [39] = 0.421, a large effect) [141]. Post-Tx changes in PMS total score, and – dependent on Tx time point – in all PMS subscales (***C4***), were associated with lowered symptoms. These findings strongly suggest that ***PM*** affects ***ER*** processes during CBT treatment of depression. Alexithymia, while not a predictor of success or remission, covaried with HRSD and was alleviated throughout Tx among remitters. Thus, assessing ***PM*** together with alexithymia identified patients that may benefit most from CBT. Further study of ***PM*** in concert with ***M*** will assess a broader spectrum of meta-cognition and better delineate the psychological mechanisms and ***ER*** processes underlying CBT adaptation, change and response.

A4. Brain Regions of Affect and ER. Affective neuroscience has framed an outline of the "emotional brain," including the regions highlighted in **Fig. 2** [180, 189]. Notably, activity in these regions 1) changes with emotion processing or during affective states, including self-awareness [92], and 2) is also indicative of cognitive operations, such as top-down attentional control [166, 180, 213]. There is growing evidence that these regions are critical for ***ER*** [166] and ***M***

meditation [66, 241]. Activity of core emotional regions (Amygala, ACC, PCC, AI) is modulated by multiple prefrontal regions, allowing up- and down-regulation of emotional processes [93, 166 241]. While emotional brain activation may differ between men and women [211], sex effects are complex and inconsistent [25]. Dysfunctions in affective processing and ***ER*** are posited to be the underlying root deficiency of mood disorders [83, 188]. Deficits in cognitive-affective processing and abnormal activations in these brain regions in response to affective stimuli are key features of MDD [54, 190, 243]. Specifically, behavioral, autonomic, and EEG evidence suggests that MDD is characterized by *hypoactivation* of right temporoparietal cortex [25], which is critically involved in emotional perception [122-123, 164]. The detection of stimulus significance (i.e. valence) is a crucial mechanism for survival, involving basic motivational systems of approach and withdrawal [19, 148]. This requires interactions between affective and cognitive processing systems of the brain [180], which reach conscious awareness when the products of affective and cognitive computations enter working memory [150]. For example, masked objects that are not consciously experienced yield activation of visual cortex but not of parietal and PFC, which are activated for unmasked objects [149]. Salient stimuli of threat or disgust prompt additional activations of affective brain regions (Amygdala, AI) [143, 231, 239], which also do not require conscious awareness (**Fig. 3**) [149]. The right temporoparietal junction (rTPJ) is recognized as a key region for detecting affective significance and modulating associated autonomic arousal [151, 196, 221]. The rTPJ has been linked to a network involving cortical (AI, ACC) and subcortical (Amygdala, Striatum) structures for detecting emotional and reward saliency [43, 196]. Interestingly, inhibition of right dorsolateral PFC increased early (110-170 ms) rTPJ activation selectively to threat [245], underscoring the role of PFC in early emotion processing and ***ER***.

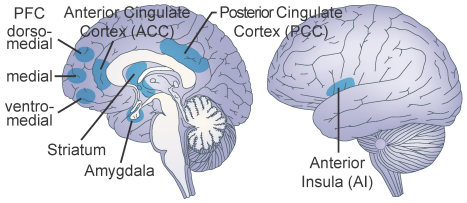


Fig. 2. Brain regions involved in emotion processing and regulation[213]. PFC: Prefrontal Cortex.

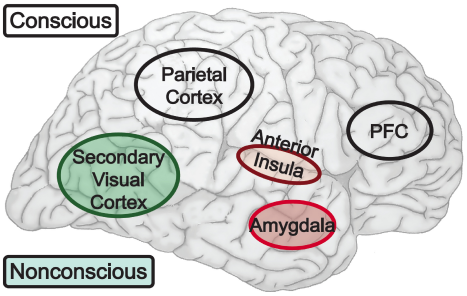


Fig. 3. Brain regions involved in conscious and nonconscious processing of visual stimuli [149].

A5. ERP Correlates of Emotion Processing. Unlike functional neuroimaging (fMRI), electrophysiological measures with ms temporal resolution are ideally suited to characterize consecutive stages of affective processing [176]. The most consistent finding is greater posterior positivity to emotional (pleasant or unpleasant) than neutral pictures. This late positive potential (LPP) emerges around 200 ms after stimulus onset, has a broad centro-parietal maximum, and affects several ERP components (P3, slow wave). It closely covaries with arousal [49, 201], suggesting extra allocation of attentional resources to stimuli that engage motivational brain circuits [18]. While unpleasant compared to pleasant pictures tend to elicit greater LPP ("negativity bias") [102], matching stimuli for motivational saliency eliminates this difference [86]. Thus, a rigorous experimental control of arousal and valence properties is critical [176], particularly when studying other, more focal components (P1 [208], N1 [133], P2 [55], N2 [10025], EPN [202]). The *International Affective Picture System* (IAPS) [20] is widely used to evoke affective reactions. While its normative ratings allow matching of valence and arousal, other features (e.g. content, complexity) remain uncontrolled [56, 122]. This makes it difficult to separate genuine emotional from cognitive effects, particularly when focusing on affective lateralization [122]. To address this challenge, we used highly-controlled stimuli that largely isolate emotional content (negative valence, high arousal [see Fig. 1 in 129]) from other confounds (***C5***). Affect was deliberately limited to negative valence because the least common denominator of emotional lateralization theories is a right hemisphere (RH) advantage for processing negative stimuli [32, 53,]. Our unique stimulus set manipulates negative affect as a single dimension in affective space [148]. It also targets right parietal regions presumed to also mediate autonomic arousal [151, 221]. These stimuli were used in a passive viewing paradigm with lateralized presentations to each visual field to directly probe each hemisphere [160]. This emotional hemifield task (EHT) yielded clear results for HC: (i) greater LPP for negative than neutral stimuli; (ii) early emotional asymmetries over right parietotemporal sites [122, 123]. While similar findings were reported by others [133, 195], laterality has not been a focus of most IAPS ERP studies [176].

A6. Neuronal Generators of Emotion ERPs. fMRI studies reported greater BOLD signal intensity to emotionally-arousing as compared to low-arousing neutral IAPS pictures in lateral-occipital, (right) parietal, and inferior-temporal visual cortex [103, 148]. The LPP has been linked to these activations as well as to other emotion regions (e.g. amygdala, ACC, AI), with subcortical activations also linked to earlier occipitotemporal ERPs [194-195]. These neuroimaging findings agree with ERP source inverse solutions [129, 133]. Using the EHT and an innovative approach that combines CSD [120, 218] and PCA [112, 114, 119] with source localization [178], we dissected the LPP into **consecutive components** reflecting **affective processing along the occipitotemporal ventral stream** [222]. These components identified the regions activated during different stages of aversive picture processing [149] (compare **Fig. 3** above and **Fig. 4E** below). ERPs (72 sites) were recorded during the EHT (N = 152) [129], transformed to reference-free CSDs [120], and submitted to temporal PCA [112] to obtain unbiased, data-driven component measures (***C9***). CSDs were more positive for negative than neutral stimuli at posterior sites (LPP, ~200 to 900 ms; **Fig. 4A**) [129]. These emotion effects were effectively summarized by factors peaking at 212 (***N2 sink***), 385 (***P3 source***) and 630 ms (***centroparietal [CP] source***). Robust emotion effects at lateral parieto-occipital sites were superimposed on all three factors. Importantly, the emotion net effect was not a unitary phenomenon but rather emerged over time and space along

the known visual object processing hierarchy [222], as revealed by distributed source inverses [178] (**Fig. 4E**; ***C9***). The validity of the emotion effects for these CSD-PCA factors was bolstered by robust correlations between self-report ratings and factor scores, indicating that more positive CSDs were associated with greater ratings of arousal ($-0.57 \geq r \geq -0.84$) and valence (i.e. unpleasantness, $0.59 \leq r \leq 0.84$) [129].

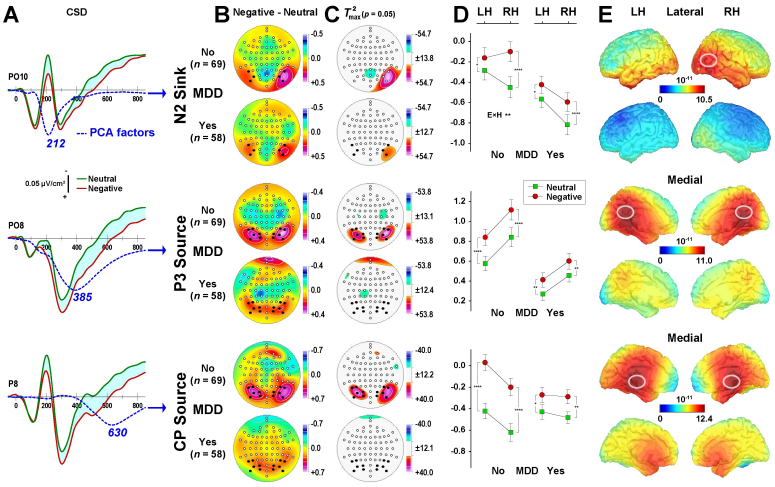


Fig. 4. Emotional effects for individuals with/-out lifetime MDD [130]. **A**: CSD waveforms and factor loadings. **B**: CSD topographies (negative-minus-neutral) corresponding to N2 sink, P3 source, and late centroparietal (CP) source. **C**: Significant differences (permutation tests [125, 157]). **D**: Means (±SEM) at representative sites (marked in B). **E**: Corresponding source inverses (sLORETA [177]) reveal sequential activation of ventral visual pathway regions (i.e. from extrastriate to ventromedial cortex; cf. **Fig. 3**).

A7. Emotion ERPs in MDD. Of vital importance for this proposal, we and others have consistently found reduced emotion ERPs in MDD [72, 123, 164] and at-risk individuals [130, 165]. Emotion ERP amplitude and asymmetry were markedly reduced in MDD patients [123], which was paralleled by abnormal autonomic responses [110, 134]. In a study of family risk for MDD [130, 234], emotion effects during the EHT (***A5***) were evaluated for subgroups of MDD risk (low/high, $n = 53/74$), lifetime diagnosis of MDD (no/yes, $n = 69/58$) or anxiety disorder (no/yes, $n = 54/73$), one at a time, by controlling for age, sex, and the other two subgroups (***C10***). Individuals with an MDD history had reduced emotion effects for P3 source ($\chi^2_1 = 4.26$, $p = .04$; Cohen's [39] $w = 0.183$) and an ensuing centroparietal (CP) source ($\chi^2_1 = 8.36$, $p = .004$; $w = 0.257$; **Fig. 4**, rows 3-6). These late ERP differences, which likely reflect *conscious* emotional appraisal, were preceded by a robust emotion × hemisphere interaction (greater N2 sink emotion effects over right extrastriate visual cortex) in individuals without a lifetime history of MDD, in contrast to those with prior MDD episodes (**Fig. 4**, rows 1-2). These earlier ERP effects presumably reflect *preconscious* categorization of salience (motivated attention) [18, 43, 149]. Overall, all unaffected risk subgroups showed the predicted emotion effects, including the early RH>LH asymmetry, whereas the at-risk subgroups showed deviations of this expected ("healthy") ERP response pattern. Of particular note are the striking similarities between **Figs. 3** and **4E** (marked with white circles).

A8. Emotion ERPs and MDD Tx response. Our ERP findings are in line with evidence of rTPJ hypoactivation during emotion processing in MDD patients [164] before treatment. Two recent studies indicated that blunted responses to emotionally-arousing stimuli may be a possible biomarker of MDD Tx success [60, 244]. In a 4-wk pre/post Tx design with a serotonergic/noradrenergic antidepressant ($N = 25$), baseline hypoactivation of rTPJ and bilateral dorsolateral PFC during IAPS presentations normalized with successful treatment [60]. Effects emerged early (150 ms), suggesting dysfunctional processing (rTPJ) and top-down ***ER*** (PFC) at a preconscious level. Similar effects were reported for 19 patients receiving 4-wk ECT or no intervention [244]. Further, greater LPP to aversive IAPS distractors, indicative of heightened attention to task-irrelevant stimuli (and attenuated top-down control [35]), predicted CBT response in patients with social anxiety ($n = 20$) and MDD ($n = 12$) [209]. Taken together, these findings strongly suggest clinical utility of assessing negative valence systems via ERPs as predictors of Tx outcome [cf. 210].

A9. ER in MDD. Neuroimaging evidence of ***ER*** in MDD [190, 192] also links increased connectivity between limbic and frontal brain regions, specifically the *left* dorsolateral PFC, to MDD treatment response. Reappraisal of aversive IAPS pictures in HC *increased* left PFC and *decreased* amygdala activation and negative experience [174, 183], underscoring the close association between cognitive/behavioral and neural phenomena during ***ER*** [183, 241]. Resting fMRI functional connectivity between cingulate cortex and *left* ventrolateral/medial PFC/AI differentially predicted MDD treatment response to CBT versus an antidepressant [63], suggesting that an increase in these LH connections was associated with remission after CBT. These findings imply different neurobiological mechanisms underlying antidepressant and CBT response in MDD, and longitudinal down-regulation of emotional brain regions via left PFC may be critical for successful CBT [191, 192]. The current proposal will test this prediction.

A10. Dichotic Listening (DL). There is consistent evidence of emotion recognition deficits in MDD [51], particularly for facial expressions but also for the emotional intonation of speech (i.e. prosody) [226]. In a study of MDD risk [23], we used a dichotic emotion recognition test (ERT) (***C6***) that yields a left ear advantage (LEA = RH dominance) for prosody in HC [27, 229]. Individuals with a lifetime diagnosis of MDD had a reduced LEA when compared to those without, consistent with rTPJ ERP deficits for processing emotional stimuli in MDD [123, 164]. Source analysis of mismatch negativity (MMN) to frequency-modulated tones that mimic emotional prosody [106] implicated generators in auditory and medial temporal cortex, particularly AI. Moreover, right-sided MMN was strongly related to emotion recognition. The possible relation of *right* inferior temporal/AI regions to MDD treatment response was found in a study of brain glucose metabolism in patients randomized to CBT or an SSRI [159]. Right-sided hypometabolism was associated with CBT remission but poor SSRI response. This raises the hypothesis that ERT performance (i.e. reduced LEA for prosody) will predict better response to CBT in MDD. In contrast, given our prior findings [25-26, 139]

replicated elsewhere [24], we predict that patients who respond to CBT will also show *increased* right ear advantage (REA = LH dominant) for verbal DL [25 for review]. This provides an opportunity to test for a double dissociation, with CBT responders having reduced emotional LEA (RH) but increased verbal REA (LH).

A11. Conceptual Model and Clinical Relevance. ***M***/***PM*** enhance ***ER*** [161, 223], a putative key mechanism for successful CBT in MDD [16] (**Fig. 5**). The corresponding cognitive (top-down) control of the 'emotional brain' [143, 182, 189] is likely mediated via PFC regions [183, 241, 243], and possibly left-lateralized [23, 25, 63]. These processes and brain activations are probed with the EHT [129] (and also ERT [23]). Specifically, our ERP findings suggest that the EHT paradigm is ideally suited for the current proposal by serving as proxy for different aspects of emotion processing and ***ER***: 1) early, automatic, and preconscious enhanced attention to negative salience involving right extrastriate cortex/rTPJ via feedback projections from ventromedial PFC or amygdala [135, 144, 195], and 2) later, conscious appraisal of negative salience involving PCC and medial-temporal cortex, including AI [150, 239]. Emotion ERPs to aversive pictures are predictive of CBT response in MDD [209]. Our prior findings (***A3***, ***A7***, ***A10***) [130] suggest that *joint*, *longitudinal* consideration of these measures may lead to biomarkers of CBT response [108] and an improved understanding of the underlying neurophysiological mechanisms. Another potential public impact of this work is health providers might be more likely to recommend CBT treatment for depression if made aware of changes in neurophysiological functioning as measured by such biomarkers.

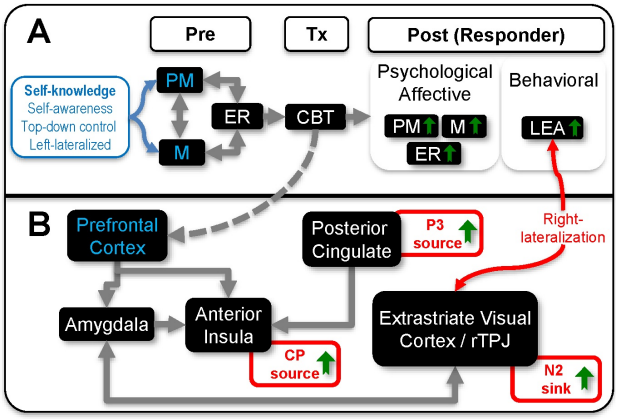


Fig. 5. Conceptual model. A. Meta-cognitive constructs and study design. B. Neural circuits and key brain regions/circuits with associated affective ERP components (red). Green up-arrows indicate predicted change after successful CBT.

B. Innovation

As a necessary first step, this R21 aims to *explore the utility* of *jointly* measuring psychological, behavioral, and electrophysiologic predictors of CBT outcome in MDD to gain a better understanding of the underlying cognitive and neurobiological mechanisms. This proposal is innovative and significant in several ways. First, it examines the prognostic value of *two* psychological constructs (***M***/***PM***) representing *different* meta-cognitive processes that are highly relevant for patients' motivation and ability to dissect feelings, thoughts, and behaviors in CBT [9, 204]. No prior study of MDD patients undergoing CBT has examined this relationship. Studying common CBT characteristics that can expose the target mechanisms underlying behavioral adaptation in CBT is important [163], as two postulated *change principals* [163], *attention* and *cognitive change*, are key to both ***M*** and ***PM***. Second, examining how ERP and behavioral measures of 'motivated' attention (i.e. automatic emotion processing) relate to CBT response holds significant promise for *understanding the neurophysiological mechanisms* of ***ER*** [166, 241] and the brain circuits associated with CBT success. The EHT paradigm serves as a proxy for dissecting processing stages and their brain regions, ranging from preconscious stimulus categorization to conscious appraisal, which will allow a determination of *when* and *where* CBT alters bottom-up emotion processing. Third, the synthesis of psychological (experiential), behavioral, and ERP measures during CBT for MDD is unique. These measures reflect different aspects of emotion processing and are therefore relevant to understanding the mechanisms underlying ***ER and CBT*** [166, 228, 241]. Their combined study will help to understand the (i) *role of emotion- and thought-related self-knowledge and self-awareness in CBT*, and (ii) *their impact on altering the hierarchical (bottom-up) processing of affective salience*. Fourth, these measures, alone or jointly, have shown promise as markers of CBT response, which will inform personalized medicine [61, 197, 238], and their combined study should facilitate the development of biomarkers of CBT success. Fifth, our comprehensive and rigorous analytic strategy takes full advantage of the temporal and spatial resolution of high-density EEG [112-115, 119, 218], without succumbing to known pitfalls of reference-dependent ERPs [120, 171].

