Novel neural circuit biomarkers of major depression response to computer-augmented CBT

NCT: NCT03096886

Document Date: May 3, 2019

Modification

Basic Info

Confirmation Number:	**cihghbcb**
Protocol Number:	**832295**
Created By:	**WONG, JOYCE X**
Principal Investigator:	**SHELINE, YVETTE I**
Protocol Title:	**Novel neural circuit biomarkers of major depression response to computer-augmented CBT (1R01MH110939 - 01A**
Short Title:	**CCBT fMRI R01**
Protocol Description:	**This is a trial of an FDA-approved treatment for MDD, computer-augmented cognitive behavioral therapy (CCBT), to examine novel potential neural circuit biomarkers of treatment response. 100 subjects total: 40 controls, 60 MDD. MDD subjects begin CCBT at the earliest scheduling availability. CCBT treatment lasts 8 wks. All subjects will have an fMRI at baseline before CCBT and a final fMRI after the treatment phase. Those beginning CCBT later will complete an additional fMRI before CCBT.**
Submission Type:	**Biomedical Research**
Application Type:	**EXPEDITED Category 3 and Category 4**

PennERA Protocol Status

Approved

Resubmission*
No

Are you submitting a Modification to this protocol?*

Yes

Current Status of Study

Study Status

Currently in Progress

If study is currently in progress, please enter the following

Number of subjects enrolled at Penn since the study was initiated

4

Actual enrollment at participating centers

0

If study is closed to further enrollment, please enter the following

Number of subjects in therapy or intervention

0

Number of subjects in long-term follow-up only

0

IRB Determination
If the change represents more than minimal risk to subjects, it must be reviewed and approved by the IRB at a convened meeting. For a modification to be considered more than minimal risk, the proposed change would increase the risk of discomfort or decrease benefit. The IRB must review and approve the proposed change at a convened meeting before the change can be implemented unless the change is necessary to eliminate an immediate hazard to the research participants. In the case of a change implemented to eliminate an immediate hazard to participants, the IRB will review the change to determine that it is consistent with ensuring the participant′s continued welfare. Examples: Convened Board Increase in target enrollment for investigator initiated research or potential Phase I research Expanding inclusion or removing exclusion criteria where the new population may be at increased risk Revised risk information with active participants Minor risk revisions that may affect a subject′s willingness to continue to participate Expedited Review Increase in target enrollment at Penn where overall enrollment target is not exceeded or potentially sponsored research Expanding inclusion or removing exclusion where the new population has the same expected risk as the previous, based on similarities of condition Revised risk information with subjects in long-term follow-up Minor risk revisions with no subjects enrolled to date
Expedited Review

Modification Summary
Please describe any required modification to the protocol. If you are using this form to submit an exception or report a deviation, enter 'N/A' in the box below.
Modifying study procedures to include an additional 15 minute computer task. Informed consent forms have been modified to include information about this computer task. Two key study personnel have been added to the study.

Risk / Benefit
Does this amendment alter the Risk/Benefit profile of the study?
No

Change in Consent
Has there been a change in the consent documents?
Yes

If YES, please choose from the options below regarding re-consenting

Our site does not plan to obtain re-consent

Deviations

Are you reporting a deviation to this protocol?*

No

Exceptions

Are you reporting an exception to this protocol?*

No

Protocol Details

Resubmission*
Yes

Study Personnel

Principal Investigator

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HS Training Completed:	**Yes**
Training Expiration Date:	**07/01/2019**
Name of course completed :	**CITI Protection of Human Subjects Research Training - ORA**

Study Contacts

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Training Expiration Date:	**03/11/2021**
Name of course completed :	**CITI Protection of Human Subjects Research Training - ORA**

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HS Training Completed:	**Yes**
Training Expiration Date:	**11/25/2020**
Name of course completed :	**CITI Protection of Human Subjects Research Training - ORA**

Other Investigator

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HS Training Completed:	**Yes**
Training Expiration Date:	**05/09/2019**
Name of course completed :	**CITI Protection of Human Subjects Research Training - ORA**

Responsible Org (Department/School/Division):

10579 - PS-Center for the Neuroscience of Depression & Stress

Key Study Personnel

Name:	**LONG, HANNAH B**
Department/School/Division:	**PS-Center for the Neuroscience of Depression & Stress**
HS Training Completed:	**Yes**
Training Expiration Date:	**06/04/2020**
Name of course completed:	**CITI Protection of Human Subjects Research Training - ORA**

Name:	**STRAVACH, GABRIELLE R**
Department/School/Division:	**School of Nursing**
HS Training Completed:	**Yes**
Training Expiration Date:	**10/09/2021**
Name of course completed:	**CITI Protection of Human Subjects Research Training - ORA**

Name:	**RAMAKRISHNAN, ARJUN**
Department/School/Division:	**NS-Neuroscience**
HS Training Completed:	**Yes**
Training Expiration Date:	**07/20/2019**
Name of course completed:	**CITI Protection of Human Subjects Research Training - ORA**

Name:	**SCULLY, MORGAN**
Department/School/Division:	**PS-Center for the Neuroscience of Depression & Stress**
HS Training Completed:	**Yes**
Training Expiration Date:	**09/20/2019**
Name of course completed:	**CITI Protection of Human Subjects Research Training - ORA**

Name:	**VOGELEY, GABRIELA**
Department/School/Division:	**PS-Center for the Neuroscience of Depression & Stress**
HS Training Completed:	**Yes**
Training Expiration Date:	**10/18/2021**
Name of course completed:	**CITI Protection of Human Subjects Research Training - ORA**

Name:	**PLATT, MICHAEL L**
Department/School/Division:	**Psychology**
HS Training Completed:	**Yes**
Training Expiration Date:	**09/05/2021**
Name of course completed:	**CITI Protection of Human Subjects Research Training - ORA**

Name:	**BYRD, CHRISTOPHER**
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HS Training Completed:	**Yes**
Training Expiration Date:	**06/25/2021**
Name of course completed:	**CITI Protection of Human Subjects Research Training - ORA**

Name:	**GREEN, GABRIELLA**
Department/School/Division:	**PS-Center for the Neuroscience of Depression & Stress**
HS Training Completed:	**Yes**
Training Expiration Date:	**01/25/2020**
Name of course completed:	**CITI Protection of Human Subjects Research Training - ORA**

Name:	**SHIMOMOTO, CHIHIRO**
Department/School/Division:	**School of Nursing**
HS Training Completed:	**Yes**
Training Expiration Date:	**09/07/2020**
Name of course completed:	**CITI Protection of Human Subjects Research Training - ORA**

Name:	**PROCIUK, MARIA L**
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HS Training Completed:	**Yes**
Training Expiration Date:	**08/13/2020**
Name of course completed:	**CITI Protection of Human Subjects Research Training - ORA**

Name:	**HEMBREE, ELIZABETH A**
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Name of course completed:	**CITI Protection of Human Subjects Research Training - ORA**

Name:	**MAKHOUL, WALID**
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HS Training Completed:	**Yes**
Training Expiration Date:	**09/03/2021**
Name of course completed:	**CITI Protection of Human Subjects Research Training - ORA**

Name:	**SEOK, DARSOL K**
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Name of course completed:	**CITI Protection of Human Subjects Research Training - ORA**

Name:	**LYU, MENGQUN**
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HS Training Completed:	**Yes**
Training Expiration Date:	**09/12/2021**
Name of course completed:	**CITI Protection of Human Subjects Research Training - ORA**

Name:	**ASELCIOGLU, IREM**
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HS Training Completed:	**Yes**
Training Expiration Date:	**05/02/2019**
Name of course completed:	**CITI Protection of Human Subjects Research Training - ORA**

Disclosure of Significant Financial Interests*
Does any person who is responsible for the design, conduct, or reporting of this research protocol have a **FINANCIAL INTEREST**?
No

Penn Intellectual Property*
To the best of the Principal Investigator's knowledge, does this protocol involve the testing, development or evaluation of a drug, device, product, or other type of intellectual property (IP) that is owned by or assigned to the University of Pennsylvania?
No

Certification
I have reviewed the *Financial Disclosure and Presumptively Prohibited Conflicts for Faculty Participating in Clinical Trials* and the *Financial Disclosure Policy for Research and Sponsored Projects* with all persons who are responsible for the design, conduct, or reporting of this research; and all required Disclosures have been attached to this application.
Yes

Biomedical Research

Clinical Trial*
Is this a clinical trial?
Yes

If Yes, please be aware that for each clinical trial conducted or supported by a Federal department or agency, one IRB-approved informed consent form used to enroll subjects must be posted by the awardee or the Federal department or agency component conducting the trial on a publicly available Federal Web site that will be established as a repository for such informed consent forms.