C. Approach

C1. Recruitment and Clinical Assessments. While MDD is more common in women [233], in part due to differences in brain development and social factors [136-137, 232], sex has *not* been a predictor or moderator of CBT outcome [48]. Right-handed [175] MDD patients (N = 60; *Beck Depression Inventory [BDI]* [12] $\geq$ 13, *Hamilton Rating Scale for Depression [HRSD]* [88] $\geq$ 14) aged 18 to 65 (~half male) will be recruited through the Depression Evaluation Service at NY State Psychiatric Institute (NYSPI), where treatment with CBT (~50% male) and outcome (~60% responder) rates also do *not* differ by sex. Apart from core demographics (sex, age, race), handedness [175], and parental socioeconomic status (SES) [74, 97], we will assess current/past exercise levels [34, 107, 227] and sleep habits [31] given their known effects on cognition and mood [13, 42, 80, 200]. With a conservative estimate of .9/.8 retention rates at baseline/post-Tx [41], the final sample size will be at least 48 (24/Tx). An initial phone screen followed by on-site clinical evaluation via structured clinical interview (SCID) [69] will ascertain eligibility (see *Human Subjects*). Existing EHT/ERT data for 48 age-, sex- and handedness-matched healthy adults (HC) [23,129] will be used as a baseline yardstick.

C2. Treatment Arms. Patients are randomized to 12 wks, 45-min weekly sessions of standardized CBT for depres-

sion [64], including *cognitive restructuring* and *behavioral activation*, or PBO – nonspecific supportive therapy that includes warmth, genuineness, and empathy [152]. PBO nonresponders may opt to receive CBT after PBO. Both arms are administered by 6 qualified therapists (3 advanced PhD students per academic year) selected by Dr. Kishon and the NYSPI head of psychology, Dr. Laura Mufson. Therapists are (i) trained in a workshop including role-playing for 1 mo on 1 excluded case, and – during the study – supervised during (ii) weekly individual sessions (Dr. Kishon) and (iii) weekly peer meetings. CBT adherence (audiotaped sessions) is assessed by an independent clinical psychologist with the *Cognitive Therapy Scale (CTS)* [240], a reliable 11-item scale [59, 224] measuring the quality of CBT delivery (total ≥ 40). Each therapist treats cohorts of 5 patients (~half male, ~half each arm, ~4 mos/cohort, start next cohort after finishing prior). Up to 2 sessions may be missed so all 12 are completed within 14 wks.

C3. Response and Remission Criteria. We define *response* as a significant reduction of symptoms (≥ 50% from baseline) and *remission* as improvement to asymptomatic within the normal range (HRSD ≤ 7; BDI ≤ 13). To obtain a continuous rather than dichotomous measure of treatment outcome, we will employ a mixed-effects model for all HRSD (every 3 wks) or BDI (weekly) ratings (R software [182]) to compute estimates of each patient's baseline score (i.e. the model's intercept) and the *rate of symptom change* over time (*slope* of HRSD or BDI scores) [131, 182].

C4. Metacognitive Measures. Different facets of ***PM*** will be assessed with the (1) *Self-Reflection and Insight Scale (SRIS; 20 items, 2 subscales)* [79] and (2) *Psychological Mindedness Scale (PMS; 45 items, 5 factors)* [40]. PMS has strong internal consistency (Cronbach's α = .87) [199] and is often used together with the *Toronto Alexithymia Scale (TAS; 20 items, 3 factors)* [5]. The TAS is inversely related to ***PM*** [14] and measures emotional awareness. The TAS has good internal consistency (α = .81) and test-retest reliability (r = .77) [6]. Two widely-used instruments will assess different aspects of ***M***. The *Mindful Attention Awareness Scale (MAAS; 15 items)* [22] measures the present-moment attentional components of ***M***. The MAAS has good internal consistency (α = .82) and corresponding convergent and discriminant validity. MAAS scores were higher in ***M*** practitioners than in matched controls [8, 21]. The *Five-Facet Mindfulness Questionnaire (FFMQ; 39 items)* [7, 8] assesses the daily-life tendency of being mindful. The widely-used *Emotion Regulation Questionnaire (ERQ; 10 items)* [82] assesses the tendency to regulate emotions via *cognitive reappraisal* and *expressive suppression*; both factors have acceptable-to-excellent reliability and validity [162, 186].

C5. Emotional Hemifield Task (EHT). ERPs will be recorded to lateralized presentations (250 ms) of negative and neutral stimuli consisting of 16 closely-matched pairs of pictures depicting facial areas of patients with skin diseases *before* and *after* surgical treatment [123, 129]. Stimuli pairs differ only in the emotionally relevant feature but are virtually identical in all other aspects (i.e. their physical stimulus properties) to avoid possible confounds of non-emotional stimulus characteristics (e.g. content, complexity, spatial frequency) [56]. Nevertheless, emotional construct validity is high as indicated by self-report ratings of valence and arousal [129] and skin conductance responses [110]. A pseudo-randomized presentation sequence (128 trials, variable 8-13 s ITI) controls hemifield (left, right) and emotion (negative, neutral) [see 123, 129 for full details]. Stimuli are mirrored for half of the trials because the affective feature is not necessarily in the picture center [28]. Participants attend to the stimuli while maintaining fixation. No manual response is required. Horizontal eye movements are monitored to warrant hemifield exposure [see 129 for details].

C6. Dichotic Listening (DL). The *ERT* is a dichotic emotion recognition test [27] in which 4 words (power, tower, dower, bower) are pronounced in 4 emotional tones (angry, happy, sad, neutral). Subjects report the two dichotically presented emotions (one from each ear) [229]. A left ear advantage (LEA) is expected for individuals with RH dominance for processing prosody [229]. A dichotic *fused words* test will provide a robust, valid (Wada Test [242]), and reliable (test-retest r = 0.85 [236]) behavioral measure of perceptual asymmetry (PA) for verbal processing. Words that rhyme (coat/goat) fuse into a single percept when simultaneously presented to each ear. The accuracy of reporting the word in either ear is expressed as a laterality score to reflect PA magnitude [99, 229]. Individuals who are LH-dominant for language yield a REA [235, 242; see 23, 139 for further details].

C7. Assessement Timeline. EHT and DL testing will be done pre- and post-treatment (**Fig. 6**) in 2-3 h sessions. Meta-cognitive self-report measures (***PM***/***M***/***ER***) will be obtained at baseline (pre-Tx), midpoint (wk 6) and the end of treatment (post-Tx). Depressive symptoms will be assessed every 3 wks (HRSD) and weekly (BDI; Clinical Global Impressions [CGI] scale) [30, 85].

		CBT or PBO [weeks]												
		pre	1	2	3	4	5	6	7	8	9	10	11	12	post
MDD	BDI	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	HRSD	x			x			x			x				x
PM	PMS	x						x							x
	SRIS	x						x							x
	TAS	x						x							x
M	MAAS	x						x							x
	FFMQ	x						x							x
ER	ERQ	x						x							x
ERP	EHT	x													x
DL	ERT	x													x

Fig. 6. Assessment of outcome measures.

C8. EEG Acquisition. Briefly, 72-channel EEGs [104, 184] are recorded at 1024 samples/s (24-bit BioSemi [17]) and exported to Neuroscan to remove DC offsets and low-frequency drifts [109]. Bipolar EOGs are interpolated via spherical splines [179] to evaluate subsequent removal of blinks (spatial PCA [169]). Epochs (-200..1500 ms, 30 Hz low pass) are optimized with proven screening procedures, some developed by our group, to identify and interpolate [179] EEG traces with amplifier drift, residual eye activity, movement or muscle artifacts [117]. ERPs are averaged from artifact-free trials, screened for electrolyte bridges [2, 216], baseline-corrected, and low-pass filtered (12.5 Hz) [see 129 for further details].

C9. CSD, PCA and sLORETA. ERPs are transformed to current source density (CSD) estimates (μV/cm^2) using a spherical spline surface Laplacian [111, 179], as detailed elsewhere [114-115, 118, 120, 125, 129]. CSDs are based on the 2nd spatial derivative of surface potentials and represent the magnitude of radial current flow entering (source) and leaving

(sink) the scalp [170-171, 218; 120 for a tutorial]. CSDs are submitted to covariance-based temporal PCA (CSD-tPCA) with unrestricted Varimax rotation [112-114, 116]. Due to the reference-free CSD transform [120, 218], tPCA factor scores directly reflect neuronal generator patterns at scalp. Unlike conventional surface potential (ERP) measures, CSDs are not biased by the imposition of an EEG reference, nor by smearing due to volume conduction [119-120, 217], allowing localized activity to be placed in the context of the full topography [114-115, 217-218]. Factors are back-projected into surface potential space [132] and submitted to sLORETA [177, 212] to estimate the putative cortical generators (distributed source inverses) underlying the identified emotion effects [129]. Of note, the previously identified CSD-tPCA factor structure can also be applied to the new EHT data to obtain component scores for N2 sink, P3 source and CP source [129, 130].

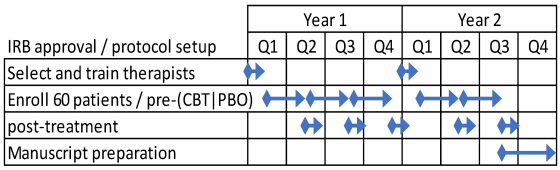
C10. Statistical Analyses and Power. Repeated measures ANOVA for mixed designs (including between- group and within-subjects pre/post variables as required) will be used for EHT/ERT measures, employing an unstructured covariance matrix (BMDP-5V [58]) with sex, age, and parental SES as covariates (handedness, exercise and sleep will be included if necessary; significant covariates will prompt further exploratory analyses). Unlike *F* statistics (4V [58]), 5V computes maximum likelihood estimates and Wald test χ^2 statistics within a linear regression model that allows imputation of missing data and inclusion of time-varying covariates (***M***/***PM***/***ER***). Nonparametric permutation tests will evaluate emotional differences in CSD topography [101, 125, 129, 157] for each group (Tx CBT/PBO, Responder/ Remitter yes/no). For the sole purpose of estimating approximate sensitivities (for small to large effect sizes, f = .1 to .4) at 80% power ($p < .05$), repeated measures ANOVA (r_{within} = .7; final N = 48) and fixed-effects ANCOVA (adding 48 HCs for baseline comparison; see ***C1***) were evaluated via G*Power [67]. Required effect sizes (f) were .32 (***H1***, ***H5***), .29 (***H2***), .21 (***H3***, ***H4***, ***H6***). The association between LEA and N2 (***H7***) will be tested with linear (Pearson's) and non-parametric correlations, allowing to detect $r \geq 0.35$ (medium effect size) at 80% power. While this suggests adequate power to detect small-medium to medium-large effect sizes for our first 3 specific aims, due to sample size feasability constraints of an R21 mechanism (time and money), we are somewhat underpowered for our 4th exploratory aim (***H8***-***H10***). To assess the prognostic value of ***PM***/***M***/***ER*** before and during CBT, and their relationship with EHT/ERT measures pre/post CBT (***H8***), we will fit separate multiple predictor, mixed-effect regression models for BDI, HRSD, rate of symptom change (***C3***), or EHT/ERT as outcomes, with time point, baseline ***PM***/***M***/***ER*** as predictors, adjusted for baseline depression scores as covariate, and subject-specific intercepts and slopes [147]. In a second model, time-varying ***PM***/***M***/***ER*** scores will be used as predictors with lagged values (baseline ***PM***/***M***/***ER*** for mid-Tx, mid-Tx ***PM***/***M***/***ER*** for post-Tx response). In secondary analyses, we will run logistic regression models with binary Tx outcome (***C3***) with baseline ***PM***/***M***/***ER*** scores as predictors [50, 58]. Effect sizes (small to large, d = .2 to .8 [39]) for the mixed-effect regression models estimated via the R library *longpower* [155] were 0.79 and 1.12 (both/single Tx arm), more than enough for the large effects in our preliminary data (***A3***); however, comparable ERP and DL effects are yet unknown but those will be generated during this R21 project. ***H9-H10***: To explore whether ***PM***/***M***/***ER*** scores pre/post Tx are mediators and/or moderators of CBT outcome and/or EHT/ERT, we will fit mixed-effect models with baseline EHT (ERT), ***PM*** (***M***/***ER***), and their interactions as predictors of time-varying depression scores during and after CBT. Then, we fit a mediation model with time-varying predictor and mediator, where lagged values of EHT (or ERT) and ***PM*** (or ***M***/***ER***) will be used to predict depression score during/post CBT. Although this R21 will not provide enough power for a formal mediation test of this exploratory aim, we will estimate and report the direct and indirect effects of EHT/ERT on depression with 95% CI. If we document meaningful effect sizes, we will pursue a larger R01 follow-up study with a sample size sufficient to achieve adequate power.

C11. Rigor and Reproducibility. The design includes MDD patients randomly assigned to CBT vs. no CBT arms required to provide pre- and post-CBT comparisons (accounting for time-dependent changes of EHT/ERT measures). While emotional ERPs have been found to be robust and stable [18], long-term test-retest reliability [10] of the EHT is currently being assessed in an independent project (MH036197; MPI: Weissman/Posner; Co-I: Kayser). The proposed mechanistic clinical trial employs CBT as a vehicle test of treatment response to assess the relationship between ***M***/***PM***/***ER*** and affective ERPs and their value as predictors of CBT response (***A11***). Self-report, clinical assessments (semi-structured interviews), and CBT procedures are standard in the field with high validity, reliability and applicability. Data processing will be blind to treatment randomization and outcome, and of all included measures. Notably, our ERP analysis is systematic, comprehensive, unbiased, and reference-free [118-120, 125, 129]. The statistical analysis will take into account all relevant variables, including sex as a biological variable and age.

C12. Potential Pitfalls and Problems. Given the proposal's complexity and the constraints of an exploratory R21, not all potentially relevant aspects can be studied in sufficient depths at this time (e.g. also obtaining HC data). However, we have identified key scientific issues, recognized to-be-assessed possible confounds (***C1***), and formulated testable hypotheses that will yield an important initial platform on which to build future work.

D. TIMELINE

Patients will participate in 2 EEG test sessions (pre/post intervention; ***C2***). EEG data processing will proceed in parallel. The timeline allows for therapist training and write-up. We already obtained IRB approval, finalized protocol setup, and successfully collected pilot data.



PHS Human Subjects and Clinical Trials Information

OMB Number: 0925-0001 and 0925-0002

Expiration Date: 03/31/2020

Are Human Subjects Involved	● Yes ❍ No
Is the Project Exempt from Federal regulations?	❍ Yes ● No
Exemption Number	❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ 6 ❑ 7 ❑ 8
Other Requested Information	

Human Subject Studies

Study#	Study Title	Clinical Trial?
1	Combining Electrophysiological, Behavioral and Psychological Measures to Target Mechanisms of Emotion Processing and Regulation During Cognitive Behavior Therapy in Depression	Yes

Section 1 - Basic Information (Study 1)

OMB Number: 0925-0001 and 0925-0002

Expiration Date: 03/31/2020

1.1. Study Title *

Combining Electrophysiological, Behavioral and Psychological Measures to Target Mechanisms of Emotion Processing and Regulation During Cognitive Behavior Therapy in Depression

1.2. Is this study exempt from Federal Regulations * ❍ Yes ● No

1.3. Exemption Number ❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ 6 ❑ 7 ❑ 8

1.4. Clinical Trial Questionnaire *

1.4.a. Does the study involve human participants?	● Yes	❍ No
1.4.b. Are the participants prospectively assigned to an intervention?	● Yes	❍ No
1.4.c. Is the study designed to evaluate the effect of the intervention on the participants?	● Yes	❍ No
1.4.d. Is the effect that will be evaluated a health-related biomedical or behavioral outcome?	● Yes	❍ No

1.5. Provide the ClinicalTrials.gov Identifier (e.g. NCT87654321) for this trial, if applicable

Section 2 - Study Population Characteristics (Study 1)

2.1. Conditions or Focus of Study

- Major Depressive Disorder (DSM-5)

2.2. Eligibility Criteria

Male or Female; Off psychotropic medication; No history of other psychopathology;

2.3. Age Limits	Min Age: 18 Years	Max Age: 65 Years
2.4. Inclusion of Women, Minorities, and Children	R21KayKis-InclusionAcrossLifespan 2019-11-12.pdf	
2.5. Recruitment and Retention Plan	R21KayKis-RecruitmentRentention 2019-11-12.pdf	
2.6. Recruitment Status	Not yet recruiting	
2.7. Study Timeline	R21KayKis-StudyTimeline 2019-11-12.pdf	
2.8. Enrollment of First Subject	07/01/2020	Anticipated

INCLUSION ACROSS THE LIFESPAN

MDD patients being 18 to 65 years of age will be recruited. Patients between 18 and 21 years are not considered children under NIH policy (see NIH Guide Notice NOT-OD-16-010). The manualized CBT intervention [64] and the nonspecific supportive therapy (PBO) considered in this study are for adults having unipolar depression. While there are different manualized CBT interventions specifically for adolescents or even younger children, the constraints on sample size in the context of an exploratory/developmental R21 research award application mandates the limitation to adult participants to warrant a sound scientific approach. The exclusion of elderly participants (> 65 years) is mandated by scientific standards, as event-related potentials, hearing tests and cognitive performance are well-known to be affected by advanced age.

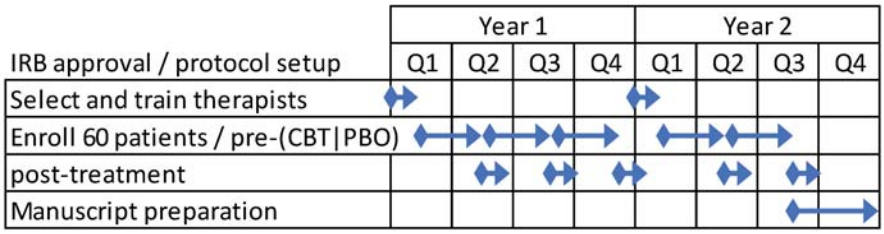
RECRUITMENT AND RETENTION PLAN

MDD patients (*N* = 60) will be recruited through the DES at NYSPI. Over the last years, neither rates for CBT treatment at the DES nor rates of CBT success have differed by sex. Accordingly, we will aim to recruit an equal number of men and women as study participants from the Washington Heights community directly surrounding the Columbia University Irving Medical Center in New York City by a Principal Investigator, a co-investigator or by a research assistant. Right-handers [174] aged 18 to 65 will be recruited: through online advertisements, including *RecruitMe* (*recruit.cumc.columbia.edu*, a CU research site aimed at aiding recruitment of study participants), Google AdWords, Facebook, Research Match, in relevant sections (i.e. volunteers, gigs, jobs); via commercial print and poster advertisements; by referrals from affiliated clinics and clinicians in private practice after advertising the study via the CU PsychoPharmacology list server; and by self-referral. We estimate that approximately 80% of those who contact the DES at NYSPI will prove eligible for the study.

We conservatively estimate retention rates at .9 at baseline and at .8 at the end of treatment (i.e. over 3-4 mos of intervention). Patients will receive psychotherapy free of charge. While participants are encouraged to complete their course of 12 treatment sessions for maximum efficacy, participation is entirely voluntary. Patients will receive 24-h reminders for their weekly treatment sessions. However, each patient may miss up to 2 sessions provided that all 12 sessions are completed within 14 wks. CBT drop-out rates have been below 15% at the DES and removal of MDD patients from the study due to serious adverse events (e.g. suicidality) has been extremely rare (i.e. only 1 case over the last decade).

STUDY TIMELINE

Our team has begun with the collection of pilot data in MDD patients already enrolled at the DES for receiving standardized CBT, with electrophysiological (EHT) and behavioral (ERT) data being obtained before and after treatment. The clinical treatment procedures, including nonspecific supportive therapy (placebo [PBO), and collection of psychological measures (PM/M), have been approved by NYSPI IRB protocol #6806R, and all EHT/ERT testing procedures have been approved by IRB #6559R. Upon notice of award, these two IRB protocols will be merged to a new NYSPI protocol for a single clinical trial. We anticipate obtaining IRB approval before the award's official start date without delay. Likewise, all protocol procedures are already in place and therefore will not require any additional setup or implementation time.



During the first month of the project, our team – with assistance of the DES – will begin the recruitment process, including placing commercial advertisements for the study throughout the local community (Washington Heights) and the greater area of New York City. At the same time, Drs. Kishon and Mufson will select, train and certify 3 qualified therapists. The therapists will then commence with the administration of weekly treatment sessions to recruited MDD patients who meet all inclusion/exclusion criteria. Recruited participants will be randomized to CBT or PBO intervention by also taking relevant constraints into account (i.e. approximate equal representation of sex, age, race/ethnicity, and handedness in each treatment arm). Each therapist will treat 5 patients at a time for about 3-4 months, after which he/she will treat another 2 batches of 5 patients. Before and after treatment, Dr. Kayser's team at the Psychophysiology Laboratory will coordinate with the DES and arrange for the EHT and ERT testing of patients. This process will repeat with the beginning of Year 2, at which time a new group of 3 therapists will be selected, trained and certified, who each will then administer treatment to 2 batches of 5 patients.

Our targeted enrollment sample size is 60 MDD patients, with 40 patients treated in Year 1, and 20 patients treated in Year 2. The above arrangement intentionally exceeds these numbers, as 3 therapists will together be able to treat 15 patients within a single batch (i.e. a total of 45 and 30 patients in Year 1 and 2, respectively). These totals include for each therapist 1 excluded training case (i.e. a total of 6 excluded patients), leaving a safety net of 9 patients that will provide a fall-back resource if there are any enrollment shortfalls, such as an unforeseen drop in recruitments or occurrence of any serious adverse event, which would challenge this timeline. However, no additional patients will be enrolled in the study in excess of the targeted sample size.

Routine EEG data processing for the EHT paradigm will proceed in parallel to data collection. Entering and processing of the behavioral data stemming from the dichotic listening tasks, and entering of all clinical and behavioral data will be proceed at the same time. Research staff involved in these tasks will be blind toward treatment randomization and clinical outcome.

Final data analysis, manuscript preparation and dissemination of findings will fall into the last 4-5 months of Year 2. At this stage, we will evaluate our hypotheses associated with Specific Aims 1-3. For our exploratory Aim 4, we will consult with our biostatistician, Dr. Ying Chen, to implement the more complex GLMM and multilevel statistical analyses. The timeline therefore will allow completion of data analysis within the proposed 2-year award period.

Inclusion Enrollment Reports

IER ID#	Enrollment Location Type	Enrollment Location
Study 1, IER 1	Domestic	New York State Psychiatric Institute (NYSPI), 1051 Riverside Drive, New York, NY 10032

Inclusion Enrollment Report 1

Using an Existing Dataset or Resource* : ❍ Yes ● No

Enrollment Location Type* : ● Domestic ❍ Foreign

Enrollment Country(ies): USA: UNITED STATES

Enrollment Location(s): New York State Psychiatric Institute (NYSPI), 1051 Riverside Drive, New York, NY 10032

Comments: All research and treatment activities will be performed at NYSPI.

Planned

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	0
Asian	2	4	0	0	6
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	3	3	1	1	8
White	20	20	4	2	46
More than One Race	0	0	0	0	0
Total	25	27	5	3	60

Cumulative (Actual)

Racial Categories	Ethnic Categories									Total
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			
	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	
American Indian/ Alaska Native	0	0	0	0	0	0	0	0	0	0
Asian	0	0	0	0	0	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0	0	0
Black or African American	0	0	0	0	0	0	0	0	0	0
White	0	0	0	0	0	0	0	0	0	0
More than One Race	0	0	0	0	0	0	0	0	0	0
Unknown or Not Reported	0	0	0	0	0	0	0	0	0	0
Total	0	0	0	0	0	0	0	0	0	0

Section 3 - Protection and Monitoring Plans (Study 1)

3.1. Protection of Human Subjects	R21KayKis-HumanSubjects 2019-11-12.pdf
3.2. Is this a multi-site study that will use the same protocol to conduct non-exempt human subjects research at more than one domestic site?	❍ Yes ● No ❍ N/A
If yes, describe the single IRB plan	
3.3. Data and Safety Monitoring Plan	R21KayKis-DataSafetyPlan 2019-11-12.pdf
3.4. Will a Data and Safety Monitoring Board be appointed for this study?	❍ Yes ● No
3.5. Overall structure of the study team	R21KayKis-StudyTeam 2019-11-15.pdf

PROTECTION OF HUMAN SUBJECTS

1. RISKS TO THE SUBJECTS

a. Human subjects' involvement and characteristics

We propose to recruit a total of 60 patients meeting DSM-V criteria for major depressive disorder (MDD) who will be equally randomized to cognitive behavioral therapy (CBT) and nonspecific supportive therapy (PBO). For the primary goal of the proposal (i.e. clarifying mechanisms underlying CBT response), it is essential to test MDD patients receiving CBT because the ultimate objective of this research is to contribute to the development of biomarkers of this disorder as diagnostic aids. The expectation is that depressed patients will benefit from CBT and reduce their depressive symptoms. A group of minimally-treated depressed patients is required by methodological standards to separate CBT-specific outcome effects from those of spontaneous recovery (placebo response). Only subjects in good physical health will be included in the project.

Language: Ability to speak and understand English is a requirement for the study. Therefore, all interviews and other study materials will be in English.

Sources of Study Information: MDD patients will be recruited through the Depression Evaluation Service (DES) at NYSPI/Columbia University (CU; see *Study Recruitment and Informed Consent* for details) and will receive initial information about the study. We have current approval from the Institutional Review Board (IRB) at New York State Psychiatric Institute (NYSPI) for recruiting MDD patients to receive CBT or PBO – nonspecific supportive therapy (IRB protocol #6806R) and to participate in pre-/post-(CBT|PBO) EHT and ERT testing (IRB #6559R) for the purpose of collecting pilot data. As these procedures are identical to the ones stated in this proposal, it is expected that this project will also be approved by the IRB.

Pre-Recruitment Screen: A brief telephone screen will be conducted at the DES with all potential participants who give verbal consent to be screened after hearing about the study. The purpose of the phone screen is to assess whether the subjects can participate in the study as MDD patients, and to tentatively rule out certain mental conditions (e.g. active psychosis, bipolar disorder), as well as use of prescribed antidepressant or over-the-counter antidepressant medications in the past month (3 months for fluoxetine). We will not exclude persons using medications for other purposes (e.g. high blood pressure, etc). The phone evaluation will take ~20-30 minutes and includes: (1) determining why the person called; (2) explaining the study and answering any questions; (3) recording subject's name, address, demographic information (age, gender, handedness), source of referral, presenting problem, psychiatric history, past treatment, social history, medical history, mental status, and provisional diagnosis. Those found eligible will be invited for further diagnostic evaluation.

In-Person Interview: Participants who pass the initial telephone screen will be asked to come to the DES at NYSPI for an evaluation that will include a structured clinical interview (SCID [69-70]), conducted by the staff of the DES. Subjects will be asked to sign an evaluation consent form beforehand. This consent form covers only the pre-enrollment evaluation. The SCID will be used to determine diagnostic eligibility for the study (see *Inclusion/ Exclusion Criteria*). At this time, participants will also be screened for any hearing loss using a standard audiogram procedure, fill-out a brief handedness questionnaire [174], and provide information about their parental socioeconomic status (SES) [74, 96].

Inclusion Criteria: Study criteria specifically require subjects to be between the ages of 18-65, right-handed and to be able to speak English well enough to comprehend and comply with protocol requirements. Participants will be recruited to achieve equal gender representation (i.e. about half male) as much as possible; in any case, however, both treatment arms will have the same ratio of male and female participants, which will be accomplished by implementing this requirement as a constraint to the randomization procedure. Medically healthy individuals will be included as MDD patients if they: (1) meet DSM-5 [3] criteria for a current MDD episode based on a structured clinical interview (SCID) [69]; (2) score greater or equal to 13 on the *Beck Depression Inventory (BDI-II)* [12] and greater or equal to 14 on the *Hamilton Rating Scale for Depression (HRSD)* [87]. Participants will be interviewed about the type and number of minutes exercise/workout per day in the past 7 days prior the evaluation, and the type/number of exercise/workout days during the past 6 months. Levels of exercise will be controlled for in the data analysis due to known effects of exercise on cognition [80] and mood [42, 199]. Likewise, participants will be screened for their sleep habits [31] which also can impact on mood [13].

Exclusion Criteria: Participants are excluded for any of the following reasons or DSM-5 criteria: (1) substance abuse or dependence (including alcohol) in last 6 months; (2) positive toxicology screen as determined by blood/ urine testing (e.g. thyroid dysfunction, street drug use); (3) history of schizophrenia or other current psychotic disorder; (4) MDD with psychotic or catatonic features; (5) Bipolar I, II Affective Disorder; (6) Organic Mental Disease; (7) significant suicidal ideation with a plan and intent, also assessed using the Columbia-Suicide Severity Rating Scale (C-SSRS) [184], that cannot be managed safely as an outpatient, or homicidal ideation

(suicidality monitored throughout study); (8) a primary diagnosis of panic disorder, obsessive-compulsive disorder, psychogenic pain disorder, anorexia/bulimia, or any unstable medical condition; (9) any recent (≤ 12 mos) history of CBT (as determined by Dr. Kishon during an in-person interview); (10) prior seizure disorder, significant head trauma or other neurological disorders; (11) lack of capacity to give informed consent. Participants are also excluded if they received psychotropic medication, over-the-counter antidepressant, or any non-CBT intervention (e.g. deep breathing, meditation/mindfulness, psychotherapy – except for minimal supportive nonspecific therapy PBO) [77] for at least 1 month prior to recruitment (3 months for fluexetine). Participants are also excluded if they have a hearing loss (>30 dB in either ear) or hearing asymmetry (>10 dB across ears).

b. Sources of Material

MDD patients will be assessed using standard interviewer and self-rating scales for assessing psychopathology and are also tested on ERP and behavioral tests (i.e. EHT [128] and ERT [23]). These data will be obtained specifically for research purposes.

CBT and PBO intervention procedures: Following established procedures at the DES, 12 sessions of individual manual-driven CBT [64] will be conducted by highly trained master degree clinicians who are approved and credentialed by Dr. Laura Mufson, the head psychologist at NYSPI. Dr. Kishon will supervise all therapists on a weekly basis. As a non-CBT intervention, nonspecific supportive therapy (PBO) will be administered in a parallel format, also consisting of 12 individual sessions. Nonspecific treatment controls for many of the common or nonspecific factors of therapy (e.g. contact with a therapist, participation in individual sessions, therapist being committed to provide support that will assist the patient, and to demonstrate allegiance to what s/he is doing). As such, treatment is neither withheld (i.e. no treatment) nor delayed (wait-list) nor is a "fake" treatment provided that is not intended to work, thereby adhering to ethical standards [104]. All CBT and PBO sessions will be audiotaped unless the subject does not consent. The audio recording will not include the subject's full name. It will be reviewed by Dr. Kishon to evaluate the treatment provided by the therapist. Audio recordings will be kept for no more than 10 years after which they will be destroyed. However, if the patient withdraws consent, audio recordings will be destroyed at that time (i.e. during or after the interview or procedure). The patient reserves the right to withdraw consent at any time prior to or during the audio taping. Following treatment protocol guidelines [64], specific tools and methods of coping with depression are given to each subject in the CBT arm. The subject will learn to use the following basic cognitive-behavioral techniques: constructing an 'Action Schedule,' setting goals, doing 'Behavioral Experiments,' and constructing a Distorted Thought Record (DTR) [64]. The patient is expected to use these tools between CBT sessions. After treatment, patients will be referred to the appropriate setting as needed. Treatment can end at any point if the patient requests so, or if his/her condition worsens significantly, in which case the patient will meet Dr. Kishon for open ended sessions until referred to an appropriate treatment (please see below for suicidal risk).

c. Potential Risks

Patients are interviewed to select potential participants for the study. Information regarding medical and psychiatric state and history are solicited from individuals at this time. Notwithstanding below considerations, these interviews and tests are in no way hazardous. However, a primary consideration in this study is the fact that we are recruiting diagnostically depressed individuals, who require careful monitoring and protection.

During the phone screen, evaluation interview, and while receiving CBT|PBO or after therapy sessions, the participants will be asked about psychiatric symptoms they have experienced in the past week, month, year or at other times in their lives. There is, of course, some risk that some participants will become distressed from discussing such matters. However, participants are always informed that they may refuse to answer any question and are made aware of psychological resources available to them. In addition, the study employs a procedure of clinical review and response for severe or urgent cases (see *Protection Against Risk*).

Participants are informed that if they become upset by this procedure, they can stop at any time. The treatment for depression provided during this study may be ineffective for some patients, and there is a possibility that patients' symptoms will worsen during the course of treatment. If subjects show significant deterioration in their symptoms based on the Hamilton Rating for Depressive Symptoms (HRSD) [87], the weekly Beck Depression Inventory (BDI-II) [12], and weekly Clinical Global Impression Scale (CGI-improvement) [30, 85] score of 6 or 7 (much or very much worse), they will be considered for study removal and will receive open-ended sessions with Dr. Kishon until referred to alternative treatments. Alternative treatments include antidepressant medications, and other psychotherapeutic modalities, including interpersonal psychotherapy for depression. Level of suicidality

will be monitored carefully at each phase of the study using the C-SSRS, and Dr. Kishon or a psychiatrist will be immediately informed as needed. Necessary steps will be taken (see *Protection Against Risks*). Inpatient psychiatric treatment is available at New York State Psychiatric Institute to research participants in the event of clinical decompensation requiring hospitalization.

In our prior work, patients and controls experienced little difficulty performing the behavioral and ERP tests. All testing procedures are designed to maximize the mental and physical comfort of the participants and represent no risk to them. Participants will also have their EEG recorded from scalp using a standard electrode cap. The procedures for measuring the EEG are non-invasive and standard for clinical research in this area and represent no risk to the subjects (see *Protection Against Risk*).

2. Adequacy of Protection Against Risks

a. Recruitment and Informed Consent

Participants will be recruited from the community directly surrounding the Columbia University Irving Medical Center in New York City by a Principal Investigator, a co-investigator or by a research assistant through any the following mechanisms: (1) online advertisements, including *RecruitMe* (*recruit.cumc.columbia.edu*, a CU research site aimed at aiding recruitment of study participants), Craigslist, Google AdWords, Facebook, Research Match, in relevant sections (i.e. volunteers, gigs, jobs); (2) commercial print and poster advertisements; (3) referrals from affiliated clinics and clinicians in private practice after advertising the study via the CU PsychoPharmacology list server; (4) self-referral. All potential participants will be referred to the DES at NYSPI. We estimate that approximately 80% of those who contact the study will prove eligible.

Patients will initially be interviewed to determine if they would be willing to participate in the project. They are given a full description of the study and all test procedures. An TBD experienced psychiatrist at the DES, and Dr. Kishon, an experienced clinical psychologist working at the DES, will supervise the initial telephone screens and the in-person diagnostic evaluations, which will include medical history, blood and urine tests. Subjects will sign consents for the in-person evaluation and those who meet all inclusion/exclusion criteria will also sign a full study consent with Dr. Kishon or Dr. Kayser.

Prospective participants will be given a full description of the research project on their initial visit to NYSPI, including ERP and behavioral tests. Because the study is a clinical trial, the informed consent documents will include a specific statement relating to posting of clinical trial information at ClinicalTrials.gov involving only de-identified data. The overwhelming majority of MDD patients will be able to comprehend the nature of the test procedures and decide whether or not they will volunteer for it. Only participants who have capacity to give informed consent will be tested in this project. If there is any question about a patient's ability to make such decision, he/she will not participate in the study but instead be referred to the appropriate setting. If they agree to participate in the study, they will be asked to sign appropriate consent forms. In the study consent form, subjects are advised fully of the procedures to be used, the amount of time required of them, the possible risks and benefits of the procedures, their right to refuse participation in the study without prejudice, their right to terminate participation at any moment without prejudice, and the name of the principal investigators.

b. Protection Against Risk

Having conducted this type of study for over several decades, we have extensive experience managing suicidal, symptomatic participants in protocols, and have learned how to pace them through study procedures providing rest periods between components. Generally, the subjects find it helpful to speak with our highly trained clinical assessors. Subjects can decline some or all of the procedures and we are continually monitoring the subjects for indications of distress or fatigue. At all times, the DES will closely monitor the participants' well-being, and will maintain its commitment to them throughout the study.

Telephone Screens: At the telephone screen, probably depressed persons who prove ineligible for the study will either be invited to participate in a more appropriate DES study, or referred for outside treatment. The same will be done with anyone who leaves the study at any point and at the end of the study.

Evaluation: The participant's first arrival at NYSPI will be for the in-person evaluation, which will be conducted at the DES. At that time the study will be explained in detail, including the purpose of the in-person screen, and she/he will be asked to sign consent for evaluation only. If the participant is found to be ineligible for the study, she/he will be compensated for the time or referred to an appropriate setting. If found to be eligible, the

individual will sign a study consent form, and the date and time for the initial EEG test session will be scheduled. If the screen reveals an urgent clinical issue (e.g. severe suicidal ideation), the staff of the DES will take steps to refer the person for immediate intervention and treatment (see *Suicidal Ideation*).

Clinical Back-Up During the Study: We will routinely have clinical back-up available, so that if necessary, a psychiatric consultation can be arranged immediately, especially in cases of suicidal concern. All participants will have the contact information for DES and of Dr. Kishon that they can use if needed, including after hours. Dr. Kishon or a TBD psychiatrist at the DES will be available for immediate consultation if any urgent issues are reported during any of the procedures. If there are signs of overt distress or worsening of symptoms, the participant will be pulled out of the study for immediate clinical care at the DES and referral to appropriate treatment as needed. Referrals for treatment will also be provided to those in need at the end of the study period.