Investigator Initiated Trial*
Is this an investigator initiated trial?
No

Drugs or Devices*
Does this research study involve Drugs or Devices?
No

IND Exemption

For studies that fall under an IND exemption, please provide the number below

For studies including IND or IDE's, please provide the number(s) below

IDE Review*
NOTE: For research involving investigational devices, you are required to review the guidance on Managing Research Device Inventory. Consult the Penn Manual for Clinical Research: https://www.med.upenn.edu/pennmanual/secure/investigational-product-management-at-sites-not-using-investigational-drug-services-(ids).html Please check the box Yes if you have reviewed the guidance.
Yes

Research Device Management*
Please indicate how research device(s) will be managed.
Not Applicable (no investigational devices)

Drug, Herbal Product or Other Chemical Element Management *
Please indicate how drugs, herbal products or other chemical entities will be managed.
Not Applicable (no drugs, herbal products or other chemical entities)

Radiation Exposure*
Are research subjects receiving any radiation exposure (e.g. X-rays, CT, Fluoroscopy, DEXA, pQCT, FDG, Tc-99m, etc.) that they would not receive if they were not enrolled in this protocol?

No

Gene Transfer*
Does this research involve gene transfer (including all vectors) to human subjects?
No

Human Source Material*
Does this research include collection or use of human source material (i.e., human blood, blood products, tissues or body fluids)?
Yes

CACTIS and CT Studies*
Does the research involve Center for Advanced Computed Tomography Imaging Services (CACTIS) and CT studies that research subjects would not receive if they were not part of this protocol?
No

CAMRIS and MRI Studies*
Does the research involve Center for Advanced Magnetic Resonance Imaging and Spectroscopy (CAMRIS) and MRI studies that research subjects would not receive if they were not part of this protocol?
Yes

Investigational Agent or Device within the Operating Room*
Does the research project involve the use of an investigational agent or device within the Operating Room?
No

Cancer Related research not being conducted by an NCI cooperative group*
Does this protocol involve cancer-related studies in any of the following categories?
No

Processing of Materials*
Will the research involve processing (such as over encapsulating, or compounding)?
No

In-House Manufacturing of Materials*
Will the research involve processing (such as over encapsulating, or compounding)?
No

Medical Information Disclosure*
Does the research proposal involve the use and disclosure of research subject's medical information for research purposes?
Yes

If the answer is YES, indicate which items is is provided with this submission:

Modified research informed consent document that incorporates HIPAA requirements

CTRC Resources*
Does the research involve CTRC resources?
No

Pathology and Laboratory Medicine Resources*
Will samples be collected by hospital phlebotomy and/or processed or analyzed by any of the clinical laboratories of the University of Pennsylvania Health System?
No

Research Involves Apheresis, Cell Collection, and/or Blood Product Collection*
Does this research involve collection of blood products in the Penn Donor Center and/or the use of apheresis for treatment or collection of cells or other blood components?
No

Research involving blood transfusion or drug infusions*
Will your research involve blood transfusion or infusion of study drug in 3 Ravdin Apheresis Unit for research purposes?
No

Trial in Radiation Oncology
Is this research a prospective trial being done in Radiation Oncology, and if so, has this protocol been approved by the Radiation Oncology Protocol committee?
N/A

Study in Radiation Oncology
Is this research a retrospective study being done in Radiation Oncology, and if so, has this project been reviewed by the Radiation Oncology Clinical Research Group?
N/A

Use of UPHS services*
Does your study require the use of University of Pennsylvania Health System (UPHS) services, tests or procedures*, whether considered routine care or strictly for research purposes?
No

Primary Focus*
Sociobehavioral (i.e. observational or interventional)

Protocol Interventions

x	**Sociobehavioral (i.e. cognitive or behavioral therapy)**
	Drug
	Device - therapeutic
	Device - diagnostic (assessing a device for sensitivity or specificity in disease diagnosis)
	Surgical
	Diagnostic test/procedure (research-related diagnostic test or procedure)
	Obtaining human tissue for basic research or biospecimen bank
	Survey instrument
	None of the above

The following documents are currently attached to this item:

There are no documents attached for this item.

Sponsors

Business Administrator

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Department budget code

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Funding Sponsors

Name:	**NATIONAL INSTITUTE OF MENTAL HEALTH/NIH/DHHS**
Type:	**UPENN Federal**

Funding sponsors billing address
If you have selected a commercial or industry sponsor, please provide the appropriate address and contact information for the Sponsor for the purposes of billing for IRB review fees (initial review, continuing review and convened modification fees apply here). If the Sponsor is not industry/ commercial, this information is not necessary to provide with your application.

Funding sponsors gift
Is this research being funded by a philanthropic gift?
No

Regulatory Sponsor

IND Sponsor

none

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Industry Sponsor

None

Project Funding*
Is this project funded by or associated with a grant or contract?
Yes

Selected Proposals

Proposal No	**Title**
10058145	**Novel neural circuit biomarkers of depression response to computer-augmented CBT**

Sponsor Funding
Is this study funded by an industry sponsor?
No

Status of contract

The following documents are currently attached to this item:

There are no documents attached for this item.

Multi-Center Research

Penn as lead
1. Is this a multi-center study where Penn is serving as the Lead Site or the Penn PI is serving as the Lead Investigator?
No

Management of Information for Multi-Center Research

Penn irb of record
2. Is this a multi-center study where the Penn IRB will be asked to serve as the IRB of Record for other external study sites?

No

Other Sites

No other sites

Protocol

Abstract
This is a trial of an FDA-approved treatment for Major Depressive Disorder (MDD), computer-augmented cognitive behavioral therapy (CCBT), to examine novel potential neural circuit biomarkers of treatment response rather than to test efficacy. We will enroll 60 subjects, 18-60 years, who are seeking treatment for a current episode of Major Depressive Disorder. We also will enroll 40 healthy controls of a similar age/sex distribution. MDD subjects will be scheduled to receive CCBT at the first available appointment; all will be scheduled within 4 weeks. All subjects will have an fMRI at baseline; MDD subjects will have an fMRI after treatment. MDD subjects scheduled to start CCBT treatment after 3 weeks will complete an additional fMRI before they begin CCBT.

Objectives

Overall objectives
The overall objectives of the study are to examine novel potential neural circuit bio-markers of treatment response to computer-augmented cognitive behavioral therapy (CCBT) for people with MDD. Aim 1: Compare baseline resting state functional connectivity and task-induced activity between MDD and controls: Hypothesis 1a): Compared with controls, depressed participants will have disruptions in resting state functional connectivity in the amygdala-cognitive-executive (C-E) network and the amygdala-default mode network (DMN); and 1b) will have decreased emotional conflict task-induced activation in rostral/dorsal anterior cingulate cortex (ACC), dorsal lateral prefrontal cortex (DLPFC), and inferior frontal gyrus (IFG). Aim 2: Assess CCBT treatment effects on resting state functional connectivity and task induced activity in MDD comparing post-CCBT treatment to pre-CCBT treatment. Hypothesis 2a) Compared with pre-CCBT neuroimaging measures, following active treatment there will be increase in C-E connectivity and decreased amygdala-DMN connectivity. 2b) These changes will be correlated with symptom reduction and 2c) increases in rostral/dorsal ACC, DLPFC and IFG activation during the emotional conflict task. Exploratory Aim: 1a) Predict the effects of baseline brain measures on treatment outcomes. Hypothesis: Using clinical decision-support algorithms, clinical outcome trajectories and differential response to treatment will be predicted from baseline data (brain connectivity, task-based activity and cortical thickness). 1b) Predict the effects of baseline executive function on treatment outcomes. Hypothesis: Using clinical decision-support algorithms, clinical outcome trajectories and differential response to treatment will be predicted from baseline executive function data. Developing such algorithms to help determine risk trajectories is important for more effective treatment assignment. Secondary Aims: Data collected from actigraphy, saliva sample, and remote monitoring via the Beiwe cellphone application will be used as preliminary evidence examining the effects of sleep-wake patterns, microbiome, and total physical activity on treatment outcomes in individuals experiencing depression.

Primary outcome variable(s)
Aim 1: 1a) resting state functional connectivity 1b) emotional conflict task-induced brain activity Aim 2 Treatment effects: 2a) amygdala-connectivity 2b) changes rostral/dorsal ACC, DLPFC and IFC activation during the emotional conflict task. Patients will serve as their own controls pre-post treatment. In addition, patients who wait longer for treatment (3-4 weeks) will be compared in a second scan with those who receive immediate treatment (1-2 weeks).

Secondary outcome variable(s)
Exploratory Aim: 1a) brain connectivity, task-based activity and cortical thickness Secondary Aims:

Data collected from actigraphy, saliva sample, and remote monitoring via the Beiwe cellphone application will be used as preliminary evidence examining the effects of sleep-wake patterns, microbiome, and total physical activity on treatment outcomes in individuals experiencing depression.

Background

FOR ADDITIONAL BACKGROUND INFORMATION AND SOURCE DOCUMENTATION, PLEASE REFER TO PROTOCOL 826910 - CCBT FMRI RESEARCH STRATEGY WITH REFERENCES. Significance of computer-augmented cognitive behavioral therapy (CCBT): The fundamental significance of the proposed research is that it will examine neural circuits that have the potential to be novel biomarkers of depression treatment response to computer-augmented cognitive behavioral therapy (CCBT). Rather than testing efficacy, our proposed clinical trial will, as outlined in NIMH NOT-14-0007, elucidate the mechanism of action of CCBT at the level of neurocircuitry. Specifically, we will continue previous research by Sheline and colleagues at Washington University and Thase and colleagues at the University of Pittsburgh, that examines CBT-induced changes in two key large-scale brain networks the Central-Executive Network (CEN) and Default Mode Network (DMN). Our current proposal will use a model of CBT that implements computer-augmented instructional modules to make therapy substantially more accessible and cost-effective compared to conventional treatment. Further, by confirming that the neurocircuitry targets found for conventional CBT can be readily engaged by computer-assisted, self-help exercises, we will open a promising new avenue of research that can lead to further refinements in the delivery and efficacy of this form of therapy. CBT is the psychotherapy with the best evidence base for the treatment of depression [1, 2]. It has established efficacy for major depressive disorder (MDD) in clinical trials in comparison both to attention-control conditions and antidepressant pharmacotherapy [1, 2]. Moreover, it is the one empirically validated form of treatment for depression that has been shown to have more durable or sustained effects that persist for months after therapy is stopped [3, 4]. However, although people seeking treatment for depression often rank CBT and related interventions as highly desirable or even more preferred than pharmacotherapy [5], in current practice the public health impact of CBT is severely restricted by the limited number of qualified therapists, their narrow geographic distribution, and the relatively high direct cost of a conventional 12-20 hour course of therapy. One strategy to address the problem of accessibility has been development of web-based CBT programs [6, 7]. The utility of computer-augmented models of therapy (or CCBT) such as Beating the Blues and Mood Gym has now been established by more than two dozen randomized controlled trials [6, 8, 9]. The Good Days Ahead (GDA) [10] model of CCBT that we propose to use in this study was developed primarily to serve as an adjunct to therapy, with the goals of complementing and streamlining the efforts of therapists. In both the original proof of concept study of Wright et al. [11] and our recently completed large scale non-inferiority study [12], outpatients with MDD obtained essentially identical benefit from treatment with GDA and 3-4 hours of therapist contact as they did with up to 20 hours of conventional CBT [7, 12]. Thus, we have shown that a substantial proportion of the therapeutic action of CBT can be shifted from the therapists office to the patients home or office and, as a result, the cost of treatment can be reduced considerably while the convenience and accessibility of therapy is increased. Further, we predict that repeated practice and mastery of the guided coping exercises developed for GDA CCBT will significantly enhance target engagement at the level of neurocircuitry. To confirm this, the amount of time patients spend on the computer will be directly measured. We anticipate that this more cost effective form of treatment delivery will have the potential to be tailored and refined to increase effectiveness. Understanding the mechanism of CCBT with Neural Circuits: Overview: Understanding the functional connectome of the human brain is a fundamental prerequisite for accurate models of both healthy brain function and dysfunction in MDD. Several reports have focused on structural and functional connectomic differences between MDD and controls [13]. Some studies have demonstrated metabolic differences, including prefrontal cortex hypometabolism [14] and amygdala hypermetabolism [15]. We first showed task-based amygdala hyperactivity in depression [16], confirmed in subsequent studies (reviewed in Hamilton et al., 2012 [17]), Further, resting state functional connectivity assessed in fMRI data is disrupted in first-episode MDD compared with controls, with increased connectivity in the DMN and diminished fronto-parietal connectivity [18]. Hypoconnectivity within the frontoparietal network and hyperconnectivity within the DMN were also reported in a meta-analysis of MDD studies [19]. We and others have speculated that amygdala hyperactivity may arise from diminished top-down regulatory connectivity from cognitive executive networks [20]. In a recent report, we found strong support for this hypothesis [21].

Study Design

Phase*
Not applicable

Design
60 subjects with MDD will be scheduled to begin CCBT early or later. Participants are randomly assigned to one of the two groups by a random number generated by the computer: (1) for Early CCBT and (2) for Later CCBT. All participant will be scheduled to start CCBT within 4 weeks after completing baseline assessments. Early CCBT participants will begin treatment within 2 weeks after the first MRI scan and Later CCBT participants will begin treatment after 2 weeks from the first MRI scan. Early CCBT participants will have two pre-treatment study visits and will be scheduled to begin CCBT within 0-14 days from Visit #1(screening visit) and after the completion of the first fMRI scan. Late CCBT Participants will have three pre-treatment study visits (detailed above) and will be scheduled to start CCBT within 15-28 days from Visit #1 (screening visit) and after completing two fMRI scans. The two fMRI scans must be at least 14 days apart from each other. CCBT treatment is 8 weeks. 40 healthy controls of similar age/sex will be recruited to serve as a comparison group for baseline MRI scanning. Members of the research team who are responsible for the assessment of outcomes will be blinded to MDD grouping.

Study duration
The study will enroll subjects for approximately 4 years (~2 subjects per month for 48 months). The length of subject participation will vary based on what group they are in. Healthy controls will participate for ~8 weeks; 2 study visits will occur within 1-3 weeks; remainder of study participation will be remote via cell phone and actigraph and one visit at end of remote monitoring. Subjects with MDD will participant for up to 8-12 weeks. Variability in the study duration for each group depends on participant and therapist availability for visits and the availability of the MRI. The project is anticipated to begin subject recruitment and data collection in January 2019 and be completed by April 2021.

Resources necessary for human research protection
Describe research staff and justify that the staff are adequate in number and qualifications to conduct the research. Describe how you will ensure that all staff assisting with the research are adequately informed about the protocol and their research related duties. Please allow adequate time for the researchers to conduct and complete the research. Please confirm that there are adequate facilities for the research.
The project will be managed by the investigators and dedicated coordinators. The investigators and staff, led by the PI, will meet monthly to review the program progress and address specific problems. Regular project reviews will be held twice annually. The investigators are experienced administrators and accomplished scientists. They have existing and effective collaborations, and this spirit will be carried forward in the proposed research. The PI has administrative experience as Director of the Center for Neuromodulation in Depression and Stress. Co-I Thase is Director of the Mood and Anxiety Program in the Psychiatry Department. Day-to-day management of the project will performed by two clinical coordinators, who will recruit patients from the Psychiatry clinics and enroll them in the study, and schedule the MRI scans and all behavioral assessments. Clinical research coordinators have been trained by the University of Pennsylvania and have experience coordinating clinical trails with these investigators. All investigators, key personnel, and study coordinators will meet prior to the study start to discuss the protocol and implementation of the protocol. All research staff will be required to review any significant changes to the protocol prior to the implementation. All staff are trained in HIPAA and CITI Human Subjects Research. Initial training (e.g. at start up), rater certification standards, ongoing quality control (QC), and methods to ensure interrater reliability at an acceptable level will be performed prior to subject contact. All clinical efficacy assessments will be done by the investigators or personnel delegated by the investigators, who are suitably trained to assess the participants. This will be monitored by assigning rater IDs. Interviews will be conducted by trained, experienced clinical coordinators and interviewers. All will receive careful and rigorous training. Interviewers will remain in frequent contact with the PI to maintain uniform assessment criteria and to resolve diagnostic and other rating issues. In addition, interviewers will meet weekly to staff any new assessments conducted. This careful review of diagnoses and symptoms is in place to maximize reliability. Our quality control procedures aim to ensure the validity of the data. This will necessitate standardization across raters every six months. All data will be entered directly into the database as it is accumulated. The PI will monitor the reliability of the data entry and insure the integrity of the database, coding, and entry

verification. Both study therapists have been certified by the Academy of Cognitive Therapy and have successfully treated (defined as scoring at least 40 on the Cognitive Therapy Scale: CTS) 10+ patients with CCBT. As the efficacy of CBT is related to therapist skill level, therapists will be supervised by Dr. Thase to ensure adherence and competent delivery. The protocol adherence rating scale used in two earlier studies of GDA will be utilized and one quarter of the sessions will be audiotaped and scored using the Cognitive Therapy Scale (CTS). A CTS score of 40 is considered minimally adequate to conduct CBT in treatment outcome studies. The Mood & Anxiety Treatment and Research Program and Center for Neuromodulation in Depression and Stress are both equipped for participant visits. MRIs will be conducted at Stellar Chance or HUP6, with the approval of CAMRIS.

Characteristics of the Study Population

Target population
60 participants with Major Depressive Disorder, in current MD episode of at least moderate severity, as indicated by the SCID-5 and MADRS (greater than or equal to 20). There will be 40 healthy control participants of similar age/sex. Combining with subjects from protocol 826910, we will enroll 37 additional MDD participants and 24 additional healthy controls through protocol 832295 to meet the overall target of 100 subjects (60 MDD, 40 Healthy controls).