Suicidal Ideation: If at the time of the interview with the research clinician (Masters or Doctoral level psychologists) in each phase of the study, or during the CBT session, the participant expresses suicidal behavior or suicidal ideation, the clinician conducts a risk assessment on the spot using the C-SSRS, in consultation with Dr. Kishon. For any participants who require emergency care, they are escorted to the emergency room where hospitalization can be arranged while the patient is in a safe environment. For participants not requiring emergency hospitalization, the clinician will contact their study therapist and assist the patient in setting up an appointment as soon as possible. If level of suicidality increases during a CBT or PBO session, the therapist will consult with Dr. Kishon during session and measures of intervention will be taken in collaboration with the patient. For participants who are being interviewed during the phone screen or evaluation phase but are not in the study, a referral will be made to either the local mobile crisis team or a clinic where they can be seen in a timely fashion. If the participant is acutely suicidal *during phone screening*, the clinician will either make arrangements for emergency care by sending a mobile crisis team and/or an ambulance to the patient's home. If a participant is acutely suicidal *during the evaluation*, he or she will be walked to the emergency room. Less acute situations will be handled by arranging for an appointment with the patient's health care provider or referrals as previously noted. *Our department provides 24 hour coverage by an M.D. in addition to having an Emergency Department. All patients are given the cell phone number for the Physician on Call and this number is also recorded on all outgoing phone messages of the clinical staff.*

EEG/ERP testing: Our highly experienced EEG technicians use EEG procedures that are standard for clinical research in this area and the procedures represent no risk to the subjects. We employ Control III disinfectant and germicide cleaning solution to safeguard against potential health hazards of repeated use of electro-cap sensors for different subjects. Moreover, we use Biosemi ActiveTwo electrode sensors that require minimal abrasion of the scalp [17].

For the EHT, which employs stimuli from a textbook of plastic surgery consisting of 16 closely matched pairs of pictures depicting facial areas of patients with dermatological diseases before (negative) and after (neutral) surgical treatment [121, 122, 128], participants will be told that they can stop the procedures at any time, in particular, if they find the negative images upsetting. They will be given a telephone number at the Study office to call if they subsequently have any questions about the procedure.

c. Data Security

To assure confidentiality, the identity of the subjects is obscured by using coding systems used for subsequent data and lab collection. All hard copies of patient research data, including psychological and neuropsychiatric ratings, and progress notes from visit sessions, will be stored in locked filing cabinets located in locked rooms throughout the length of the study. Only limited access by staff members and trained specialists is permitted. Presentation of data to anyone outside the research staff, such as for purposes of research reports, will not include identifying information. Computer data will be stored on Bitlocker-encrypted hard drives in a coded database, which is password and firewall protected. Names, addresses and any other identifying information of study individuals (e.g. age, sex) or families will be kept in an entirely separate, locked location. All data and files are kept under lock and key, and only staff members have access to these data.

All individual information obtained will be held strictly confidential. No information that might in any way lead to the identification of the source will be made public. All raw data from the study will be kept in locked files and identified by ID number only. The EEG recordings and processed ERP data will be placed in a secure archive, identified by number only, which can be requested by the participants at a later date if they should have need. The consent forms will be stored in a separate and secure location from data obtained using the other data collection methods. All study data will be used for research purposes only and retained, at a minimum, until the research project is completed. All Study personnel will receive Human Subjects and HIPAA training to ensure compliance with IRB and research ethics guidelines. Electronic data will be protected on a secure server behind

a firewall and in accordance with HIPAA regulations. All PHIs will be stored on a SQL server with access permitted on the basis of need.

IRB Approval and Certificate of Confidentiality: Every aspect of the Study has had previous Columbia University - NYS Psychiatric Institute IRB approval, as well as being covered by a Federal Certificate of Confidentiality. The proposed study will likewise obtain Columbia-NYSPI IRB approval and a Federal Certificate of Confidentiality will also be obtained.

3. Potential Benefits

Participants having depressive symptoms will receive psychiatric assessment, as well as psychotherapeutic treatment for depression provided by skilled clinicians. If this treatment is ineffective, participants will be referred to psychiatric services for further treatment, including antidepressant medication or an alternative form of psychotherapy. Patients who were randomly assigned to nonspecific supportive therapy (PBO) and failed to show clinical improvement may opt to receive CBT at the end of the study period.

The benefit to society is the knowledge gained in our understanding of neurophysiologic and neurocognitive function in depression as it relates to the mechanism of change via CBT and in identifying (bio-)markers of clinical response to CBT. Specifically, the benefits to others through this research is to elucidate predictors of treatment outcome for CBT for depression, thereby increasing our ability to match treatments to patients effectively, and decrease the burden of ineffectively treated depression.

4. Importance of the Knowledge to be Gained

This study will contribute toward delineating the mechanism by which change occurs during cognitive behavior therapy (CBT) for unipolar depression and the development of cost-effective tests for identifying patients who may benefit from different pharmacological or cognitive treatments. The study findings should yield an increased understanding of the neurophysiological and neurocognitive basis of treatment response in mood disorders and could help elucidate whether there are specific neurophysiological biomarkers of CBT treatment response that provide a measurable indicator of change in how an individual processes emotional stimuli. In addition to adding to general knowledge of emotional processing and neurological changes associated with CBT, a potential public health impact of this work is that some patients and providers might be more likely to engage in (or recommend) CBT treatment for depression if they are aware of known changes in neurophysiological functioning as measured by such biomarkers. Participation in this project should entail little in the way of risk to the participants. We believe that the knowledge to be gained from this study far outweighs the potential risks.

DATA AND SAFETY MONITORING PLAN

As the proposed study meets the criteria for a clinical trial, a Data Safety and Monitoring Plan (DSMP) as required by the NIH will be used. Due to the low-risk nature of the proposed study, the study team in close coordination with the Depression Evaluation Service (DES) at New York State Psychiatric Institute (NYSPI) will perform all data and safety monitoring.

The proposed study will be reviewed by the Institutional Review Board (IRB) at the New York State Psychiatric Institute (NYSPI). After the initial approval, annual review is required by the IRB for all research protocols, during which careful re-review of the protocol, consent forms, adverse events, progress, and dropouts/discharges is obtained. In addition, all studies involving human subjects are periodically and systematically reviewed by the NYSPI Quality Assurance Staff. They assure protocol compliance by comparing research charts to the IRB protocol.

The PIs will assume all responsibility for monitoring of data collection and participant safety. Procedures are in place to notify the IRB, the NYS Office of Research Protection (as well as the FDA and the Project Officer, if needed) within 48 hours should any adverse events occur. All adverse events will also be documented in the annual progress reports. An adverse event is any unwanted experience or event occurring during the course of a study or clinical trial. An adverse event will be defined as serious whenever the outcome: is fatal or life-threatening; is significantly or permanently disabling or incapacitating; requires or prolongs inpatient hospitalization; results in permanent disability; results in a congenital anomaly; or is unusual and potentially serious. An adverse event is defined as unexpected whenever the nature and severity of the event is not consistent with the known product information or treatment course.

The PIs will monitor the study for any adverse events, although we do not anticipate any given the nature of the study. All serious adverse events (SAEs) will be reported to the IRB: a) death – immediately; b) life-threatening – within 7 calendar days; c) all other SAEs – within 15 calendar days. Should there be a serious adverse event that occurs that increases the risks to the participants, the study will be stopped, an investigation will be conducted, and a findings report will be generated before the study is resumed.

OVERALL STRUCTURE OF THE STUDY TEAM

Principal Investigators: R. Jürgen Kayser, Ph.D.; Ronit Kishon, Ph.D.

Drs. Kayser and Kishon have shared overall responsibility for the entire program of research including design, treatment, analysis, and reporting of the proposed research.

Other Significant Contributors: Gerard E. Bruder, Ph.D.; Steven Hollon, Ph.D.

Drs. Bruder and Hollon will advise the PIs on all aspects of the research that falls within their specific area of expertise, including CBT, experimental implementation, and collection and analysis of dichotic listening behavioral data.

Laboratory Manager / EEG Technician (Psychophysiology Lab): Lidia Wong, M.A.

Project Coordinator (DES): TBH Research Assistant

Psychiatrist (DES): TBD

Biostatistician: Ying Chen, M.D., M.S.

Section 4 - Protocol Synopsis (Study 1)

4.1. Brief Summary

This R21 application aims to clarify the neurobiological mechanisms by which change occurs during cognitive behavior therapy (CBT) for major depressive disorder (MDD). This hypothesis-driven study will explore the association between the psychological constructs of psychological mindedness (PM) and mindfulness (M) during the time course of CBT for MDD, and its relationship to electrophysiological and behavioral measures of automatic (i.e. stimulus-driven or bottom-up) emotion processing. This objective is motivated by the following rationale: PM and M represent different meta-cognitive processes of self-knowledge deemed critical for emotion regulation (ER) and CBT success. Event-related potentials (ERPs) to salient affective pictures reflect different stages of motivated attention. Using advanced analytic EEG techniques, we have linked these stages to the hierarchical activation of 'emotional' brain regions along the occipitotemporal ventral stream, ranging from preconscious stimulus categorization (right secondary visual cortex, right temporoparietal junction) to conscious appraisal (posterior cingulate cortex, ventromedial cortex). Importantly, blunted ERP responses to emotionally-arousing stimuli have been observed in clinical depression, and hypoactivation of right temporoparietal and dorsolateral prefrontal regions normalize after successful antidepressant or electroconvulsive treatment. A dichotic emotion recognition test, which provides an auditory measure of bottom-up emotion processing in form of a left ear (right hemisphere) advantage for recognizing the emotional intonation of speech patterns, has revealed behavioral deficits in MDD patients. Moreover, an increased right ear advantage for verbal stimuli (left hemisphere) is seen in CBT responders. Employing a sample of 60 MDD patients randomly assigned to CBT or nonspecific supportive therapy (placebo), we will obtain psychological, electrophysiological, behavioral and clinical outcome measures of response to 12 weeks of CBT in a pre-post treatment design to determine: (1) when and where in the brain automatic emotion processing is altered by CBT; (2) if changes in emotional responding are moderated or mediated by meta-cognitive processes of self-knowledge; and, (3) if these measures, alone or in combination, have promise as markers of CBT treatment response. Existing ERP and behavioral data for healthy adults (HC) obtained using the same experimental protocols will provide normative (yardstick) data. This study brings together experienced clinical psychologists and psychiatrists doing treatment and research in depression with investigators having expertise in affective neuroscience and electrophysiological studies in MDD. It will provide a critical new step for outlining the affective-cognitive and neurophysiological mechanisms of ER by which change through CBT occurs. Apart from their theoretical relevance, the findings of this project will also aid in developing novel and more targeted interventions and in identifying patients who may benefit most from CBT for unipolar depression.

4.2. Study Design

4.2.a. Narrative Study Description

This research aims to elucidate mechanisms through which change occurs during cognitive behavior therapy (CBT) for depression. Assessing meta-cognitive processes of self-knowledge (top-down), electrophysiological and behavioral correlates of emotion processing (bottom-up), and their relation to treatment outcome will provide new insights into the mechanisms of emotion regulation deficits in depression. It will also contribute toward the clinical goal of identifying patients who may benefit most from CBT for unipolar depression.

4.2.b. Primary Purpose — Basic Science

4.2.c. Interventions

Type	Name	Description
Behavioral (e.g., Psychotherapy, Lifestyle Counseling)	Cognitive Behavior Therapy (CBT)	Following established procedures at the Depression Evaluation Service (DES) at NYSPI, 12 sessions of individual manual-driven CBT (Emery, 2000) will be conducted by highly trained master degree clinicians who are approved and credentialed by Dr. Laura Mufson, the head psychologist at NYSPI. Dr. Kishon will supervise all therapists on a weekly basis.
Behavioral (e.g., Psychotherapy, Lifestyle Counseling)	Nonspecific Supportive Therapy (placebo [PBO])	As a non-CBT intervention that includes warmth, genuineness and empathy (Linde et al., 2011), nonspecific supportive therapy (PBO) will be administered in a parallel format to CBT, also consisting of 12 individual sessions.

4.2.d. Study Phase — Other

exploratory/development, mechanistic study to obtain pilot/feasibility data for larger proposal

Is this an NIH-defined Phase III Clinical Trial? ❍ Yes ● No

4.2.e. Intervention Model: Parallel

4.2.f. Masking: ● Yes ❍ No

❑ Participant ❑ Care Provider ☑ Investigator ☑ Outcomes Assessor

4.2.g. Allocation: Randomized

4.3. Outcome Measures

Type	Name	Time Frame	Brief Description
Primary	17-item Hamilton Rating Scale for Depression (HRSD)	pre- (baseline) to post treatment, monthly	standard clinical instrument (Hamilton, 1960) to assess symptom severity in major depressive disorder (MDD)
Primary	Beck Depression Inventory (BDI-II)	pre- (baseline) to post-treatment, weekly	standard clinical instrument (Beck, 1966) to assess symptom severity in depression
Primary	HRSD rate of symptom change over time (slope)	post-treatment	To obtain a continuous measure of treatment outcome, we will employ a mixed-effects model for all HRSD ratings to compute estimates of each patient's rate of symptom change over time (slope of HRSD scores; Petkova et al., 2017)
Primary	BDI-II rate of symptom change over time (slope)	post-treatment	To obtain a continuous measure of treatment outcome, we will employ a mixed-effects model for all BDI ratings to compute estimates of each patient's rate of symptom change over time (slope of BDI scores; Petkova et al., 2017)
Primary	N2 sink (ERP, Emotional Hemifield Task)	pre- and post-treatment	Early (212 ms peak latency) emotional ERP LPP subcomponent derived from combined CSD-tPCA approach (Kayser et al., 2016, 2017) reflecting asymmetrical neuronal sources involving striate and prestriate cortex in the occipital lobe, with a maximum activation in the right middle temporal gyrus
Primary	P3 source (ERP, Emotional Hemifield Task)	pre- and post-treatment	Mid-latency (385 ms peak latency) emotional ERP LPP subcomponent derived from combined CSD-tPCA approach (Kayser et al., 2016, 2017) reflecting neuronal sources involving medial parietal lobe, with a maximum activation in the posterior cingulate cortex
Primary	CP source (ERP, Emotional Hemifield Task)	pre- and post-treatment	Late (630 ms peak latency) emotional ERP LPP subcomponent derived from combined CSD-tPCA approach (Kayser et al., 2016, 2017) reflecting bilateral generator sources within the temporal lobe, with a maximum activations in uncus and the inferior temporal area
Primary	LEA ERT (dichotic listing behavior, Emotional Recognition Task)	pre- and post-treatment	measures extent of right hemisphere dominance or left ear advantage (LEA) for recognizing prosody during a dichotic emotional recognition task (Bruder et al., 2015)
Secondary	REA Fused Words (dichotic listing behavior)	pre- and post-treatment	measures extent of left hemisphere dominance or right ear advantage (REA) for verbal processing (Bruder et al., 1997, 2017)

Other	Clinical Global Impressions [CGI] scale	pre- (baseline) to post-treatment, weekly	standard clinical instrument (Guy, 1976) to assess symptom severity and change in depression (required by IRB)
Primary	Responder Yes/No	post-treatment	binary outcome: greater or equal 50% reduction of symptoms from baseline for either HRSD or BDI score
Primary	Remitter Yes/No	post-treatment	binary outcome: improvement to asymptomatic within normal range (HRSD less or equal 7; BDI less than 13)
Primary	Self-Reflection and Insight Scale (SRIS)	pre- (baseline), mid-point (6 wks), post treatment	20-item SRIS measures Self-Reflection and Insight as two core aspects of dispositional Psychological Mindedness (PM)
Primary	Psychological Mindedness Scale (PMS)	pre- (baseline), mid-point (6 wks), post treatment	45-item PMS measures (1) willingness to understand oneself/others; (2) openness to new ideas/capacity to change; (3) access to feelings; (4) belief in the benefits of discussing one's problems; (5) interest in the meaning of behavior as aspects of dispositional Psychological Mindedness (PM)
Secondary	Toronto Alexithymia Scale (TAS)	pre- (baseline), mid-point (6 wks), post treatment	20-item TAS is inversely related to PM and measures the inability of emotional awareness
Primary	Mindful Attention Awareness Scale (MAAS)	pre- (baseline), mid-point (6 wks), post treatment	15-item MAAS measures the attentional components of dispositional Mindfulness (M)
Primary	Five-Facet Mindfulness Questionnaire (FFMQ)	pre- (baseline), mid-point (6 wks), post treatment	FFMQ assesses the psychological aspects of Mindfulness (M)
Primary	Emotion Regulation Questionnaire (ERQ)	pre- (baseline), mid-point (6 wks), post treatment	ERQ assesses the tendency to regulate emotions via cognitive reappraisal and expressive suppression

4.4. Statistical Design and Power — R21KayKis-StatDesignPower 2019-11-15.pdf

4.5. Subject Participation Duration — 3-4 months

4.6. Will the study use an FDA-regulated intervention? — ❍ Yes ● No

4.6.a. If yes, describe the availability of Investigational Product (IP) and Investigational New Drug (IND)/ Investigational Device Exemption (IDE) status

4.7. Dissemination Plan — R21KayKis-DisseminationPlan 2019-11-12.pdf

STATISTICAL DESIGN AND POWER

The basic study design is a two-group pre-/post-treatment design (N = 60, n = 30/Tx arm). Given assumed retention rates of .9 at baseline (pre-Tx) and .8 after the intervention (post-Tx), we anticipate a sample size of N = 54 (n = 27/Tx arm) at baseline, and N = 48 (n = 24/Tx arm) post-treatment. Accordingly, repeated measures ANOVA for mixed designs (including between- and within-subjects variables as required) will be used for EHT/ERT measures, employing an unstructured covariance matrix (BMDP-5V [58]) with sex, age, and parental SES as covariates (handedness, exercise and sleep scores will be included if necessary; significant covariates will prompt further exploratory analyses). Unlike F statistics (4V[58]), 5V computes maximum likelihood estimates and Wald test χ^2 statistics within a linear regression model that allows imputation of missing data (e.g. unbalanced designs due to missing observations) and inclusion of time-varying covariates (M/PM). The 5V program is especially suited to longitudinal studies.

For baseline comparison purposes (i.e. to evaluate the predicted hypoarousal to emotional stimuli in MDD), existing EHT/ERT data from healthy adults [23,129] will be used. Using these data, 48 healthy controls (HCs) will be matched to the present MDD patients with regard to sex, age, and handedness, thereby providing a meaningful yardstick.