Subjects enrolled by Penn Researchers
61

Subjects enrolled by Collaborating Researchers
0

Accrual
The MDD participants will be primarily recruited from the Outpatient Clinics of the University of Pennsylvania, including the Mood and Anxiety Disorders program, student health and the general adult psychiatry programs. These programs see 400+ new patients with depressive disorders each year and contributed 72 unmedicated MDD participants across 30 months to the recently completed noninferiority study of CCBT. Should the need arise, we also can recruit from the Philadelphia VA Medical Centers Behavioral Health Laboratory (PVAMC-BHL). As the BHL continuously screens from the primary care clinical population of the PVAMC, it will serve as a rich secondary recruitment resource for individuals for this study. As an example, from August 2013 to August 2014, 1,298 individuals between ages 18 and 45 completed assessments within the BHL. Of the 1,194 individuals who completed full assessments, approximately 29.4% screened positive for MDD, providing an ample participant base from which to recruit. We thus anticipate no difficulty enrolling depressed patients into this study. Up to 120 participants will be consented for participation; however we anticipate that approximately 10% will screen fail and another 10% will either drop out during the study or have unusable scanner data; therefore, we aim to have 60 participants with MDD and 40 healthy control participants who complete the entire study with usable data. C.10.1 Power Analysis For Aim 1, based on our pilot data, we assume that DLPFC in HC is positively correlated with amygdala with correlation of r=0.1, while in contrast it is negatively correlated in MDD with correlation r=-0.1 (standard deviation 0.07). Similarly, our pilot data indicates that IFC in MDD is 70% less correlated with the amygdala than in HC (standard deviation 0.07). Given 60 MDD patients and 40 HC at baseline, we have excellent power (80%) to detect the differences between MDD and HC for their baseline amygdala connectivity in DLPFC and IFC. For subgroup analysis in subjects of each sex separately, we will also have 80% power to detect differences between MDD and HC. Similarly, for baseline task measures, the pilot data indicate up to two-fold higher activation in HC in the four targeted regions (ACC, DLPFC, IFC), indicating that will also have 80% power to detect such differences between MDD and HC (in males and females separately, as well as combining sexes) at the 95% confidence level adjusting for the number of tests. For Aim 2, based on our pilot data, the correlation between IFC and amygdala will increase by 0.09 after CCBT (standard deviation 0.05), and the correlation between precuneus and amygdala will decrease by 0.08 (standard deviation 0.04). We will have 80% power to identify treatment effects comparing the data from 30 MDD patients receiving CCBT in 1-2 weeks with untreated data from the subjects receiving CCBT in 3-4 weeks. We will also have 80% power to detect different treatment effects in males and females separately. For longitudinal changes in activation, we

will have 80% power to detect 20% (combined) / 26% (in each sex) or more activation in R IFC after CCBT, 19% / 28% or more in L IFC , 95% / 137% or more in ACC and 50% / 71% in DLPFC. The pilot data indicate that the activation changes will be sufficiently large to exceed these minimum detectable effects.

Key inclusion criteria
Adults 18 - 60 years old, gender inclusive 2. Willing to not take psychotropic medications for the duration of the study 3. Fluent in English (both verbally and written) 4. Able and willing to provide consent 5. Must have regular access to computer at home 6. Must own a smart phone (iPhone or Android) Experimental group 1) Diagnosis of MDD, experiencing current episode as determined by SCID-5 2) Current MDE of moderate severity, as determined by MADRS score of 20 or higher Control group 1) No history of MDD in lifetime 2) No indication of current, significant depressive symptoms, as determined by MADRS score of 8 or lower

Key exclusion criteria
Diagnosis of severe or poorly controlled concurrent medical disorders that may cause depression or require medication that could cause depressive symptoms 2. Unwilling to provide informed consent 3. Diagnosis of concurrent DSM-5 (SCID) psychiatric disorders: any psychotic or organic mental disorder, bipolar disorder, active alcohol or drug dependence, primary anxiety disorder or primary eating disorders (primary refers to the diagnosis associated with the most functional impairment) 4. Diagnosed (DSM-5 criteria) by the clinical coordinator with attention deficit hyperactivity disorder, learning disorder, borderline personality disorder, antisocial personality disorder, or paranoid personality disorder 5. Cannot complete questionnaires written in English 6. Have not completed at least a 10th grade education or a GED 7. Represent an active suicide risk 8. Have MRI contraindications (e.g., foreign metallic implants, pacemaker, severe claustrophobia) Experimental group 1) Score less than 20 on the MADRS at either the initial or a second interview 2) Have previously failed to respond to a trial of at least 8 weeks of CBT conducted by a certified therapist) 3) Are currently demonstration a response to antidepressant/psychotropic medication (individuals taking a psychotropic medication may stop taking it for the purpose of the study ONLY if they are not receiving clinical benefits from taking it and after meeting with one of the study doctors to discuss the risks/benefits of discontinuing the medication and other treatment options) Control group 1) Must have no lifetime history of a major depressive episode 2) Must score below 8 on the MADRS

Vulnerable Populations

	Children Form
	Pregnant women (if the study procedures may affect the condition of the pregnant woman or fetus) Form
	Fetuses and/or Neonates Form
	Prisoners Form
	Other
x	**None of the above populations are included in the research study**

The following documents are currently attached to this item:

There are no documents attached for this item.

Populations vulnerable to undue influence or coercion
Vulnerable populations are not specifically being targeted or recruited for this study. However, individuals who are economically disadvantaged or are employees or students of Penn may still participate in the study, as they would have equal potential to benefit from the study as any other participants. Pregnant women will not be included in the study as there is the potential for unforeseen risks of an MRI on the fetus or pregnant women. Women of child-bearing potential will be asked to attest that they are not currently pregnant. Only individuals who are able to provide consent for themselves and have at minimum of a 10th grade education or a GED can participate.

Subject recruitment
The MDD participants will be primarily recruited from the Outpatient Clinics of the University of Pennsylvania, including the Mood and Anxiety Disorders program, student health, the general adult

psychiatry programs, and various other Penn affiliated clinics. Should the need arise, we also can recruit from the Philadelphia VA Medical Centers Behavioral Health Laboratory (PVAMC-BHL). Participants with MDD and healthy controls will also be recruited through the community through flyers, brochures, and printed advertisements in newspapers and public transportation avenues (advertising materials will be IRB approved prior to distribution). Furthermore, we will utilize the Internet in recruitment, specifically Craigslist, the CNDS University-sponsored website, iConnect and the CNDS Facebook page (UPenn - Center for Neuromodulation in Depression and Stress); as well as Penn newsletters. All online postings will be IRB-approved prior to posting. Additionally, we will be using the IRB-approved protocol #826348, A Feasibility Study: Department of Psychiatry Research Initiative (PI: Yvette Sheline, MD). Protocol #826348 is a pilot study the will continue through August 2017; the study collects basic contact and psychiatric intake information from Penn Behavioral Health Corporate Services & Departmentally. Only individuals who meet the basic criteria for this study will be contacted. Please see details of 826348 for further information, if necessary. We will be incorporating Penn Data Store (part of DAC) as a recruitment resource. We will send the DAC a list of basic inclusion criteria for a report every 2 weeks. Due to the sensitive nature of the diagnosis (depression) we are seeking, we will first be contacting potential participant's diagnosing provider requesting to contact his/her patient; we will send an EPIC message to the provider, attaching the patient's chart to the message. We will not be viewing the patient's EMR. We will attempt to contact the provider 2 times via EPIC and we will seek expressed approval for permission to contact each patient (we will not contact any patients for which we have not received written approval from their diagnosing provider).We will attempt (up to 2 times) to contact the patient/potential participant. If these individuals have an email on file, we will first attempt to contact via email; otherwise we will use the phone number provided in EPIC. Please find scripts attached for the 1st provider email, 2nd provider email, participant email, and phone script (participant). We would prefer to use EPIC; however, we don't know how likely providers are to respond to this and would like to have the secure share or email with password-protected attachment as an option. If using secure share or email, we ask that the provider indicate "yes" or "no" on the document for each of the patients we wish to contact. The provider will then send that password protected document to us. This protocol has been approved to use email and provide a password-protected document which includes the patient PHI; password is sent in a separate email. Patient PHI in this encrypted document sent to physicians will include only first name, last name, and MRN. This is the minimum necessary information we provide physicians so that they may correctly identify the patients we would like to reach out to about this study. The MRN will prevent errors in the situation where patients may have the same names. Lastly, we will recruit through Penn's Office of Clinical Research iConnect volunteer registry database. Volunteers who have consented to be contacted regarding studies of interest will be sorted by relevant diagnoses and invited by study team members to fill out an online self survey to determine eligibility. Research staff will receive the volunteers contact information through the Office of Clinical Research. Volunteer's contact information will be acquired through Penn's Office of Clinical Research. If these individuals have an email on file, we will first attempt to contact via email; otherwise we will use the phone number provided. Additionally, we will utilize the pre-screener tool on iConnect to decrease false positives and increase participation from subjects who are willing to commit to the study. Because these are general questions not containing protected health information and are answered with only yes or no choices, we do not feel the need to include a HIPAA waiver of authorization on iConnect prior to volunteers completing the pre-screener. In order to facilitate the enrollment of interested subjects in multiple studies, center-wide general pre-screening forms phone screen and self-report screen will be used. The Center for Neuromodulation in Depression and Stress has numerous studies that all are closely related, in both purpose and eligibility criteria, a general pre-screening (both phone and self-report) has been created. The CNDS general screener has been approved for all other studies at the center, such as protocols 819654, 824132, and 825761. Many participants will be eligible for multiple studies and will be presented the opportunity to participate in all studies that they are eligible for. An additional benefit of a shared or general prescreening is that participants who do not qualify for a specific study can be informed of other studies they are eligible for. It will be clearly explained to all individuals that this pre-screening is for multiple studies and that their information will be stored in REDCap (option given to have screening done on paper).