For the ERP measures that include a 72-site component topography (N2 sink, P3 source, CP source), non-parametric permutation tests will also evaluate emotional differences in CSD topography [101, 125, 127, 129, 157] for each group (Tx [CBT/PBO], Responder/Remitter [yes/no]). This serves a dual purpose. First, it will provide an unbiased evaluation of component- and group-specific emotional effects (see Kayser et al., 2017). Second, it will allow an unbiased identification of regions-of-interests (ROIs) that best characterize (or maximize) emotional effects (i.e. negative-greater-than-neutral stimuli), which in turn can then be used as ROIs in a repeated measures ANOVA as described above (e.g. including hemisphere and/or sites as additional within-subjects variables; e.g. Kayser et al., 2016, 2017).

To test whether CBT responders having reduced emotional LEA but increased verbal REA (i.e. double dissociation with a secondary behavioral outcome measure), dichotic listing task (ERT vs. Fused Words) will be included as another within-subject variable in a repeated measures ANOVA as described above.

For the sole purpose of estimating approximate sensitivities (for small to large effect sizes, f = .1 to .4) at 80% power (p < .05), repeated measures ANOVA (r_{within} = .7; final N = 48) and fixed-effects ANCOVA (adding 48 HCs for baseline comparison) were evaluated via G*Power[67]. Required effect sizes (f) were .32 (***H1***, ***H5***), .29 (***H2***), .21 (***H3***, ***H4***, ***H6***). The association between LEA and N2 (***H7***) will be tested with linear (Pearson's) and non-parametric correlations, allowing to detect $r \geq 0.35$ (medium effect size) at 80% power.

While this suggests adequate power to detect small-medium to medium-large effect sizes for our first 3 specific aims, due to the limitations of an exploratory R21 mechanism (time and money) that imposes feasability constraints on sample size, we are somewhat underpowered for our 4th exploratory aim (***H8***-***H10***).

To assess the prognostic value of PM/M before and during CBT, and their relationship with EHT/ERT measures pre/post CBT (***H8***), we will fit separate multiple predictor, mixed-effect regression models for BDI, HRSD, rate of symptom change (using a mixed-effects model for all monthly HRSD or all weekly BDI ratings will estimate the improvement [decline of depressed symptoms over time for each patient [131, 182]), or EHT/ERT as outcomes, with time point, baseline PM/M/ER as predictors, adjusted for baseline depression scores as covariate, and subject-specific intercepts and slopes [147]. In a second model, time-varying PM/M/ER scores will be used as predictors with lagged values (baseline PM/M/ER for mid-Tx, mid-Tx PM/M/ER for post-Tx response). In secondary analyses, we will run logistic regression models with binary Tx outcome (responder/remitter yes/no) with baseline PM/M/ER scores as predictors [50, 58].

Effect sizes (small to large, d = .2 to .8 [39]) for the mixed-effect regression models – estimated via the R library *longpower* [155] – were 0.79 and 1.12 (both/single Tx arm), more than enough for the large effects observed in our preliminary data for PM/M measures; however, comparable ERP and DL effects are yet unknown but those will be generated during this R21 project. ***H9-H10***: To explore whether PM/M scores pre/post Tx are mediators and/or moderators of CBT outcome and/or EHT/ERT, we will fit mixed-effect regression models with baseline EHT (ERT), PM (M, ER), and their interactions as predictors of time-varying depression scores during and after CBT. Then, we fit a mediation model with time-varying predictor and mediator, where lagged values of EHT (or ERT) and PM (or M, or ER) will be used to predict depression score during/post CBT. Although this R21 will not provide enough power for a formal mediation test of this exploratory aim, we will estimate and report the direct and indirect effects of EHT/ERT on depression with 95% CI. If we document meaningful effect sizes, we will pursue a larger R01 follow-up study with a sample size sufficient to achieve adequate power.

DISSEMINATION PLAN

Upon notice of award, the principal investigators (Drs. Kayser and Kishon) or a designee will be responsible for registering the clinical trial and reporting the summary results in ClinicalTrials.gov, as outlined in the NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information. NYSPI/RFMH has a Clinical Trials Disclosure Policy which establishes institutional requirements to comply with the NIH policy and applicable federal regulations. The NYSPI Office of Clinical Research is available to support investigators with registering or entering summary results into the ClinicalTrials.gov database.

Record information will be entered within the timelines specified in the policy. Once a record is established, the PIs will confirm accuracy of record content; resolve problems; and maintain records including content update and modifications. The PIs will also be responsible for reporting *Results* and *Adverse Events* at the conclusion of the project. Informed consent documents will include a statement that the study will be posted on ClinicalTrials.gov.

As this proposal represents a mechanistic clinical trial with high relevance to basic science, we also anticipate dissemination of findings as manuscript submissions to high-impact journals (e.g. *Biological Psychiatry*, *NeuroImage: Clinical*, *Psychophysiology*, *International Journal of Psychophysiology*, *Psychological Medicine*, *Psychiatry Research: Neuroimaging*) and as presentations by the PIs at scientific meetings.

BIBLIOGRAPHY & REFERENCES CITED

1 Aldao A, Nolen-Hoeksema S, Schweizer S (2010). Emotion-regulation strategies across psychopathology: A meta-analytic review. Clin. Psychol. Rev. 30(2):217-237.

2 Alschuler DM, Tenke CE, Bruder GE, Kayser J (2014). Identifying electrode bridging from electrical distance distributions: a survey of publicly-available EEG data using a new method. Clin. Neurophysiol. 125(3):484-490.

3 American Psychiatric Association (Eds.) (2013). *Diagnostic and Statistical Manual of the Mental Disorders. Fifth Edition (DSM-5)*. American Psychiatric Association, Washington, DC.

4 Anderson AK, Christoff K, Panitz D, De Rosa E, Gabrieli JD (2003). Neural correlates of the automatic processing of threat facial signals. J. Neurosci. 23(13):5627-5633.

5 Bagby RM, Parker JD, Taylor GJ (1994). The twenty-item Toronto Alexithymia Scale--I. Item selection and cross-validation of the factor structure. J. Psychosom. Res. 38(1):23-32.

6 Bagby RM, Taylor GJ (1997). Measurement and validation of the alexithymia construct. In: G.J. Taylor, R.M. Bagby, J.D.A. Parker (Eds.), *Disorders of affect regulation: alexithymia in medical and psychiatric illness*, Cambridge University Press, Cambridge, MA, pp. 46-66.

7 Baer RA, Smith GT, Allen KB (2004). Assessment of mindfulness by self-report: the Kentucky inventory of mindfulness skills. Assessment 11(3):191-206.

8 Baer RA, Smith GT, Hopkins J, Krietemeyer J, Toney L (2006). Using self-report assessment methods to explore facets of mindfulness. Assessment 13(1):27-45.

9 Barber JP, DeRubeis RJ (1989). On second thought: where the action is in cognitive therapy for depression. Cogn. Ther. Res. 13(5):441-457.

10 Beauducel A, Debener S, Brocke B, Kayser J (2000). On the reliability of augmenting/reducing: peak amplitudes and principal components analysis of auditory evoked potentials. J Psychophysiol 14(4):226-240.

11 Beck AT (2016). *The self in understanding and treating psychological disorders* (Kyrios M, Moulding R, Doron G, Bhar S, Nedeljkovic M, Mikulincer M, Eds.). Cambridge: Cambridge University Press. *doi: 10.1017/CBO9781139941297*

12 Beck AT, Steer RA, Brown GK (1996). *Beck Depression Inventory. Second Edition (BDI-II)*. The Psychological Corporation: Harcourt Brace & Company, New York, NY.

13 Becker NB, Jesus SN, Joao KADR, Viseu JN, Martins RIS (2017). Depression and sleep quality in older adults: a meta-analysis. Psychol. Health Med. 22(8):889-895.

14 Beitel M, Cecero JJ (2003). Predicting psychological mindedness from personality style and attachment security. J. Clin. Psychol. 59(1):163-172.

15 Beitel M, Ferrer E, Cecero JJ (2005). Psychological mindedness and awareness of self and others. J. Clin. Psychol. 61(6):739-750.

16 Berking M, Ebert D, Cuijpers P, Hofmann SG (2013). Emotion regulation skills training enhances the efficacy of inpatient cognitive behavioral therapy for major depressive disorder: a randomized controlled trial. Psychother. Psychosom. 82:234-245.

17 BioSemi, Inc. (2001). ActiveTwo - Multichannel, DC amplifier, 24-bit resolution, biopotential measurement system with active electrodes (http://www.biosemi.com). Author, Amsterdam, NL.

18 Bradley MM (2009). Natural selective attention: orienting and emotion. Psychophysiology 46(1):1-11.

19 Bradley MM, Keil A, Lang PJ (2012). Orienting and emotional perception: facilitation, attenuation, and interference. Front. Psychol. 3:493.

20 Bradley MM, Lang PJ (2007). The International Affective Picture System (IAPS) in the study of emotion and attention. In: J.A. Coan, J.J.B. Allen (Eds.), *Handbook of Emotion Elicitation and Assessment*, Oxford University Press, New York, pp. 29-46.

21 Brisbon NM, Lowery GA (2011). Mindfulness and levels of stress: a comparison of beginner and advanced Hatha Yoga practitioners. J. Relig. Health. 50(4):931-941.

22 Brown KW, Ryan RM (2003). The benefits of being present: mindfulness and its role in psychological well-being. J. Pers. Soc. Psychol. 84(4):822-848.

23 Bruder GE, Alvarenga J, Abraham K, Skipper J, Warner V, Voyer D, Peterson BS, Weissman MM (2016). Brain laterality, depression and anxiety disorders: new findings for emotional and verbal dichotic listening in individuals at risk for depression. Laterality 21:525-548. *doi: 10.1080/1357650X.2015.1105247*

24 Bruder GE, Haggerty A, Siegle GJ (2017). A quick behavioral dichotic word test is prognostic for clinical response to cognitive therapy for depression: a replication study. Psychiatry Res. 248:13-19.

[25] Bruder GE, Stewart JW, McGrath PJ (2017). Right brain, left brain in depressive disorders: Clinical and theoretical implications of behavioral, electrophysiological and neuroimaging findings. Neurosci. Biobehav. Rev. 78:178-191.

[26] Bruder GE, Stewart JW, Mercier MA, Agosti V, Leite P, Donovan S, Quitkin FM (1997). Outcome of cognitive-behavioral therapy for depression: relation to hemispheric dominance for verbal processing. J. Abnorm. Psychol. 106(1):138-144.

[27] Bryden MP, MacRae L (1988). Dichotic laterality effects obtained with emotional words. Neuropsychiatry Neuropsychol. Behav. Neurol. 1(3):171-176.

[28] Bryson SE, McLaren J, Wadden NP, MacLean M (1991). Differential asymmetries for positive and negative emotion: hemisphere or stimulus effects? Cortex 27(3):359-365.

[29] Butler AC, Chapman JE, Forman EM, Beck AT (2006). The empirical status of cognitive-behavioral therapy: a review of meta-analyses. Clin. Psychol. Rev. 26(1):17-31.

[30] Busner J, Targum SD (2007). The clinical global impressions scale: applying a research tool in clinical practice. Psychiatry (Edgmont) 4(7):28-37.

[31] Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ (1989). The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 28(2):193-213.

[32] Campbell R (1982). The lateralization of emotion: a critical review. Int. J. Psychophysiol. 17(2-3):211-229.

[33] Carlson EN (2013). Overcoming the barriers to self-knowledge: mindfulness as a path to seeing yourself as you really are. Perspect. Psychol. Sci. 8:173-186.

[34] Caspersen CJ, Powell KE, Christenson GM (1985). Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Rep. 100(2):126-131.

[35] Cecero JJ, Beitel M, Prout T (2008). Exploring the relationships among early maladaptive schemas, psychological mindedness and self-reported college adjustment. Psychol. Psychother. 81(1):105-118.

[36] Chambers R, Gullone E, Allen NB (2009). Mindful emotion regulation: an integrative review. Clin. Psychol. Rev. 29(6):560-572.

[37] Clark DME, Fairburn CG (1997). Science and practice of cognitive behaviour therapy. Oxford University Press, New York.

[38] Coffey KA, Hartman M, Fredrickson BL (2010). Deconstructing mindfulness and constructing mental health: understanding mindfulness and its mechanisms of action. Mindfulness 1(4):235-253.

[39] Cohen J (1988). *Statistical power analysis for the behavioral sciences (2nd Ed.)*. Hillsdale, NJ, Erlbaum.

[40] Conte HR, Ratto R, Karasu TB (1996). The psychological mindedness scale: factor structure and relationship to outcome of psychotherapy. J. Psychother. Pract. Res. 5(3):250-259.

[41] Cooper AA, Conklin LR (2015). Dropout from individual psychotherapy for major depression: a meta-analysis of randomized clinical trials. Clin. Psychol. Rev. 40:57-65.

[42] Cooney G, Dwan K, Mead G (2014). Exercise for depression. JAMA 311(23):2432-2433.

[43] Corbetta M, Shulman GL (2002). Control of goal-directed and stimulus-driven attention in the brain. Nat. Rev. Neurosci. 3(3):201-215.

[44] Corcoran KM, Farb N, Anderson A, Segal ZV (2010). Mindfulness and emotion regulation: outcomes and possible mediating mechanisms. In: Kring AM, Sloan DM (Eds.) *Emotion Regulation and Psychopathology: A Transdiagnostic Approach to Etiology and Treatment*, New York, NY, US: The Guilford Press, pp 339-355.

[45] Cousin G, Page D (2015). Does patients' pretreatment trait-mindfulness predict the success of cognitive psychotherapy for emotion regulation? Mindfulness 6(2):186-191.

[46] Cuijpers P, Cristea IA, Karyotaki E, Reijnders M, Hollon SD (2019). Component studies of psychological treatments of adult depression: a systematic review and meta-analysis. Psychother. Res. 29:15-29.

[47] Cuijpers P, Noma H, Karyotaki E, Cipriani A, Furukawa TA (2019). Effectiveness and acceptability of cognitive behavior therapy delivery formats in adults with depression: a network meta-analysis. JAMA Psychiatry 76:700-707.

[48] Cuijpers P, Weitz E, Twisk J, Kuehner C, Cristea I, David D, et al (2014). Gender as predictor and moderator of outcome in cognitive behavior therapy and pharmacotherapy for adult depression: an “individual patient data” meta-analysis. Depress. Anxiety 31(11):941-951.

[49] Cuthbert BN, Schupp HT, Bradley MM, Birbaumer N, Lang PJ (2000). Brain potentials in affective picture processing: covariation with autonomic arousal and affective report. Biol. Psychol. 52(2):95-111.

[50] Cox DR (1958). The regression analysis of binary sequences. J. Roy. Stat. Soc. B. 20(2):215-242.

[51] Dalili MN, Penton Voak IS, Harmer CJ, Munafo MR (2015). Meta-analysis of emotion recognition deficits in major depressive disorder. Psychol. Med. 45(6):1135-1144.

[52] David D, Montgomery GH (2011). The scientific status of psychotherapies: a new evaluative framework for evidence-based psychosocial interventions. Clin. Psychol. Sci. Pract. 18(2):89–99.

[53] Davidson RJ (1995). Cerebral asymmetry, emotion, and affective style. In: Davidson RJ, Hugdahl K (Eds.), *Brain Asymmetry*, MIT Press, Cambridge, MA, pp. 361-387.

[54] Davidson RJ, Jackson DC, Kalin NH (2000). Emotion, plasticity, context, and regulation: perspectives from affective neuroscience. Psychol. Bull. 126(6):890-909.

[55] Delplanque S, Lavoie ME, Hot P, Silvert L, Sequeira H (2004). Modulation of cognitive processing by emotional valence studied through event-related potentials in humans. Neurosci. Lett. 356(1):1-4.

[56] Delplanque S, N'diaye K, Scherer K, Grandjean D (2007). Spatial frequencies or emotional effects? A systematic measure of spatial frequencies for IAPS pictures by a discrete wavelet analysis. J. Neurosci. Methods 165(1):144-150.

[57] DeRubeis RJ, Hollon SD, Amsterdam JD, Shelton RC, Young PR, Salomon RM, O'Reardon JP, Lovett ML, Gladis MM, Brown LL, Gallop R (2005). Cognitive therapy vs medications in the treatment of moderate to severe depression. Arch. Gen. Psychiatry 62(4):409-416.

[58] Dixon WJ (Ed.) (1992). *BMDP Statistical Software Manual: To Accompany the 7.0 Software Release*. University of California Press, Berkeley, CA.

[59] Dobson KS, Shaw BF, Vallis TM (1985). Reliability of a measure of the quality of cognitive therapy. Br. J. Clin. Psychol. 24(4):295-300.

[60] Domschke K, Zwanzger P, Rehbein MA, Steinberg C, Knoke K, Dobel C, Klinkenberg I, Kugel H, Kersting A, Arolt V, Pantev C, Junghöfer M (2015). Magnetoencephalographic correlates of emotional processing in major depression before and after pharmacological treatment. Int. J. Neuropsychopharmcol. 19(2):1-9. *doi: 10.1093/ijnp/pyv093*

[61] Dore BP, Silvers JA, Ochsner KN (2016). Toward a personalized science of emotion regulation. Soc. Personal. Psychol. Compass. 10:171-187.

[62] Driessen E, Hollon SD (2010). Cognitive behavioral therapy for mood disorders: efficacy, moderators and mediators. Psychiatr. Clin. North Am. 33:537-555.

[63] Dunlop BW, Rajendra JK, Craighead WE, Kelley ME, McGrath CL, Choi KS, et al (2017). Functional connectivity of the subcallosal cingulate cortex and differential outcomes to treatment with cognitive-behavioral therapy or antidepressant medication for major depressive disorder. Am. J. Psychiatry 174(6):533-545.

[64] Emery G (2000). *Overcoming Depression. A Cognitive-behavior Protocol for the Treatment of Depression*. Oakland: New Harbinger Publications.

[65] Etkin A, Buchel C, Gross JJ (2015). The neural bases of emotion regulation. Nat. Rev. Neurosci. 16:693-700.

[66] Falcone G, Jerram M (2018). Brain activity in mindfulness depends on experience: a meta-analysis of fMRI studies. Mindfulness 9:1319-1329.

[67] Faul F, Erdfelder E, Lang AG, Buchner A (2007). G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 39(2):175-191.

[68] Fernandez KC, Jazaieri H, Gross JJ (2016). Emotion regulation: a transdiagnostic perspective on a new RDoC domain. Cogn. Ther. Res. 1-15. *doi: 10.1007/s10608-016-9772-2*

[69] First MB, Spitzer RL, Gibbon M, Williams JBW (1994). The structural clinical interview for DSM-IV Axis-I Disorders - Patient Edition (SCID-I/P, Version 2.0). Biometrics Research Department, New York State Psychiatric Institute, New York, NY.

[70] First MB, Spitzer RL, Gibbon M, Williams JBW (1996). Structured Clinical Interview for DSM-IV Axis-I Disorders - Non-patient Edition (SCID-NP). Biometrics Research Department, New York State Psychiatric Institute, New York, NY.