Will the recruitment plan propose to use any Penn media services (communications, marketing, etc.) for outreach via social media avenues (examples include: Facebook, Twitter, blogging, texting, etc.) or does the study team plan to directly use social media to recruit for the research?
Yes

Please identify which method(s) of social media you will utilize, the content of the text to be used, and the method(s) for posting this information (i.e., using Penn supported communication services). When proposing the text to utilize, please be aware of any social media limitations (i.e., number of characters allowed in a tweet) and any appropriate confidentiality practices necessary to be compliant with posting research recruitment text.*
Facebook is currently the only social media platform we plan to use for advertising for this study. Our unit's Facebook page is UPenn - Center for Neuromodulation in Depression and Stress; in which we will only post IRB-approved study advertisements for on-going studies in our program.

The following documents are currently attached to this item:

There are no documents attached for this item.

Subject compensation*
Will subjects be financially compensated for their participation?
Yes

The following documents are currently attached to this item:

There are no documents attached for this item.

If there is subject compensation, provide the schedule for compensation per study visit or session and total amount for entire participation, either as text or separate document

Subject compensation will vary by study group. MDD participants will receive $75.00 for the 1st MRI, $100.00 for the 2nd MRI, and $125.00 for the 3rd MRI, if applicable. MDD subjects have the potential to receive an additional $50.00 bonus for completing all of the Good Days Ahead homework for CCBT and 85% of the remote monitoring (e.g., Beiwe self-reports) and Good Days Ahead adherence questions (e.g. Ethica self-reports). Therefore, MDD participants can receive up to $225.00 to $350.00 total. IF PARTICIPANTS IN THIS ARM ARE ALSO PARTICIPATING IN PROTOCOL 824132, THEY WILL NOT RECEIVE THE $75.00 PAYMENT FOR THE INITIAL MRI SCAN; PARTICIPANTS WILL BE COMPENSATED FOR THIS SCAN THROUGH PROTOCOL 824132. THEREFORE, THE MAXIMUM COMPENSATION FROM THIS PROTOCOL, FOR DUAL PARTICIPANTS, WILL BE $150 OR $$275.00. Subject payments for the patient participants increase incrementally for MRI visits to encourage study completion; the bonus of $50.00 for CCBT exercise completion & remote self-reports is to encourage treatment compliance. These participants will additionally be receiving diagnostic assessments and treatment for their depression at no cost. Healthy Controls will receive $20.00 for completing screening assessments and $95.00 for the MRI scan. Participants will receive a bonus of $15 for completing 85% of the remote self-reports on Beiwe. Therefore, healthy controls can receives total of $130.00 if study is completed. Since healthy controls do not have the potential to benefit from diagnostic assessments or treatment, they will receive the aforementioned compensation to encourage healthy individuals to participate. IF HEALTHY CONTROL PARTICIPANTS ARE ALSO PARTICIPATING IN PROTOCOL 824132, THEY WILL NOT RECEIVE THE $95.00 PAYMENT FOR THE INITIAL MRI SCAN; PARTICIPANTS WILL BE COMPENSATED FOR THIS SCAN THROUGH PROTOCOL 824132. THEREFORE, THE MAXIMUM COMPENSATION FROM THIS PROTOCOL, FOR DUAL PARTICIPANTS, $35. Participants will receive their human subjects payment at the end of their own study participation. Subjects will be compensated through University of Pennsylvania supported Greenphire ClinCard. This is a reloadable prepaid card (similar to a debit/credit card) which allows funds to be available immediately. Study staff will provide participants with a ClinCard Cardholder FAQ: US document (attached). Subjects who do not feel comfortable with the Greenphire ClinCard may be compensated by a check, in lieu of the ClinCard. We are not stating this option in the ICF, as we would prefer all participants to use the ClinCard for consistency; however, we acknowledge that not all individuals will feel comfortable with this method and therefore, if a participant expresses discomfort, we will then verbally offer them the option of being paid with a check. If participants opt to have the payment provided to them in the form of a check; it will be mailed to their home address. Participants will be required to complete a C-2 and a W-9, including providing their full social security number, in order to receive the study payment.

Study Procedures

Suicidal Ideation and Behavior
Does this research qualify as a clinical investigation that will utilize a test article (ie- drug or biological) which may carry a potential for central nervous system (CNS) effect(s)?
No

Procedures
Participants will complete a phone screen or a online self-report screener to determine eligibility. If the participant is eligible, they will be scheduled for an in-person screening visit. Information collected during the pre-screening will not be used in the data analysis; pre-screening information will be collected and retained in REDCap. Participants will be asked to authorize the release of the medical records for the purposes of determining their eligibility for this study. Individuals who are patients in the Penn system will be asked for verbal consent during the pre-screening to release their PennChart electronic medical record. Data from the PennChart electronic medical record will be viewed only. The information will not be downloaded or stored. Individuals who are not in the Penn system will be asked to complete an medical record release authorization form at the screening visit after their have signed the informed consent. Upon receipt of their medical records, personal health information and identitifiers will be redacted to mitigate the risk of lost of confidentiality and privacy. Visit 1 (Screening) - all participants will have the study described to them in detail, including the risks and study procedures as outlined in the informed consent form and will sign the ICF and HIPAA authorization, prior to any study procedures being completed. Participants will be screened for symptoms of psychological disorders and severity of major depressive symptoms by a trained research team member. If determined eligible, HEALTHY CONTROLS will be scheduled for return to complete a 1-hour fMRI scan and baseline visit, in which self-report measures, including reports of mood, behavior, and thoughts will be collected, as well as neuropsychological testing. Healthy controls will begin "Remote Monitoring" by being given an actigraph to wear 24 hours a day for 8 weeks and will have Beiwe installed on their cell phones. The mobile application has two elements: Passive data collection: Behavior data is gathered unobtrusively through a background process on the mobile device. The background process is launched automatically by the application once the user logs in. After the initial logon, the process continues to be automatically launched whenever it is not already running (on phone restart or other events that terminate the process). Active data collection: Surveys and other self-report data are gathered through user input. This is achieved in two ways: (i) the user receives a notification that a survey is available and upon launch the application and they are shown all the surveys available at that time. Controls will return for an in-person visit following the 8 weeks of remote monitoring to return actigraph, have Beiwe disabled from cell phone, and receive ClinCard compensation. If determined eligible at screening, MDD (EXPERIMENTAL GROUP) participants will begin CCBT treatment within 4 weeks after completing baseline assessments. Half of the depressed participants will begin 8 weeks of CCBT within 2 weeks from completing baseline assessments (Early CCBT), and the other half after 2 weeks from completing pre-treatment baseline assessments (Later CCBT). Participants are randomly assigned to either (1) Early CCBT or (2) Later CCBT based on the a number randomly generated by the computer. All MDD participants will receive 8 weeks of CCBT within 4 weeks from completing baseline assessments. Participation duration may vary depending on the scheduling availability of the therapists, participants, and also our facilities. All CCBT participants will be scheduled for return for Visit 2 to complete a 1-hour fMRI scan and baseline visit, in which self-report measures, including reports of mood, behavior, and thoughts will be collected, as well as neuropsychological testing. Participants will begin "Remote Monitoring" by being given an actigraph to wear 24 hours a day for 8 weeks and will have Beiwe installed on their cell phones (see above for details of Beiwe). MDD subjects who are scheduled to begin CCBT after 2 weeks (Later CCBT) will complete an additional fMRI scan when they return to begin treatment. For the Later CCBT participants, the 2nd MRI scan is at least 2 weeks and up to 4 weeks from the 1st pre-treatment MRI scan. MDD participants will also have Ethica installed on their cell phones at their and complete 1 question/day regarding Good Days Ahead adherence on Ethica for 8 weeks when they being CCBT treatment. Again, this will be dependent on when subjects begin CCBT. Ethica will be used for active data collection, which includes surveys and other self- report data are gathered through user input. This is achieved in two ways: (i) the user receives a notification that a survey is available and upon launching the application they are shown all the surveys available at that time. Participants will complete Good Days Ahead (GDA) computer training at their CCBT Week 1 visit. They will have CBT Clinical Contact with a licensed psychologist/psychiatrist at Weeks 1, 2, 4, 6, 8, & 9 of treatment. Additionally,

outcome measures will be assessed by an independent clinical evaluator (without knowledge of treatment assignment) at every in-person study visit. Weeks 3, 5 & 7 will be completed off-site (at home, preferably). Participants will have a final 1-hour fMRI scan at end of study during CCBT Week 9, in which self-report measures, including reports of mood, behavior, and thoughts will be collected, as well as neuropsychological testing. Both MDD and healthy control participants will complete a 15-minute computer task called "The Foraging Task" examining their responses to rewards during Visit 2. Foraging task Details: At the beginning of each trial, participants hold fixation on a central fixation square for 2.5 seconds. Afterwards the square turned green signaling they could make a choice. They needed to move the joystick to the nearby bush to earn a reward, displayed after a short period of time called handling time.On subsequent trials, participants could choose to go back to the same bush (stay). Reward however diminished for every subsequent attempt. At any point they could decide that the reward they are getting in that bush is not high enough and that they wanted to travel to a new non-depleted bush. If they wanted to leave and go to the next bush, they needed to move the joystick to the square on the other side of the screen, and then the bushes started sliding down as if they were traveling to the next bush.The amount of time it took to travel to the next bush depended on the environment. In one block it took 5s to travel to the next bush and in another it took 20s. There were unlimited number of bushes in the environment but they had a finite time in each one (6 min x 2 blocks).The remuneration would be based on the amount of berries they have collected by the end of the session. PLEASE SEE ATTACHED TABLES SHOWING SCHEDULE OF PROCEDURES FOR EACH STUDY GROUP. PARTICIPANTS WHO ARE ALSO PARTICIPATING IN THE 824132 PROTOCOL WILL PARTICIPATE IN BOTH STUDIES SIMULTANEOUSLY. VISITS 1&2 OF THE CURRENT PROTOCOL ARE MOSTLY ENCOMPASSED WITHIN THE FULL 824132 PROTOCOL, WITH THE EXCEPTION OF SOME SELF-REPORT MEASURES AND ANY CCBT PROCEDURES THAT WOULD OCCUR AT VISIT 2 FOR THE IMMEDIATE CCBT GROUP; THEREFORE THE DURATION OF THE FIRST 2 STUDY VISITS FOR DUAL PARTICIPANTS WILL BE SLIGHTLY LONGER THAN FOR THOSE WHO ONLY PARTICIPATE IN THIS CCBT PROTOCOL.

The following documents are currently attached to this item:

There are no documents attached for this item.

Deception
Does your project use deception?
No

International Research
Are you conducting research outside of the United States?
No

Analysis Plan
C.10. Statistical Analysis: Aim 1: Aim 1a: To assess whether there is a baseline difference in amygdala connectivity in MDD compared to the controls, we will use a two-stage data-driven approach. The first step will use multivariate distance- based matrix regression (MDMR) [85] to conduct a brain-wide test using the connectivity maps with the amygdala as the seed region (adjusted for in-scanner motion). This fully data-driven approach examines the functional connections between the amygdala and each region of the brain, and serves as an omnibus test of whether depression symptoms and treatment are associated with connectomic differences. We will then apply functional principal component regression (fPCR) to the amygdala-seeded correlation maps to assess patterns of baseline amygdala-connectivity that are associated with MDD adjusting for age and sex. fPCR extracts patterns that optimally explain variation in the baseline amygdala connectome across groups through eigenimages, and hence has more power than voxel-wise searches. These eigenimages indicate which regions contribute most to these patterns. The principal scores are generated by projecting each connectivity map onto the corresponding eigenimages, yielding a measure of the amount of signal for each subject that can be explained by a particular eigenimage. Guided by hypotheses generated based on the pilot observations, we will fit fPCR separately in the target networks CEN and DMN using the 7-network solution of Yeo et al. [86] and test the relationship between the principal scores in MDD compared to controls using logistic regression adjusting for motion, age, and sex. For eigenimages with scores differing between MDD and HC, the spatial pattern will be characterized using a structural (Harvard-Oxford) and functional (Craddoc-200) atlas. We expect for fPCR to provide more sensitive and specific measurement of patterns of MDD-related amygdala- dysconnectivity in the CEN and DMN than regional averaging,

which we will also conduct for comparison. Aim 1b: To assess baseline differences between MDD and HC in Emotional Conflict task-induced activation in the dorsal ACC, DLPFC, and IFC, we will apply two approaches: First, perform the voxel-wise general linear model to detect group differences on the AHIF-AHIN contrast; Secondly, we will conduct brain-wide fPCR to explore variations that are associated with depression symptoms while controlling the anxiety symptoms. All analyses will be adjusted for age and sex, and corrected for multiple comparisons by controlling the false discovery rate. Aim 2: Aim 2a: To assess the effect of CCBT on the functional connectome, we will test for differences in amygdala-connectivity between MDD patients who receive treatment immediately (within 1-2 weeks of screening) and those who receive treatment later (within 3-4 weeks of screening). We will examine deficits identified in Aim 1 to compare the MDD groups treated immediately (1-2 weeks) vs. treated later (3-4 weeks for changes in these regions, adjusting for motion, age and gender. We will also conduct a whole-brain feature search through structured functional principal component analysis (SFPCA) [87]. SFPCA incorporates the longitudinal design complexity and models variation in amygdala-connectivity induced by CCBT through dimension-reduced principal components that are associated with longitudinal changes. Instead of generating contrasts for each hypothesis, it utilizes all available data by explicitly modeling the correlation structures among the observed connectivity maps. Aim 2b: To assess changes of the conflict task-induced activity in ACC, DLPFC, and IFC, we will use the same techniques of SFPCA and targeted mixed-effects modeling adjusting for age and sex. We will also investigate the correlation between the patterns of treatment-induced connectivity and activation normalization. Further, we will investigate the dose-response relationship between total time engaged in CCBT and changes in brain connectivity and activity. Exploratory Aim: We will first use PCR to predict treatment response after CCBT using the baseline amygdala-connectivity map. To avoid overfitting, we will evaluate the prediction performance using bootstrapped cross-validation by iteratively applying learning predictive patterns to 90% of the subjects and testing on the remaining 10%. We will assess treatment response using continuous score changes in depression and anxiety, and remission status (defined by MADRS10 after CCBT). For continuous measures of response, we will assess predicted mean-square error (MSE) for symptomatic change in two ways: first, we will simply estimate the predictive performance of the principal scores. Next, we will compare a predictive model based on regression with only baseline depression scores to a model with both baseline scores and principal scores to assess the added value of the imaging markers. For remission status, we will assess both the predictive performance of the principal scores and the added value of these markers above baseline depression scores and other demographics (age, sex, socio-economic status) using receiver- operator characteristic (ROC) curve analysis. Differences in the performance will be assessed by building confidence intervals for increased area under the curve (AUC) using bootstrapped cross-validation. We will apply the same techniques to the contrast of parameter maps from the conflict task, as well as to the cortical thickness maps. We will build second stage meta-classifiers that integrate the patterns found using these functional and structural imaging measures using generalized linear modeling, which will allow us to integrate the imaging predictors with age, sex, and other demographic information. To assess the importance of baseline executive function measures, we will examine the improvement in predictive performance by including these into the meta-classifiers. Other machine learning algorithms such as support vector machines and random forests, as well as collaborative learning will also be explored to achieve optimal performance. We will also assess the amount of model improvement by incorporating joint resting-state, task-based activation, and cortical thickness patterns into the previous PCR model by calculating c-statistics and prediction indices (such as net reclassification improvement and integrated discrimination improvement etc.) sequentially. Finally, we will investigate sparse patterns of association between imaging measures and depression phenotypic measures using sparse canonical correlation analysis. ***NOTE REGARDING DATA ANALYSIS WITH PROTOCOL 826910*** Procedures and data elements are the same between #826910 and #832295, therefore they will not need to be reconciled. The data from the two study will be added together. Participant data from the Immediate CCBT group from #826910 and the early CCBT group from #832295 will be grouped together for analysis. Participant data from the Wait-list Followed by CCBT group from #826910 and the delayed CCBT group in #832295 will be grouped together for analysis.

The following documents are currently attached to this item:

There are no documents attached for this item.

Data confidentiality

- x **Paper-based records will be kept in a secure location and only be accessible to personnel involved in the study.**
- x **Computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords.**

  Prior to access to any study-related information, personnel will be required to sign statements agreeing to protect the security and confidentiality of identifiable information.
- x **Wherever feasible, identifiers will be removed from study-related information.**

  A Certificate of Confidentiality will be obtained, because the research could place the subject at risk of criminal or civil liability or cause damage to the subject's financial standing, employability, or liability.
- x **A waiver of documentation of consent is being requested, because the only link between the subject and the study would be the consent document and the primary risk is a breach of confidentiality. (This is not an option for FDA-regulated research.)**
- x **Precautions are in place to ensure the data is secure by using passwords and encryption, because the research involves web-based surveys.**

  Audio and/or video recordings will be transcribed and then destroyed to eliminate audible identification of subjects.