[71] Flavell JH (1979). Metacognition and cognitive monitoring: a new area of cognitive developmental inquiry. Am. Psychol. 34(10):906-911.

[72] Foti D, Olvet DM, Klein DN, Hajcak G (2010). Reduced electrocortical response to threatening faces in major depressive disorder. Depress. Anxiety 27(9):813-820.

[73] Frank DW, Dewitt M, Hudgens-Haney M, Schaeffer DJ, Ball BH, Schwarz NF, Hussein AA, Smart LM, Sabatinelli D (2014). Emotion regulation: quantitative meta-analysis of functional activation and deactivation. Neurosci. Biobehav. Rev. 45:202-211.

[74] Freedman LZ, Hollingshead AB (1957). Neurosis and social class. I. Social interaction. Am. J. Psychiatry 113(9):769-775.

[75] Fresco DM (2013). Tending the garden and harvesting the fruits of behavior therapy. Behav. Ther. 44(2):177-179.

[76] Goldberg SB, Tucker RP, Greene PA, Davidson RJ, Wampold BE, Kearney DJ, Simpson TL (2018). Mindfulness-based interventions for psychiatric disorders: a systematic review and meta-analysis. Clin. Psychol. Rev. 59:52-60.

[77] Goyal M, Singh S, Sibinga EM, Gould NF, Rowland Seymour A, Sharma R, et al (2014). Meditation programs for psychological stress and well-being: a systematic review and meta-analysis. JAMA Intern. Med. 174(3):357-368.

[78] Grant AM (2001). Rethinking psychological mindedness: metacognition, self-reflection, and insight. Behav. Change 18(1):8-17.

[79] Grant AM, Franklin J, Langford P (2002). The self-reflection and insight scale: a new measure of private self-consciousness. Soc. Behav. Pers. 30(8):821-835.

[80] Greer TL, Furman JL, Trivedi MH (2017). Evaluation of the benefits of exercise on cognition in major depressive disorder. Gen. Hosp. Psychiatry 49:19-25.

[81] Groenewold NA, Opmeer EM, de Jonge P, Aleman A, Costafreda SG (2013). Emotional valence modulates brain functional abnormalities in depression: evidence from a meta-analysis of fMRI studies. Neurosci. Biobehav. Rev. 37:152-163.

[82] Gross JJ, John OP (2003). Individual differences in two emotion regulation processes: implications for affect, relationships, and well-being. J. Pers. Soc. Psychol. 85:348-362.

[83] Gross JJ, Munoz RF (1995). Emotion regulation and mental health. Clin. Psychol. Sci. Pract. 2(2):151-164.

[84] Guendelman S, Medeiros S, Rampes H (2017). Mindfulness and emotion regulation: insights from neurobiological, psychological, and clinical studies. Front. Psychol. 8:220.

[85] Guy W (1976). Clinical Global Impressions (028-CGI). In: W. Guy (Ed.), *ECDEU Assessment Manual for Psychopharmacology, Revised Edition*, NIMH Publication, Rockville, MD, pp. 217-222.

[86] Hajcak G, Weinberg A, MacNamara A, Foti D (2012). ERPs and the study of emotion. In: S.J. Luck, E.S. Kappenman (Eds.), *The Oxford Handbook of Event-Related Potential Components*, Oxford University Press, New York, pp. 441-472.

[87] Hall JA (1992). Psychological-mindedness: a conceptual model. Am. J. Psychother. 46(1):131-140.

[88] Hamilton M (1960). A rating scale for depression. J. Neurol. Neurosurg. Psychiatry 23:56-62.

[89] Hargus E, Crane C, Barnhofer T, Williams JMG (2010). Effects of mindfulness on meta-awareness and specificity of describing prodromal symptoms in suicidal depression. Emotion 10:34-42.

[90] Harrington R, Loffredo DA, Perz CA (2014). Dispositional mindfulness as a positive predictor of psychological well-being and the role of the private self-consciousness insight factor. Pers. Ind. Diff. 71:15-18.

[91] Heppner WL, Spears CA, Vidrine JI, Wetter DW (2015). Mindfulness and emotion regulation. In: Ostafin BD, Robinson MD, Meier BP (Eds.), *Handbook of Mindfulness and Self-Regulation* (pp. 107-120). New York: Springer Science +Business Media.

[92] Herwig U, Kaffenberger T, Jancke L, Bruhl AB (2010). Self-related awareness and emotion regulation. NeuroImage 50:734-741.

[93] Herwig U, Opialla S, Cattapan K, Wetter TC, Jancke L, Bruhl AB (2018). Emotion introspection and regulation in depression. Psychiatry research Neuroimaging 277:7-13.

[94] Hofmann SG (2014). Toward a cognitive-behavioral classification system for mental disorders. Behav. Ther. 45(4):576-587.

[95] Hofmann SG, Asmundson GJ (2008). Acceptance and mindfulness-based therapy: new wave or old hat? Clin. Psychol. Rev. 28(1):1-16.

[96] Hofmann SG, Asmundson GJ, Beck AT (2013). The science of cognitive therapy. Behav. Ther. 44(2):199-212.

[97] Hollingshead AB (1975). *Four factor index of social status (Unpublished manuscript)*. Yale University, New Haven, CT.

[98] Horowitz MJ (2002). Self- and relational observation. J. Psychother. Integr. 12(2):115-127.

[99] Hugdahl K, Bodner T, Weiss E, Benke T (2003). Dichotic listening performance and frontal lobe function. Brain Res. Cogn. Brain Res. 16(1):58-65.

[100] Hugdahl K, Westerhausen R, Alho K, Medvedev S, Laine M, Hamalainen H (2009). Attention and cognitive control: unfolding the dichotic listening story. Scand. J. Psychol. 50(1):11-22.

[101] Huo M, Heyvaert M, Van den Noortgate W, Onghena P (2013). Permutation tests in the educational and behavioral sciences: a systematic review. Methodology. 2013 May 13. Online first publication. 1-17. *doi: 10.1027/1614-2241/a000067.*

[102] Ito TA, Larsen JT, Smith NK, Cacioppo JT (1998). Negative information weighs more heavily on the brain: the negativity bias in evaluative categorizations. J. Pers. Soc. Psychol. 75(4):887-900.

[103] Jarrett RB, Vittengl JR (2015). The efficacy of cognitive behavioral therapy for depression. In: Wells A, Fisher PL (Eds.), *Treating Depression: MCT, CBT and Third Wave Therapies* (pp. 52-80), John Wiley & Sons Ltd.

[103] Junghöfer M, Sabatinelli D, Bradley MM, Schupp HT, Elbert TR, Lang PJ (2006). Fleeting images: rapid affect discrimination in the visual cortex. Neuroreport 17(2):225-229.

[104] Jurcak V, Tsuzuki D, Dan I (2007). 10/20, 10/10, and 10/5 systems revisited: their validity as relative head-surface-based positioning systems. Neuroimage 34(4):1600-1611.

[105] Kadzin AE (2015). Treatment as usual and routine care in research and clinical practice. Clin. Psychol. Rev. 42:168-178.

[106] Kantrowitz JT, Hoptman MJ, Leitman DI, Moreno-Ortega M, Lehrfeld JM, Dias E, Sehatpour P, Laukka P, Silipo G, Javitt DC (2015). Neural substrates of auditory emotion recognition deficits in schizophrenia. J. Neurosci. 35(44):14909-14921.

[107] Karageorghis CI, Vencato MM, Chatzisarantis NL, Carron AV (2005). Development and initial validation of the Brunel Lifestyle Physical Activity Questionnaire. Br. J. Sports Med. 39(5):23.

[108] Kaunhoven RJ, Dorjee D (2017). How does mindfulness modulate self-regulation in pre-adolescent children? An integrative neurocognitive review. Neurosci. Biobehav. Rev. 74():163-184.

[109] Kayser J (2003). Polygraphic Recording Data Exchange - PolyRex (http://psychophysiology.cpmc.columbia.edu/PolyRex.htm). Department of Biopsychology, New York State Psychiatric Institute.

[110] Kayser J (2008). Ereignisbezogene elektrodermale und cortikale Indikatoren der Lateralisation von Emotion Event-related electrodermal and cortical indices of emotional lateralization. In: W. Janke, M. Schmidt-Daffy, G. Debus (Eds.), *Experimentelle Emotionspsychologie: Methodische Ansätze, Probleme und Ergebnisse* Experimental Psychology of Emotion: Methodological Approaches, Problems and Results, Pabst Science Publishers, Lengerich, pp. 523-545.

[111] Kayser J (2009). Current Source Density (CSD) Interpolation using Spherical Splines - CSD Toolbox. Version 1.1 *http://psychophysiology.cpmc.columbia.edu/CSDtoolbox.html*. Division of Cognitive Neuroscience, New York State Psychiatric Institute.

[112] Kayser J, Tenke CE (2003). Optimizing PCA methodology for ERP component identification and measurement: theoretical rationale and empirical evaluation. Clin. Neurophysiol. 114(12):2307-2325.

[113] Kayser J, Tenke CE (2005). Trusting in or breaking with convention: towards a renaissance of principal components analysis in electrophysiology. Clin. Neurophysiol. 116(8):1747-1753.

[114] Kayser J, Tenke CE (2006a). Principal components analysis of Laplacian waveforms as a generic method for identifying ERP generator patterns: I. Evaluation with auditory oddball tasks. Clin. Neurophysiol. 117(2):348-368.

[115] Kayser J, Tenke CE (2006b). Principal components analysis of Laplacian waveforms as a generic method for identifying ERP generator patterns: II. Adequacy of low-density estimates. Clin. Neurophysiol. 117(2):369-380.

[116] Kayser J, Tenke CE (2006c). Consensus on PCA for ERP data, and sensibility of unrestricted solutions. Clin. Neurophysiol. 117(3):703-707.

[117] Kayser J, Tenke CE (2006d). Electrical distance as a reference-free measure for identifying artifacts in multichannel electroencephalogram (EEG) recordings. Psychophysiology 43:S51. *http://psychophysiology.cpmc.columbia.edu/mmedia/spr2006/ElecDistArti.pdf*

[118] Kayser J, Tenke CE (2010). In search of the Rosetta Stone for scalp EEG: converging on reference-free techniques. Clin. Neurophysiol. 121(12):1973-1975.

[119] Kayser J, Tenke CE (2015a). Hemifield-dependent N1 and event-related theta/delta oscillations: an unbiased comparison of surface Laplacian and common EEG reference choices. Int. J. Psychophysiol. 97(3):258-270.

[120] Kayser J, Tenke CE (2015b). Issues and considerations for using the scalp surface Laplacian in EEG/ERP research: a tutorial review. Int. J. Psychophysiol. 97(3):189-209.

[121] Kayser J, Tenke CE (2015c). On the benefits of using surface Laplacian (current source density) methodology in electrophysiology. Int. J. Psychophysiol. 97(3):171-173.

[122] Kayser J, Tenke C, Nordby H, Hammerborg D, Hugdahl K, Erdmann G (1997). Event-related potential (ERP) asymmetries to emotional stimuli in a visual half-field paradigm. Psychophysiology 34(4):414-426.

[123] Kayser J, Bruder GE, Tenke CE, Stewart JE, Quitkin FM (2000). Event-related potentials (ERPs) to hemifield presentations of emotional stimuli: differences between depressed patients and healthy adults in P3 amplitude and asymmetry. Int. J. Psychophysiol. 36(3):211-236.

[124] Kayser J, Tenke CE, Gates NA, Kroppmann CJ, Gil RB, Bruder GE (2006). ERP/CSD indices of impaired verbal working memory subprocesses in schizophrenia. Psychophysiology 43(3):237-252.

[125] Kayser J, Tenke CE, Gates NA, Bruder GE (2007). Reference-independent ERP old/new effects of auditory

and visual word recognition memory: joint extraction of stimulus- and response-locked neuronal generator patterns. Psychophysiology 44(6):949-967.

[126] Kayser J, Tenke CE, Gil RB, Bruder GE (2009). Stimulus- and response-locked neuronal generator patterns of auditory and visual word recognition memory in schizophrenia. Int J Psychophysiol 73(3):186-206.

[127] Kayser J, Tenke CE, Kroppmann CJ, Fekri S, Alschuler DM, Gates NA, Gil R, Harkavy-Friedman JM, Jarskog LF, Bruder GE (2010). Current source density (CSD) old/new effects during recognition memory for words and faces in schizophrenia and in healthy adults. Int J Psychophysiol 75(2):194-210.

[128] Kayser J, Tenke CE, Kroppmann CJ, Alschuler DM, Fekri S, Gil R, Jarskog LF, Harkavy-Friedman JM, Bruder GE (2012). A neurophysiological deficit in early visual processing in schizophrenia patients with auditory hallucinations. Psychophysiology 49(9):1168-1178.

[129] Kayser J, Tenke CE, Abraham K, Alschuler DM, Alvarenga JE, Skipper J, Warner V, Bruder GE, Weissman MM (2016). Neuronal generator patterns at scalp elicited by lateralized aversive pictures reveal consecutive stages of motivated attention. NeuroImage 142:337-350.

[130] Kayser J, Tenke CE, Abraham KS, Alschuler DM, Alvarenga JE, Skipper J, Warner V, Bruder GE, Weissman MM (2017). Motivated attention and family risk for depression: neuronal generator patterns at scalp elicited by lateralized aversive pictures reveal blunted emotional responsivity. NeuroImage: Clinical 14:692-707.

[131] Kayser J, Tenke CE, Petkova E, Wong LYX, Wickramaratne P, Alschuler DM, et al (2018). Loudness dependency of auditory evoked potentials (LDAEP) as a differential predictor of antidepressant treatment response in major depressive disorder (MDD): results from the sertraline/placebo-controlled EMBARC study. Biol Psychiatry 83:S383-S384.

[132] Kayser J, Tenke CE, Svob C, Gameroff MJ, Miller L, Skipper J, Warner V, Wickramaratne P, Weissman MM (2019, in revision). Family risk for depression and prioritization of religion or spirituality: early neurophysiological modulations of motivated attention. Front. Hum. Neurosci.

[133] Keil A, Bradley MM, Hauk O, Rockstroh B, Elbert T, Lang PJ (2002). Large-scale neural correlates of affective picture processing. Psychophysiology 39(5):641-649.

[134] Keil A, Smith JC, Wangelin BC, Sabatinelli D, Bradley MM, Lang PJ (2008). Electrocortical and electrodermal responses covary as a function of emotional arousal: a single-trial analysis. Psychophysiology 45(4):516-523.

[135] Keil A, Sabatinelli D, Ding M, Lang PJ, Ihssen N, Heim S (2009). Re-entrant projections modulate visual cortex in affective perception: evidence from Granger causality analysis. Hum. Brain Mapp. 30:532-540.

[136] Kendler KS, Gardner CO (2014). Sex differences in the pathways to major depression: a study of opposite-sex twin pairs. Am. J. Psychiatry 171(4):426-435.

[137] Kessler RC (2003). Epidemiology of women and depression. J. Affect. Disord. 74(1):5-13.

[138] Kingston T, Dooley B, Bates A, Lawlor E, Malone K (2007). Mindfulness-based cognitive therapy for residual depressive symptoms. Psychol. Psychother. 80(2):193-203.

[139] Kishon R, Abraham K, Alschuler DM, Keilp JG, Stewart JW, McGrath PJ, Bruder GE (2015). Lateralization for speech predicts therapeutic response to cognitive behavioral therapy for depression. Psychiatry Res. 228(3): 606-611.

[140] Kishon R, Westphal M, Geronazzo-Alman L, Miller J, Cheng B, Love M, David G, Sarda A, Stewart JW (2016). Psychological mindedness and alexithymia as predictors of treatment outcome in CBT for depression. Presented at the *50th Annual Convention of the Association for Behavioral and Cognitive Therapies (ABCT)*, New York, NY, October 27-30.

[141] Kishon R, Geronazzo-Alman L, Westphal M, Chen Y, Green D, Sarda A, Love M, Cheng B, Stewart JW, Hollon SD (2019). Psychological mindedness and alexithymia predict symptom reduction in cognitive behavior therapy for major depressive disorder. Int. J. Cogn. Ther., in press.

[142] Kraemer HC, Wilson GT, Fairburn CG, Agras WS (2002). Mediators and moderators of treatment effects in randomized clinical trials. Arch. Gen. Psychiatry 59(10):877-883.

[143] Kragel PA, LaBar KS (2016). Decoding the nature of emotion in the brain. Trends Cogn. Sci. 20:444-455.

[144] Kragel PA, Reddan MC, LaBar KS, Wager TD (2019). Emotion schemas are embedded in the human visual system. Sci. Adv. 5:eaaw4358.

[145] Kral TRA, Schuyler BS, Mumford JA, Rosenkranz MA, Lutz A, Davidson RJ (2018). Impact of short- and long-term mindfulness meditation training on amygdala reactivity to emotional stimuli. NeuroImage 181:301-313.

[146] Kuyken W, Warren FC, Taylor RS, Whalley B, Crane C, Bondolfi G, Hayes R, Huijbers M, Ma H, Schweizer S, Segal Z, Speckens A, Teasdale JD, Van Heeringen K, Williams M, Byford S, Byng R, Dalgleish T (2016). Efficacy of mindfulness-based cognitive therapy in prevention of depressive relapse: an individual patient data meta-analysis from randomized trials. JAMA Psychiatry 73:565-574.

[147] Laird NM, Ware JH (1982). Random-effects models for longitudinal data. Biometrics 38(4):963-974.

[148] Lang PJ, Bradley MM (2010). Emotion and the motivational brain. Biol. Psychol. 84:437-450.

[149] LeDoux JE (2015). *Anxious: using the brain to understand and treat fear and anxiety*. Penguin Books, New York.

[150] LeDoux JE, Brown R (2017). A higher-order theory of emotional consciousness. Proc. Natl. Acad. Sci. USA. 114:E2016-e2025.

[151] Lettieri G, Handjaras G, Ricciardi E, Leo A, Papale P, Betta M, Pietrini P, Cecchetti L (2019). Emotionotopy: Gradients encode emotion dimensions in right temporo-parietal territories. bioRxiv:463166.

[152] Linde K, Fässler M, Meissner K (2011). Placebo interventions, placebo effects and clinical practice. Philos. Trans. R. Soc. Lond. B Biol. Sci. 366:1905-1912.

[153] Lohr JM (2011). What is (and what is not) the meaning of evidence-based psychosocial intervention? Clin. Psychol. Sci. Pract. 18(2):100–104.

[154] Lopez-Lopez JA, Davies SR, Caldwell DM, Churchill R, Peters TJ, Tallon D, Dawson S, Wu Q, Li J, Taylor A, Lewis G, Kessler DS, Wiles N, Welton NJ (2019). The process and delivery of CBT for depression in adults: a systematic review and network meta-analysis. Psychol. Med. 49:1937-1947.