Subject Confidentiality

All participants will be given a unique identifier number (Subject ID number) that will be utilized to code all collected data, both electronically and on hard copies. Hard-copy data and Informed Consents: All data and informed consent documents that are collect on paper/hard-copies will be kept at the University of Pennsylvania, in the Center for Neuromodulation for Depression and Stress on the 3rd floor of the Richards Building. Data will be coded with the Subject ID number and will be kept separately from the informed consent documents. All hard-copy data and ICFs will be stored behind two physical locks; only study staff will have access to this secure environment. Electronic data: All electronic data collected from will be stored on REDCap, which is an institutionally-approved third-party computing environment. REDCap will be used to collect some data directly (e.g., self-report questionnaires will be answered directly in REDCap, no paper/hard-copies will exist). Additionally, any data that is collected first via hard copy/paper format (e.g., SCID) will be entered into REDCap following collection. Only study staff will have access to the data. Members of the study team will have varying access levels; dependent on their role in the study; the REDCap project administrator is the primary clinical research coordinator for this study, she will determine the least amount of access needed for each team member and give permissions to data based on the minimum necessary rule. There will be one key that links the subject ID number with the participants full names and contact information. This key will stored on a University, institutionally secured and managed network drive and device. Furthermore, the key will be password-protected; this password will only be shared with study staff. New staff will be trained on confidentiality prior to handling any records. BEIWE INFORMATION Data collected from Beiwe is stored securely on the mobile device temporarily. At regular intervals, the application checks for an available connection to the WWW. If such a connection is available, the data is transmitted over a secure connection to the server and deleted from the device. If a connection is not available or if a transmission is not successful, the data continues to be stored on the device until it is transmitted successfully. The data collected through the device includes data such as call and sms logs (including call/sms time, call duration, sms length, and phone number), location and device usage. Private information such as actual content of voice calls or sms messages or emails is never read, recorded or transmitted. Beiwe Data Storage, Encryption and Server Security The data described above is encrypted and transmitted to the server over a secure 128- bit SSL 3.0 connection using the HTTPS protocol. Extra care is taken to ensure that the request cannot be spoofed or imitated by an attacker through the use of unique keys that are generated dynamically for every API request through a unique identifier and client secret that is embedded inside the application and cannot be accessed by any user or application. Beiwe linux-based servers are protected using a firewall and access control lists (ACLs), and access is restricted to Beiwe employees and contractors. Superuser activity and researcher activity on the server is logged for security and auditing. The servers are regularly updated and patched with latest security updates to ensure that there are no known threats. These servers host the database where the data is stored. Linux- based servers and access to the servers is

restricted to a few users responsible for maintaining and testing the database. For additional security, all the data that has personally identifiable information about the participant (such as e-mail) is stored in aseparate database from the one that has the data collected from the users and data related to the studies. The passively collected data from the phones as well as the actively-reported survey information is stored in the second database. Phone numbers and other such private information stored in this database are anonymized by hashing over the identifiers so that there is no threat to privacy because the data is not human readable anymore. Beiwe Data Access (through Web Dashboard) Researchers and study staff have access to the web dashboard through an account on the site. Information pertaining to a study is only available to researchers and study staff associated with that study. Participants or researchers not involved in the study cannot access the data through the dashboard. Data accessed through the dashboard is also transmitted through 128-bit SSL 3.0 connection using the HTTPS protocol. HTTP access is disabled. Researchers or study staff can invite participants through the web dashboard. They are provided an option to use the study participants name or a coded identifier as is suitable for their study protocol. The coded identifier (or name) is used to refer to the participant on the dashboard pages and in communication with the participants. Data available on the dashboard includes aggregated or processed data about the participants related to the amount of data being collected (number of location samples, number of phone calls), time-related information such as when surveys were taken, and processed data such as GBI features (from passive data) or survey scores (for surveys that have scoring associated with them). Researchers are also notified when passive data is not being collected from a participant or when participant is not answering surveys. ETHICA INFORMATION (all information below was taken directly from website ethicadata.com) Data collected from Ethica is stored securely on the mobile device temporarily. At regular intervals, the data transmitted over a secure connection to the specified server in and encrypted format and deleted from the device once the uploaded data is validated. In the case that the phone is hacked, the upload that is redirected to another server would be useless without the key, which is stored separately on a secure server. The data collected through Ethica includes the Good Days Ahead: Questions & Prompts (IRB approved on 8/7/17). This study data does not contain any explicit personal identification information and may contain data that can be reversed engineered to implicitly extract the participant's identity. Ethica will have information such as participant phone numbers for the purposes of registration. Enrollment into the research study in the Ethica phone app is based on invitation only. Ethica Data Storage, Encryption and Server Security All data on the device is encrypted using industry standard techniques (SSL/TLSencrypted network data transfer). In the event that the phone is lost or stolen, the data is protected. Data is stored in an encrypted format in a directory on the phone allocated by operating system for this purpose. A small cache of recent data (usually the past hour) is kept in volatile memory on the phone to aid in context detection for survey triggering. Because it is stored in random locations in the phones RAM this data is essentially unreachable to anything but the program itself. Data from this directory is periodically uploaded to the server specified by the Researcher in the study settings in its encrypted format. Even if the phone were hacked, and the upload redirected to another server the data would be useless to the hacker without the key, stored separately on a secure server. Once on the secure server, the data is decrypted, parsed, and inserted into an internal server. As soon as the data is successfully uploaded to the servers, uploaded data is validated, and then the data is wiped from the phones. Ethica Data Access (through Web Dashboard) Researchers have access to the Study Data database in order to monitor and analyze the data they have received for the study. None of the researchers will have access to the Metadata database. This ensures the Research team does not have access to the Participants explicit personal identification information. Request of waiver of documentation of consent for PRESCREENING activity only; phone and self-report screening will be captured via RedCap. Participants are informed of this and given the option to verbally consent; however, we will not be providing them a copy of this, as some individuals will not actually participate in the study and therefore the only link between the subject and the study would be the consent document and the primary risk is a breach of confidentiality. Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following: - What protected health information (PHI) will be collected from subjects in this study - Who will have access to that information and why - Who will use or disclose that information - The rights of a research subject to revoke their authorization for use of their PHI. In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period. SUBJECTS WHO CHOOSE TO PARTICIPATE IN PROTOCOL 824132 IN

TANDEM WITH THIS PROTOCOL WILL PROVIDE WRITTEN PERMISSION (WITHIN ICF) TO HAVE THEIR DATA SHARED BETWEEN STUDIES. THERE WILL BE NO ADDITIONAL DOCUMENTATION RETAINED FOR THIS STUDY THAT IDENTIFIES THESE SUBJECTS AS PARTAKING IN BOTH STUDIES

Sensitive Research Information*

Does this research involve collection of sensitive information about the subjects that should be excluded from the electronic medical record?

No

Subject Privacy

Privacy refers to the person's desire to control access of others to themselves. Privacy concerns people, whereas confidentiality concerns data. Describe the strategies to protect privacy giving consideration to the following: The degree to which privacy can be expected in the proposed research and the safeguards that will be put into place to respect those boundaries. The methods used to identify and contact potential participants. The settings in which an individual will be interacting with an investigator. The privacy guidelines developed by relevant professions, professional associations and scholarly disciplines (e.g., psychiatry, genetic counseling, oral history, anthropology, psychology).

Privacy refers to the person's desire to control access of others to themselves. Privacy concerns people, whereas confidentiality concerns data. Describe the strategies to protect privacy giving consideration to the following: The degree to which privacy can be expected in the proposed research and the safeguards that will be put into place to respect those boundaries. The methods used to identify and contact potential participants. The settings in which an individual will be interacting with an investigator. The privacy guidelines developed by relevant professions, professional associations and scholarly disciplines (e.g., psychiatry, genetic counseling, oral history, anthropology, psychology). Several safeguards will be put into place for protecting the privacy of participants and the confidentiality of research material. Staff members will be trained to understand the importance of privacy and confidentiality. Information gathered about individual participants is maintained in secured storage areas at the site. All aspects of the informed consent process are done in a private consultation room. Study procedures will occur in a private room by personnel trained in following procedures in a manner in which the privacy of the participant is maintained. Only information, images, and biological samples necessary for the completion of this study will be collected. All computer data obtained from the laboratory and from research interviews will be de-identified and then only identified by a code number. All data will be kept in locked file cabinets behind locked doors and only made available to qualified research personnel. All data will be de-identified and only code numbers will appear on any data and documents used for evaluation or statistical analysis for this study. Publications emanating from this research will not identify individual patients. HIPAA compliance will be enforced as per University of Pennsylvania policy. Reports from patients clinical records concerning research observations will not be available to outside medical facilities without the written consent of the participant.

Data Disclosure

Will the data be disclosed to anyone who is not listed under Personnel?