[155] Lu K, Luo X, Chen PY (2008). Sample size estimation for repeated measures analysis in randomized clinical trials with missing data. Int. J. Biostat. 4(1):9.

[156] Ma SH, Teasdale JD (2004). Mindfulness-based cognitive therapy for depression: replication and exploration of differential relapse prevention effects. J. Consult. Clin. Psychol. 72(1):31-40.

[157] Maris E (2004). Randomization tests for ERP topographies and whole spatiotemporal data matrices. Psychophysiology 41(1):142-151.

[158] Mauss IB, Robinson MD (2009). Measures of emotion: a review. Cogn. Emot. 23(2):209-237.

[159] McGrath CL, Kelley ME, Holtzheimer PE, Dunlop BW, Craighead WE, Franco AR, Craddock RC, Mayberg HS (2013). Toward a neuroimaging treatment selection biomarker for major depressive disorder. JAMA Psychiatry 70(8):821-829.

[160] McKeever WF (1986). Tachistoscopic methods in neuropsychology. In: J.H. Hannay (Ed.), *Experimental Techniques in Human Neuropsychology*, Oxford University Press, New York, pp. 167-211.

[161] McLellan LF, Stapinski LA, Peters L (2019). Pre-treatment CBT-mindedness predicts CBT outcome. Cognit. Ther. Res. 43:303-311.

[162] Melka SE, Lancaster SL, Bryant AR, Rodriguez BF (2011). Confirmatory factor and measurement invariance analyses of the emotion regulation questionnaire. J. Clin. Psychol. 67:1283-1293.

[163] Mennin DS, Ellard KK, Fresco DM, Gross JJ (2013). United we stand: emphasizing commonalities across cognitive-behavioral therapies. Behav. Ther. 44(2):234-248.

[164] Moratti S, Rubio G, Campo P, Keil A, Ortiz T (2008). Hypofunction of right temporoparietal cortex during emotional arousal in depression. Arch. Gen. Psychiatry 65(5):532-541.

[165] Moratti S, Strange B, Rubio G (2015). Emotional arousal modulation of right temporoparietal cortex in depression depends on parental depression status in women: first evidence. J. Affect. Disord. 178:79-87.

[166] Morawetz C, Bode S, Derntl B, Heekeren HR (2017). The effect of strategies, goals and stimulus material on the neural mechanisms of emotion regulation: a meta-analysis of fMRI studies. Neurosci. Biobehav. Rev. 72:111-128.

[167] National Institute of Mental Health (2016). RDoC Matrix. *http://www.nimh.nih.gov/research-priorities/rdoc/constructs/rdoc-matrix.shtml*.

[168] Nelson TO, Narens L (1990). Metamemory: a theoretical framework and new findings. In: G.H. Bower (Ed.), *The Psychology of Learning and Motivation: Advances in Research and Theory (Vol. 26)*, Academic Press, San Diego, CA, pp. 215-141.

[169] NeuroScan, Inc. (2003). SCAN 4.3 - Vol. II. EDIT 4.3 - Offline analysis of acquired data (Document number 2203, Revision D). Compumedics Neuroscan, El Paso, TX.

[170] Nunez P (1981). *Electric fields of the brain*. Oxford University Press, New York.

[171] Nunez PL, Srinivasan R (2006). *Electric fields of the brain: the neurophysics of EEG*. Oxford University Press, New York.

[172] Nyklicek I, Majoor D, Schalken PA (2010). Psychological mindedness and symptom reduction after psychotherapy in a heterogeneous psychiatric sample. Compr. Psychiatry 51(5):492-496.

[173] Ochsner KN, Beer JS, Robertson ER, Cooper JC, Gabrieli JD, Kihsltrom JF, D'Esposito M (2005). The neural correlates of direct and reflected self-knowledge. Neuroimage 28(4):797-814.

[174] Ochsner KN, Bunge SA, Gross JJ, Gabrieli JD (2002). Rethinking feelings: an FMRI study of the cognitive regulation of emotion. J. Cogn. Neurosci. 14(8):1215-1229.

[175] Oldfield RC (1971). The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9(1):97-113.

[176] Olofsson JK, Nordin S, Sequeira H, Polich J (2008). Affective picture processing: an integrative review of ERP findings. Biol. Psychol. 77(3):247-265.

[177] Pascual-Marqui RD (2002). Standardized low-resolution brain electromagnetic tomography (sLORETA): technical details. Methods Find. Exp. Clin. Pharm. 24:5-12.

[178] Pascual-Marqui RD, Michel CM, Lehmann D (1994). Low resolution electromagnetic tomography: a new method for localizing electrical activity in the brain. Int. J. Psychophysiol. 18(1):49-65.

[179] Perrin F, Pernier J, Bertrand O, Echallier JF (1989). Spherical splines for scalp potential and current density mapping Corrigenda EEG 02274, EEG Clin. Neurophysiol, 1990, 76, 565. Electroenceph. Clin. Neurophysiol. 72(2):184-187.

[180] Pessoa L (2017). A network model of the emotional brain. Trends Cogn. Sci. 21:357-371.

[181] Pessoa L, Medina L, Hof PR, Desfilis E (2019). Neural architecture of the vertebrate brain: implications for the interaction between emotion and cognition. Neurosci. Biobehav. Rev. 107:296-312.

[182] Petkova E, Ogden RT, Tarpey T, Ciarleglio A, Jiang B, Su Z, et al (2017). Statistical Analysis Plan for Stage 1 EMBARC (Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care) Study. Contemp. Clin. Trials Commun. 6:22-30.

[183] Pico-Perez M, Radua J, Steward T, Menchon JM, Soriano-Mas C (2017). Emotion regulation in mood and anxiety disorders: A meta-analysis of fMRI cognitive reappraisal studies. Prog. Neuropsychopharmacol. Biol. Psychiatry 79:96-104.

[184] Pivik RT, Broughton RJ, Coppola R, Davidson RJ, Fox N, Nuwer MR (1993). Guidelines for the recording and quantitative analysis of electroencephalographic activity in research contexts. Psychophysiology 30(6):547-558.

[185] Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA, et al (2011). The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am. J. Psychiatry 168(12):1266-1277.

[186] Preece DA, Becerra R, Robinson K, Gross JJ (2019). The Emotion Regulation Questionnaire: psychometric properties in general community samples. J. Pers. Assess. 1-9. Epub ahead of print 2019 Feb 5. *doi: 10.1080/00223891.2018.1564319*

[187] Quevedo K, Martin J, Scott H, Smyda G, Pfeifer JH (2016). The neurobiology of self-knowledge in depressed and self-injurious youth. Psychiatry Res. Neuroimaging 254:145-155.

[188] Repetti RL, Taylor SE, Seeman TE (2002). Risky families: family social environments and the mental and physical health of offspring. Psychol. Bull. 128(2):330-366.

[189] Riedel MC, Yanes JA, Ray KL, Eickhoff SB, Fox PT, Sutherland MT, Laird AR (2018). Dissociable meta-analytic brain networks contribute to coordinated emotional processing. Hum. Brain Mapp. 39:2514-2531.

[190] Rive MM, van Rooijen G, Veltman DJ, Phillips ML, Schene AH, Ruhe HG (2013). Neural correlates of dysfunctional emotion regulation in major depressive disorder. A systematic review of neuroimaging studies. Neurosci. Biobehav. Rev. 37(102):2529-2553.

[191] Rubin-Falcone H, Weber J, Kishon R, Ochsner K, Delaparte L, Dore B, Zanderigo F, Oquendo MA, Mann JJ, Miller JM (2018): Longitudinal effects of cognitive behavioral therapy for depression on the neural correlates of emotion regulation. Psychiatry Res. Neuroimaging. 271:82-90.

[192] Rubin-Falcone H, Weber J, Kishon R, Ochsner K, Delaparte L, Dore B, et al. (2019): Neural predictors and effects of cognitive behavioral therapy for depression: the role of emotional reactivity and regulation. Psychol. Med. 1-15. Epub ahead of print 2019 Feb 11. *doi: 10.1017/S0033291718004154*

[193] Ruggiero GM, Spada MM, Caselli G, Sassaroli S (2018). A historical and theoretical review of cognitive behavioral therapies: from structural self-knowledge to functional processes. J. Ration. Emot. Cogn. Behav. Ther. 36:378-403.

[194] Sabatinelli D, Lang PJ, Keil A, Bradley MM (2007). Emotional perception: correlation of functional MRI and event-related potentials. Cereb. Cortex 17(5):1085-1091.

[195] Sabatinelli D, Keil A, Frank DW, Lang PJ (2013). Emotional perception: correspondence of early and late event-related potentials with cortical and subcortical functional MRI. Biol. Psychol. 92(3):513-519.

[196] Sagliano L, Vela M, Trojano L, Conson M (2019). The role of the right premotor cortex and temporo-parietal junction in defensive responses to visual threats. Cortex 120:532-538.

[197] Sanislow CA, Pine DS, Quinn KJ, Kozak MJ, Garvey MA, Heinssen RK, Wang PS, Cuthbert BN (2010).

Developing constructs for psychopathology research: research domain criteria. J. Abnorm. Psychol. 119(4):631-639.

198 Sauer S, Walach H, Schmidt S, Hinterberger T, Lynch S, Bussing A, Kohls N (2013). Assessment of mindfulness: review on state of the art. Mindfulness 4:3-17.

199 Shill MA, Lumley MA (2002). The Psychological Mindedness Scale: factor structure, convergent validity and gender in a non-psychiatric sample. Psychol. Psychother. 75(2):131-150.

200 Schuch FB, Vancampfort D, Richards J, Rosenbaum S, Ward PB, Stubbs B (2016). Exercise as a treatment for depression: a meta-analysis adjusting for publication bias. J. Psychiatr. Res. 77:42-51.

201 Schupp HT, Cuthbert BN, Bradley MM, Cacioppo JT, Ito T, Lang PJ (2000). Affective picture processing: the late positive potential is modulated by motivational relevance. Psychophysiology 37(2):257-261.

202 Schupp HT, Junghöfer M, Weike AI, Hamm AO (2003). Emotional facilitation of sensory processing in the visual cortex. Psychol. Sci. 14(1):7-13.

203 Segal ZV, Williams JMG, Teasdale JD (2002). *Mindfulness-based cognitive therapy for depression: A new approach to preventing relapse*. Guilford Press, New York.

204 Sheppard LC, Teasdale JD (2000). Dysfunctional thinking in major depressive disorder: a deficit in metacognitive monitoring? J. Abnorm. Psychol. 109(4):768-776.

205 Siegle GJ, Steinhauer SR, Friedman ES, Thompson WS, Thase ME (2011). Remission prognosis for cognitive therapy for recurrent depression using the pupil: utility and neural correlates. Biol. Psychiatry 69(8):726-733.

206 Siegle GJ, Thompson WK, Collier A, Berman SR, Feldmiller J, Thase ME, Friedman ES (2012). Toward clinically useful neuroimaging in depression treatment: prognostic utility of subgenual cingulate activity for determining depression outcome in cognitive therapy across studies, scanners, and patient characteristics. Arch. Gen. Psychiatry 69(9):913-924.

207 Sloan E, Hall K, Moulding R, Bryce S, Mildred H, Staiger PK (2017). Emotion regulation as a transdiagnostic treatment construct across anxiety, depression, substance, eating and borderline personality disorders: a systematic review. Clin. Psychol. Rev. 57:141-163.

208 Smith NK, Cacioppo JT, Larsen JT, Chartrand TL (2003). May I have your attention, please: electrocortical responses to positive and negative stimuli. Neuropsychologia 41(2):171-183.

209 Stange JP, MacNamara A, Barnas O, Kennedy AE, Hajcak G, Phan KL, et al (2017). Neural markers of attention to aversive pictures predict response to cognitive behavioral therapy in anxiety and depression. Biol. Psychol. 123:269-277.

210 Stange JP, MacNamara A, Kennedy AE, Hajcak G, Phan KL, Klumpp H (2017). Brain-behavioral adaptability predicts response to cognitive behavioral therapy for emotional disorders: a person-centered event-related potential study. Neuropsychologia. 2017 Jun 22. Epub ahead of print. *doi: 10.1016/j.neuropsychologia. 2017.06.027.*

211 Stevens JS, Hamann S (2012). Sex differences in brain activation to emotional stimuli: a meta-analysis of neuroimaging studies. Neuropsychologia 50(7):1578-1593.

212 Tadel F, Baillet S, Mosher JC, Pantazis D, Leahy RM (2011). Brainstorm: a user-friendly application for MEG/EEG analysis. Comput. Intell. Neurosci. 879716:1-13.

213 Tang YY, Hölzel BK, Posner MI (2015). The neuroscience of mindfulness meditation. Nat. Rev. Neurosci. 16(4): 213-225.

214 Teasdale JD (1999). Metacognition, mindfulness and the modification of mood disorders. Clin. Psychol. Psychother. 6(2):146-155.

215 Teasdale JD, Moore RG, Hayhurst H, Pope M, Williams S, Segal ZV (2002). Metacognitive awareness and prevention of relapse in depression: empirical evidence. J. Consult. Clin. Psychol. 70(2):275-287.

216 Tenke CE, Kayser J (2001). A convenient method for detecting electrolyte bridges in multichannel electroencephalogram and event-related potential recordings. Clin. Neurophysiol. 112(3):545-550.

217 Tenke CE, Kayser J (2005). Reference-free quantification of EEG spectra: combining current source density (CSD) and frequency principal components analysis (fPCA). Clin. Neurophysiol. 116(12):2826-2846.

218 Tenke CE, Kayser J (2012). Generator localization by current source density (CSD): implications of volume conduction and field closure at intracranial and scalp resolutions. Clin. Neurophysiol. 123(12):2328-2345.

219 Teper R, Segal ZV, Inzlicht M (2013). Inside the mindful mind: how mindfulness enhances emotion regulation through improvements in executive control. Curr. Dir. Psychol. Sci. 22:449-454.

220 Tolin DF (2010). Is cognitive-behavioral therapy more effective than other therapies? A meta-analytic review. Clin. Psychol. Rev. 30(6):710-720.

221 Tranel D, Damasio H (1994). Neuroanatomical correlates of electrodermal skin conductance responses.

Psychophysiology 31(5):427-438.

222 Ungerleider LG, Haxby JV (1994). 'What' and 'where' in the human brain. Curr. Opin. Neurobiol. 4(2):157-165.

223 Vaidyanathan S, Menon V, Sarkar S (2018). Identifying patient profiles suitable for cognitive behavior Therapy: The role of psychological mindedness. J. Neurosci. Rural. Pract. 9:654-655.

224 Vallis TM, Shaw BF, Dobson KS (1986). The Cognitive Therapy Scale: psychometric properties. J. Consult. Clin. Psychol. 54(3):381-385.

225 van den Hurk PA, Janssen BH, Giommi F, Barendregt HP, Gielen SC (2010). Mindfulness meditation associated with alterations in bottom-up processing: psychophysiological evidence for reduced reactivity. Int. J. Psychophysiol. 78(2):151-157.

226 Van Rheenen TE, Rossell SL (2013). Is the non-verbal behavioural emotion-processing profile of bipolar disorder impaired? A critical review. Acta Psychiatr. Scand. 128(3):163-178.

227 Vencato MM, Karageorghis CI, Priest DL, Nevill AM (2017). Concurrent validity and cross-validation of the Brunel Lifestyle Physical Activity Questionnaire. J. Sci. Med. Sport 20(8):766-770.

228 Visted E, Vollestad J, Nielsen MB, Schanche E (2018). Emotion regulation in current and remitted depression: a systematic review and meta-analysis. Front. Psychol. 9:756.

229 Voyer D, Bowes A, Soraggi M (2009). Response procedure and laterality effects in emotion recognition: implications for models of dichotic listening. Neuropsychologia 47(1):23-29.

230 Wadlinger HA, Isaacowitz DM (2011). Fixing our focus: training attention to regulate emotion. Pers. Soc. Psychol. Rev. 15:75-102.

231 Wager TD, Kang J, Johnson TD, Nichols TE, Satpute AB, Barrett LF (2015). A Bayesian model of category-specific emotional brain responses. PLoS Comput. Biol. 11:e1004066.

232 Weissman MM (2014). Treatment of depression: men and women are different? Am. J. Psychiatry 171(4):384-387.

233 Weissman MM, Leaf PJ, Holzer CE 3rd, Myers JK, Tischler GL (1984). The epidemiology of depression. an update on sex differences in rates. J. Affect. Disord. 7(3-4):179-188.

234 Weissman MM, Wickramaratne P, Nomura Y, Warner V, Verdeli H, Pilowsky DJ, Grillon C, Bruder G (2005). Families at high and low risk for depression: a 3-generation study. Arch. Gen. Psychiatry 62(1):29-36.

235 Wexler BE (1988). Dichotic presentation as a method for single hemisphere stimulation studies. In: K. Hugdahl (Ed.), *Handbook of Dichotic Listening*, Wiley & Sons, New York, pp. 87-115.

236 Wexler BE, Halwes T (1983). Increasing the power of dichotic methods: the fused rhymed words test. Neuropsychologia 21(1):59-66.

237 Wheeler MS, Arnkoff DB, Glass CR (2017). The neuroscience of mindfulness: how mindfulness alters the brain and facilitates emotion regulation. Mindfulness 8:1471-1487.

238 Williams LM (2016). Precision psychiatry: a neural circuit taxonomy for depression and anxiety. Lancet Psychiatry 3:472-480.

239 Wright P, He G, Shapira NA, Goodman WK, Liu Y (2004). Disgust and the insula: fMRI responses to pictures of mutilation and contamination. Neuroreport 15(15):2347-2351.

240 Young J, Beck AT (1980). *Cognitive Therapy Scale: Rating Manual (Unpublished manuscript)*. University of Pennsylvania, PA.

241 Young KS, van der Velden AM, Craske MG, Pallesen KJ, Fjorback L, Roepstorff A, Parsons CE (2018). The impact of mindfulness-based interventions on brain activity: a systematic review of functional magnetic resonance imaging studies. Neurosci. Biobehav. Rev. 84:424-433.

242 Zatorre RJ (1989). Perceptual asymmetry on the dichotic fused words test and cerebral speech lateralization determined by the carotid sodium amytal test. Neuropsychologia 27(10):1207-1219.

243 Zilverstand A, Parvaz MA, Goldstein RZ (2017). Neuroimaging cognitive reappraisal in clinical populations to define neural targets for enhancing emotion regulation. A systematic review. NeuroImage 151:105-116.

244 Zwanzger P, Klahn AL, Arolt V, Ruland T, Zavorotny M, Salzer J, Domschke K, Junghöfer M (2016). Impact of electroconvulsive therapy on magnetoencephalographic correlates of dysfunctional emotional processing in major depression. Eur. Neuropsychopharmacol. 26(4):684-692.

245 Zwanzger P, Steinberg C, Rehbein MA, Brockelmann AK, Dobel C, Zavorotnyy M, Domschke K, Junghöfer M (2014). Inhibitory repetitive transcranial magnetic stimulation (rTMS) of the dorsolateral prefrontal cortex modulates early affective processing. NeuroImage 101:193-203.

Consent Summary Page

- **Overview**

Below is a summary of the study that you are asked to participate in. This outline is meant to be a guide for you to use while considering the study and reading the consent form. It is not meant to replace the consent form, which you will have to sign if you decide to participate in the study. The consent form contains detailed information about the study and about the risks which you will need to consider before making your decision. Read the consent form carefully and discuss it with others before deciding to take part. And remember that, even if you agree to participate, you can change your mind at any time.
The purpose of the study is to compare two forms of therapy for depression *Cognitive Behavior Therapy (CBT)* and *Nonspecific supportive treatment*, and examine whether their effectiveness relates to concepts about self and others. In each therapy you will receive 12 individual sessions. You will not be able to choose which therapy you will receive but both are considered effective for treating depression. Precautionary measures will be taken to prevent the transmission of COVID-19 in experimental processes. Most of your visits will be conducted remotely using the telephone or HIPAA-compliant video teleconferencing.

- **Voluntary**

As with all research, this is a voluntary study, and you do not have to participate if you do not want to. Also, you may stop participating at any time.

- **Alternative Treatments/Alternatives to Participation**

Medications, interpersonal psychotherapy (IPT), dialectic behavior therapy (DBT), group therapy.

- **Procedures**

1. Evaluation for Major Depression Disorder (remote session).
2. Self-report study measures (beginning, midpoint, end) done online.
3. EEG and cognitive tests (beginning and end) done in the lab at NYSPI.
4. 12 weekly sessions of Cognitive Behavior Therapy for Depression or 12 weekly sessions of Supportive Therapy for Depression(remote sessions).
5. Participants cannot be on psychotropic medications during the study. Medicating for depression will not be part of this study.
6. Participants will be interviewed about symptoms of depression every 3 weeks, and will fill a self-report measure on their symptoms every week (remote sessions, and measures done online).

- **Risks and Inconveniences**

This study includes some risks and discomforts (please refer to the consent form for further details and explanations of these risks). These include no change of your depressive symptoms. Sometimes psychotherapy might increase sadness and anxiety.
You should exercise caution when traveling in public and follow public health guidelines, such as wearing masks in public and avoiding crowds. It is important for you to stay informed about public health recommendations and guidelines regarding COVID-19, such as those issued by the Centers for Disease Control (CDC.gov) and local government guidelines and directives. If you have questions about how you will travel for appointments, or do not feel safe traveling, please let us know, and be advised that you can call to reschedule visits

- **Benefits**

Although some benefit is possible such as reduction of depressive symptoms, you may not have any benefit if the treatment is not effective.

- **Questions**

You may contact the study principal investigator, Ronit Kishon, at 646 724 4171 with any question

CONSENT FORM Study # 6806R
Cognitive Behavior Therapy for Depression

Purpose and Overview

The purpose of the study is to compare two forms of therapy for depression since we still can't predict which one will be more helpful for a particular person. Previous studies suggested that *Cognitive Behavior Therapy (CBT)* is an effective treatment for depression in nearly half of the individuals who do it, however there are others who do not benefit from it. *Nonspecific supportive treatment* focuses on meeting with a therapist, receiving support, having one's hope restored, and overcoming demoralization. In each of the treatments you will receive12 virtual sessions. You will be randomly assigned to one or the other. The purpose of this study is to explore whether your concepts about yourself and others are related to the effectiveness of each of the treatments. Also, you will be asked to consent to participate in Dr. Kayser's study (#6559) for the purpose of behavioral and electrophysiological tests at two time points that will contribute to our study. The aim is to learn more about brain function in people who are depressed and receive different types of talk therapy.

Voluntary

Participation in this research study is voluntary. If you decide not to participate, or if you later decide to stop participating, you will not lose any benefits to which you are otherwise entitled. A decision not to participate or withdraw your participation will not affect your current or future treatment at the New York State Psychiatric Institute or Columbia University Medical Center. If you are determined to be eligible for the study and later stop your participation for any reason, the study principal investigator, Dr. Kishon will treat you until the appropriate referral will be in place. You will be notified of significant new findings that may relate to your willingness to continue to participate in the study.

Alternative Treatments/ Alternatives to Participation

You do not have to participate in this study to receive treatment for your depression. CBT and nonspecific supportive therapy can be obtained outside of study participation. There are medications that have been shown to be effective for depression and can be prescribed by your regular physician. There are also other non-medication treatments for depression beside CBT such as interpersonal psychotherapy, or group therapy.

Procedures

Precautionary measures will be taken to prevent the transmission of COVID-19 in experimental processes. All your visits in this protocol will be conducted remotely using the telephone or HIPAA-compliant video teleconferencing. In this study most of the evaluation process and all psychotherapy sessions will be done virtually. We will discuss with you the technology HIPAA-compliant platforms to be used and any concerns you may have, such as access to a private space in which to take calls, or accessibility—access at home to adequate devices, cell signal, or Wi-Fi. In the CBT treatment, you will receive 12 weekly remote psychotherapy sessions that last about 50 minutes each. The treatment involves being asked questions about your thoughts and feelings, as well as learning skills to manage them. In nonspecific supportive therapy you will also receive 12 sessions that last 50 minutes each. In the sessions you will receive support and understanding for your problems, so to have your hope

restored and to overcome demoralization.

Study measures:
You will be interviewed remotely and you will fill some self-report measures online for a total of an hour and 15 minutes before treatment, in week 6, and after 12 weeks when the treatment is completed. We will also ask you before each session to fill a self-report measure that takes 5 minutes so we can monitor your symptoms. Every 3 weeks we will interview you for 15 minutes, again with the intention of monitoring your level of symptoms. The brain tests will be administered in Dr. Kayser's study(#6559).

Medications during the study:
You can participate in the study if you did not take prescribed antidepressant, or over the counter antidepressant medications, in the past month (three months for fluoxetine). You will be able to continue receiving psychotherapy sessions in the study if your clinical condition will initiate your outside physician to prescribe psychotropic medications.

The study doctors will end your study participation if they determine it is no longer in your best interest. In addition, you may stop participating in this study at any time for any reason. If you stop participating in the study before 12 weeks end**,** the study principal investigator, Dr. Kishon, will continue to see you for sessions until an appropriate referral will be made. Completion of the study is not required for you to receive these sessions by Dr. Kishon.

Cognitive Behavior Therapy and Nonspecific Supportive Therapy – Audiotaping:
You will be audiotaped during your treatment visits. The audio recording will be used for education, research or training purposes only. Any audio recording will not include your full name, and will be reviewed by Dr. Kishon who will evaluate the treatment provided by therapists in this study. The audio recordings are kept for no more than 10 years after which they will be destroyed. If you withdraw your consent, audio recordings can be destroyed during or after the interview or procedure.

Treatment After the End of the Study:
After the study is over, the Principal Investigator, Dr. Kishon, will meet with you, and answer any questions you may have. If after completion of the study you have not improved, you will receive referrals for continuation of psychotherapy and/or medications. You will be able to see Dr. Kishon for weekly sessions until the referral is in place.

Investigator Initiated Discontinuation of Study:
There may be times when the investigator carrying out this study decides to stop the study even though you may wish to continue to participate. Examples include missing 4 number of sessions or not responding to repeated attempts to contact you.

Risks and Inconveniences
The primary risk of participating in this study is that the treatment may not help your symptoms. If you do not improve it may be up to 12 weeks from the time you enter the study until you would be provided with another type of treatment. Therefore, if you do not improve, participating in this study will delay your receiving treatment for up to 12 weeks with medications and other psychotherapies known to be helpful. The risks of psychotherapy treatment include the possibility of increased anxiety or sadness, and the therapists will try to help you with that if it occurs. We anticipate that the risks of study participation are no greater than those encountered in routine clinical treatment. However, you may be withdrawn from

the study and offered other treatment.

Benefits:
A direct benefit to you is the possibility that the treatments will help your symptoms of depression. In addition, your participation may help researchers learn more about how to treat depression. There may be no benefit to you if the treatment is not effective.

The knowledge gained from this study may contribute to a better understanding of psychiatric disorders, and it may contribute to the development of objective measures for diagnosis and treatment selection.

Confidentiality
All records will be stored in locked files and will be kept confidential to the extent permitted by law. Records will be available to research staff, and to Federal, State and Institutional regulatory personnel (who may review records as part of routine audits).

Your name and other personal identifying information will be stored in an electronically secure database at New York State Psychiatric Institute. Research data that is entered into the computer will be stored according to study ID. A master list linking the patient name to the assigned ID is kept in a separate file. In order to access, the computer and appropriate data files, the staff member must know have knowledge of the password and be given rights to access the data by the data manager.
All data that is transmitted via computer is encoded and identifying information is removed.
A description of this clinical trial will be available on http://www.ClinicalTrials.gov , as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Your private information could be used for future research studies or distributed to another investigator for future research studies, with or without identifiers. Should any of the information gathered from you be used for scientific publications or presentations, you will be protected through the use of a system of codes that will not reveal the identity of individuals. Any report based on this study will only be used as grouped information without mention or description of the individual participants.

The NYSPI Remote Communications Guidance will be followed to ensure protection of confidentiality. This discussion and documentation of consent is carried out in a HIPAA – compliant teleconference as well as the psychotherapy sessions. Instruments to be completed will be completed via REDCap, a HIPAAA-compliant platform to ensure confidentiality. Our research assistants will assist you in using those platforms.

In case of Injury
Federal regulations require that we inform participants about our institution's policy with regard to compensation and payment for treatment of research-related injuries. If you believe that you have sustained an injury as a result of participating in a research study, you may contact the Principal Investigator Dr. Ronit Kishon at 646-724-4171 so that you can review the matter and identify the medical resources that may be available to you.

In case of injury, New York State Psychiatric Institute will provide short-term emergency medical treatment, which has been determined to be necessary by New York State Psychiatric Institute's doctors, and which is within the capability of New York State Psychiatric Institute to provide. In addition, we will provide assistance in arranging follow up care in such instances.

New York State Psychiatric Institute and Research Foundation for Mental Hygiene do not provide compensation or payment for treatment of research related injuries. However, you should be aware that you do not give up your legal right to seek such compensation through the court by participating in this research.

Questions

Dr. Kishon will answer to the best of her ability any questions that the participant may have now or in the future about the research procedures, or about the subject's response to the procedures. She can be

reached during the day, and outside of regular business hours at 646-724-4171. Dr. Kishon can be called outside of regular business hours for important issues that should not wait until the next business day. In the case of an EMERGENCY go to your nearest emergency room and call Dr. Kishon.

If you have any questions about your rights as a research participant, want to provide feedback, or have a complaint, you may call the NYSPI Institutional Review Board (IRB). (An IRB is a committee that protects the rights of participants in research studies). You may call the IRB Main Office at (646)774-7155 during regular office hours.

You will be given a copy of the signed Consent Form.

Documentation of Consent

I voluntarily agree to participate in the research study described above.

Name:_____ (print)

Signed _____Study Participant

Date: _____

I have discussed the proposed research with this participant including the risks, benefits, and alternatives to participation (including the alternative of not participating in the research). The participant has had an opportunity to ask questions and in my opinion is capable of freely consenting to participate in this research.

Name:_____(print)

Signed:_____ Person Designated to Obtain Consent

Date:_____

08/26/2020

New York State Psychiatric Institute (NYSPI)
Authorization to Use or Disclose Health Information during a Research Study

Protocol Number: #6806 **Principal Investigator:** Ronit Kishon Ph.D.

Name of Study: Cognitive Behavior Therapy for Depression

Before researchers can use or share any identifiable health information ("Health Information") about you as part of the above study (the "Research"), the New York State Psychiatric Institute (NYSPI) is required to obtain your authorization. You agree to allow the following individuals and entities to use and disclose Health Information about you as described below:

- New York State Psychiatric Institute (NYSPI), your doctors and other health care providers, if any, and
- The Principal Investigator and his/her staff (together "Researchers"). Researchers may include staff of NYSPI, the New York State Office of Mental Health (OMH), Research Foundation for Mental Hygiene, Inc. (RFMH), and Columbia University (CU), provided such staff is a part of the study, and
- Providers of services for the Research at CU, NYSPI and/or RFMH, such as MRI or PET, or Central Reference Laboratories (NKI), if indicated in the consent form**.**

1. The Health Information that may be used and/or disclosed for this Research includes:

☑ All information collected during the Research as told to you in the Informed Consent Form.
☐ Health Information in your clinical research record which includes the results of physical exams, medical and psychiatric history, laboratory or diagnostic tests, or Health Information relating to a particular condition that is related to the Research.
☐ Additional information may include:

2. **The Health Information listed above may be disclosed to:**

☑ Researchers and their staff at the following organizations involved with this Research:
Nathan Kline Institute (where laboratory specimens are analyzed)

☐ The Sponsor of the Research,

and its agents and contractors (together, "Sponsor"); and
☑ Representatives of regulatory and government agencies, institutional review boards, representatives of the Researchers and their institutions to the level needed to carry out their responsibilities related to the conduct of the research.
☐ Private laboratories and other persons and organizations that analyze your health information in connection with this study

☐ Other (family members or significant others, study buddies, outside agencies etc.) Specify:

3. By giving permission to release your Health Information as described above, you understand that your Health Information may be disclosed to individuals or entities which are not required to comply with the federal and state privacy laws which govern the use and disclosure of personal Health Information by NYSPI. This means that once your Health

Information has been disclosed to a third party which does not have to follow these laws (e.g., a drug company or the Sponsor of the Research), it may no longer be protected under the HIPAA or NYS Mental Hygiene Law requirements but is subject to the terms of the consent form and may be subject to other state or federal privacy laws or regulations.

4. Please note that:

- You do not have to sign this Authorization form, but if you do not, you may not be able to participate in the study or receive study related care. You may change your mind at any time and for any reason. If you do so, you may no longer be allowed to participate in the study. If you withdraw this Authorization the research staff and the Sponsor, if this is sponsored research, may still use or disclose Health Information containing identifying information they already have collected about you as needed to maintain the reliability of the research. Any request to withdraw this Authorization must be made in writing to (enter name and contact information below):

  Ronit Kishon Ph.D.
  1051 Riverside Drive
  New York, NY 10032

- While the Research is going on, you may not be allowed to review the Health Information in your clinical research record that has been created or collected by NYSPI. When this research has been completed you may be allowed to see this information. If it is needed for your care, your Health Information will be given to you or your Doctor.

5. This Authorization does not have an end date.

6. You will be given a copy of this form after you have signed it.

I agree to the use and disclosure of Health Information about me as described above:

_____ _____

Signature of Participant/ Legal Representative Date

_____

Printed Name of Participant

_____

Relationship of Legal Representative to Participant (if applicable)

We also ask you or your legal representative to initial the statements below:

☐ **I have received a copy of the NYSPI/OMH Notice of Privacy Practices.**

Different facets of psychological mindedness will be assessed with the (1) Self-Reflection and Insight Scale (SRIS; 20 items, 2 subscales), and (2) Psychological Mindedness Scale (PMS; 45 items, 5 factors) PMS has strong internal consistency (Cronbach's á = .87) 199 and is often used together with the Toronto Alexithymia Scale (TAS; 20 items, 3 factors). The TAS is inversely related to PM and measures emotional awareness. The TAS has good internal consistency (á = .81) and test-retest reliability (r = .77). Two widely-used instruments will assess different aspects of mindfulness. The Mindful Attention Awareness Scale (MAAS; 15 items) 22 measures the present-moment attentional components of mindfulness. The MAAS has good internal consistency (á = .82) and corresponding convergent and discriminant validity. MAAS scores were higher in mindfulness practitioners than in matched controls . The Five-Facet Mindfulness Questionnaire (FFMQ; 39 items) assesses the daily-life tendency of being mindful. The widely-used Emotion Regulation Questionnaire (ERQ; 10 items) assesses the tendency to regulate emotions via cognitive reappraisal and expressive suppression; both factors have acceptable-to-excellent reliability and validity.

The present exploratory study proposed to examine relationships between psychological mindedness, mindfulness, alexithymia, and symptoms of depression across 12 weeks of CBT. Given that CBT aims to improve metacognitive skills that facilitate purposeful changes in thoughts and behaviors(Clark and Fairburn 1997a, 1997b; Fresco et al. 2010; Ingram and Hollon 1986), measuring those metacognitive variables during treatment may contribute to a better understanding of emotion regulation processes that are critical to symptom reduction in CBT.

The present study aims (1) to determine whether high pre-therapy levels of psychological mindedness, mindfulness and low levels of alexithymia predicted decreases in depressive symptoms across the course of treatment, and (2) whether changes in psychological mindedness, alexithymia and mindfulness during therapy were associated with a decrease of depressive symptoms from baseline to posttreatment;(3)whether changes in these metacognitive variables are associated with an increase in emotional regulation as measures by the ERQ.

Generalized linear mixed model (GLMM), with an identity link and a random intercept for each subject, will be used to examine the two study questions. It will be used to analyze whether baseline levels of psychological mindedness, alexithymia, and mindfulness (for the whole scale and the factors that compose each scale) will be associated with decrease of depressive symptom levels from baseline to posttreatment.
GLMM will be used to examine whether changes in psychological mindedness, alexithymia and mindfulness (total scores and factors), measured at baseline, week 6, and week 12, will be associated with a decrease of depressive symptoms levels from pretreatment to posttreatment and with an increase of emotion regulation (measured at baseline, week 6, and at week 12). In both analyses, we will control for demographic variables: age, years of education, gender, race, employment, and baseline depressive symptoms as measured by BDI-II and HRSD-17.In GLMM, the data are permitted to exhibit correlation between repeated measures and non-constant variability. GLMM, therefore, provides the flexibility of modeling not only the means of the data (with fixed-effects parameters) but their variances and covariance as well (with random-effects parameters). Fixed effects describe the impact of known measured covariates, as in the standard linear model, where such effects are assumed to hold over a broad population of individuals. That is, if the set of possible levels of the covariate are fixed and reproducible, the covariate was modeled using a fixed-effect parameter. Fixed-effects were modeled for psychological mindedness, TAS scores, time, and mindfulness the following six demographic variables: gender, age, race (white/non-white), current employment status (employed/unemployed). The need for covariance parameters is due to the presence of repeated measurements taken on the same subjects at three time points; these repeated measurements are correlated or exhibit variability that changes. The most common covariance structure to handle repeated measurements derives from the use of random-effects parameters, which are additional estimated random variables assumed to affect the variability of the data. The variances of the random-effects parameters, commonly known as variance components, become the covariance parameters for this particular structure. A random intercept will be included for each subject. GLMMs will fit with the restricted maximum likelihood method (REML). GLMMs will be implemented with the PROC MIXED procedure in SAS, version 9.3 (SASInstituteInc 2011).