The following entities may have access to the data if requested: 1) Hospital or University representatives, to complete Hospital or University responsibilities 2) University of Pennsylvania's Institutional Review Board, 3) future collaborators for the advancement of scientific knowledge

Data Protection*

- x **Name**
- x **Street address, city, county, precinct, zip code, and equivalent geocodes**
- x **All elements of dates (except year) for dates directly related to an individual and all ages over 89**
- x **Telephone and fax number**
- x **Electronic mail addresses**
- x **Social security numbers**
- x **Medical record numbers**
- **Health plan ID numbers**
- **Account numbers**
- **Certificate/license numbers**
- **Vehicle identifiers and serial numbers, including license plate numbers**
- **Device identifiers/serial numbers**
- **Web addresses (URLs)**
- **Internet IP addresses**
- **Biometric identifiers, incl. finger and voice prints**
- **Full face photographic images and any comparable images**
- **Any other unique identifying number, characteristic, or code**
- **None**

Does your research request both a waiver of HIPAA authorization for collection of patient information and involve providing Protected Health Information ("PHI") that is classified as a "limited data set" (city/town/state/zip code, dates except year, ages less than 90 or aggregate report for over 90) to a recipient outside of the University of Pennsylvania covered entity?
No

Tissue Specimens Obtained as Part of Research*
Are Tissue Specimens being obtained for research?
Yes

Tissue Specimens - Collected during regular care*
Will tissue specimens be collected during regulator clinical care (for treatment or diagnosis)?
No

Tissue Specimens - otherwise discarded*
Would specimens otherwise be discarded?
No

Tissue Specimens - publicly available*
Will tissue specimens be publicly available?
No

Tissue Specimens - Collected as part of research protocol*
Will tissue specimens be collected as part of the research protocol?
Yes

Tissue Specimens - Banking of blood, tissue etc. for future use*
Does research involve banking of blood, tissue, etc. for future use?
Yes

Genetic testing
If genetic testing is involved, describe the nature of the tests, including if the testing is predicative or exploratory in nature. If predictive, please describe plan for disclosing results to subjects and provision

of genetic counseling. Describe how subject confidentiality will be protected Note: If no genetic testing is to be obtained, write: "Not applicable."
Saliva will be collected for exploratory genetic testing to explore biomarkers that may contribute to depression at an undetermined date; samples will be stored at the Translational Research Laboratories on Penn's campus. All samples will be coded with subject ID number and date of collection. No PHI will be kept with the samples.

Consent

1. Consent Process

Overview
Informed consent will be obtained at the initial screening visit, prior to any study procedures being conducted. All research team members will be trained on how to obtain informed consent. Trained staff will talk through the informed consent form with the participant, allowing the participant time to ask questions. All participant questions will be answered prior to them signing the consent form; participants will be given the opportunity to review the consent form with their families, friends, or physicians if they so choose. Participants will be encouraged to take their time to make a decision about participating prior to signing the consent form. The informed consent will be written at an 8th grade reading level. Individuals who are not capable of providing consent for themselves will not be eligible to participate; this include individuals who are not fluent in the English language or have any disability that would not allow them to be able to consent for themselves (e.g., intellectual disabilities).

Children and Adolescents
Children aged 18-21 will be included in the proposed study. The investigators have had ample previous experience working with subjects of this age, and all study procedures are appropriate for this age range.

Adult Subjects Not Competent to Give Consent
Individuals who are not able to provide informed consent for themselves will not be enrolled in this study. All participants must not have a diagnosis of intellectual disability or any form of dementia; all participants must have a 10th grade education or GED.

2. Waiver of Consent

Waiver or Alteration of Informed Consent*
No Waiver Requested

Minimal Risk*

Impact on Subject Rights and Welfare*

Waiver Essential to Research*

Additional Information to Subjects

Written Statement of Research*
No

If no written statement will be provided, please provide justificiation

The following documents are currently attached to this item:

There are no documents attached for this item.

Risk / Benefit

Potential Study Risks

The primary risks of Major Depressive Disorder are suffering, symptom burden, and despair including the risk of attempting or completing suicide, as well as persistent disability in family, social, and vocational roles. As in everyday practice, patients with suicidal ideation who cannot be treated on an outpatient basis will be excluded from this study. Whereas there are significant risks of suffering from depression, there are only a few additional potential risks involved in this study. In this regard, CCBT is an efficient form of delivery of the best-studied psychotherapy for depression, for which there is good evidence of efficacy across numerous studies. There are no known risks of using the computer software employed in this study, Good Days Ahead, nor for CBT as a broader class of therapy other than possibility that the treatment will prove to be ineffective for a subset of patients. For the depressed group, there is the added potential risk of delaying the start of specified therapy as they are scheduled to begin CCBT either within 2 weeks or after 2 weeks from completing baseline assessments. This risk is offset by the remote monitoring of symptoms using the Beiwe cell phone app during wait-time to begin CCBT treatment. It is important to note that patients typically at least 4 or more weeks to receive therapy in the community, thus, this is standard care. Delayed treatment conditions have been the most commonly used standard of comparison for generations of studies on psychosocial treatments of depressed and provide the most clear-cut way to uncouple the considerable effects of spontaneous remission and nonspecific benefits from the more specific effects of CCBT. Although in our past studies it is rare (i.e., less than 1 per 200) for a patient in protocol to experience a suicidal crisis or the onset of psychosis, if such worsening would develop, the patient would be withdrawn from the protocol, hospitalized if necessary, and treated with whatever type of therapy seems most clinically indicated. Participants also will be asked to provide permission to be contacted if they miss visits to help ensure close monitoring of their conditions. The utility and safety of the form of CCBT used in this trial has been documented by previous studies and is, at the least, comparable to the interventions that people might receive in non-research settings. Likewise, the clinical assessments, including both self-reports and observer ratings, are basically hazard-free, with the possible exceptions that participants may find the assessments tiresome. There is the remote possibility that confidentiality could be breached. There are no known risks associated with MRI scans for healthy subjects except that participants may experience discomfort as they will be required to lie still in a confined area. Participants may experience claustrophobia (fear of enclosed spaces and/or anxious feelings accompanied by fast heart rate or shortness of breath) within the MRI scanner. In addition, the scanner produces a loud repetitive knocking noise during the study that some people find bothersome.

Potential Study Benefits

Participants may not receive any benefits from participating in this research. However, participants may experience a decrease in depressive symptoms. There will be no direct benefit to healthy control participants. Importance of the Knowledge to be Gained: Major Depressive Disorder is a recurrent, disabling, potentially lethal illness. Although CBT has established efficacy, its utility is limited by the availability of experienced therapists and the cost of a full course of therapy. In clinical practice, people who receive treatment for depression are much more likely to receive antidepressant medications than CBT, and antidepressants have an intent-to-treat effectiveness of no more than 50% under optimized circumstances (see, for example, Trivedi et al., 2006 [7]). Moreover, the largest component of an antidepressant response is attributable to so called nonspecific benefits, which in some analyses of clinical trial results can account for 75% of the clinical benefit [8]. Even when antidepressant treatments are partially effective, residual symptoms and psychosocial impairment often persist, which makes it imperative to improve existing therapies or create new therapies, sequences, and/or combinations. The chance of relapse and recurrence is particularly high during the 6 to 9 months after patients discontinue acute phase antidepressant medication. Although no more effective than antidepressants in the shortrun, acute phase CBT alone has been shown to reduce the risk of relapse/recurrence for some number of months after termination of therapy. As there are relatively few skilled and well-trained CBT therapists, any procedure that improves the efficiency of therapy will have great public health significance by rendering treatment more available to more people. By evaluating the benefit of CCBT, we will be able to ascertain if this model of therapy will substantially improve the efficiency of therapy. Beyond the potential benefits of further establishing the merits of CCBT, there is the potential for improving therapy inherent in further clarifying the mechanism of action in terms of the impact of treatment on relevant neural circuits. If, as predicted, the specific benefit of CCBT is derived from strengthening cognitive/executive control over dysfunctional limbic-frontal circuits, then

further refinements in the delivery of CCBT, such as massing practice of relevant coping exercises, could prove to enhance treatment efficacy and further strengthen the durability of gains.

Alternatives to Participation (optional)
Participants have the option to not participate. Participants will be told of alternative treatments for depression, including medications, somatic treatments (e.g., TMS, ETC), and talk therapy outside of the context of this study.

Data and Safety Monitoring
This study has been approved by Dr. Judith M. Rumsey for investigator-level monitoring on 5/17/17. No DSMB is required. The principal investigator will review ongoing study procedures, discuss serious adverse events (SAEs) and other safety issues, and to evaluate ongoing methods for maintaining data integrity and confidentiality. Should the investigator develop any concerns on the basis of information provided by the study team, she may request to examine hard or electronic copies of participants' research records from any of the study sites. In transferring such information, participants' identities will be protected by transferring only data that are de-identified (hard copies) and/or encrypted (electronic data). In considering the frequency of meetings, we have tried to strike a proper balance between maintaining participant safety and the integrity of the study, and the consequent time, workload, and cost to the study budget in preparing reports. Annual meetings will be sufficient during the submission of the annual continuing review.

The following documents are currently attached to this item:

There are no documents attached for this item.

Risk / Benefit Assessment
Potential Benefits Versus Risks of the Research to Patients and Others. We believe that the risks associated with this study are small and are offset by the potential benefits that patients may receive from participating. Any treatment for depression is associated with some chance of failure to respond or subsequent relapse/recurrence; in this particular trial there is the additional risk resulting from the delayed start of CCBT by up to 4 weeks depending on what group they are randomly assigned to. However, this is no different from usual standard of care treatment given that starting treatment as a new patient will take at least 4 weeks when scheduling with mental health service providers in the community outside of this study.. The protocols are designed to provide high quality clinical care to consenting participants, which generally exceed the standards of care for non-research settings in Philadelphia. Study participants are evaluated longitudinally and more rigorously in this protocol than they are typically in standard clinical practice. Thus, whether the adverse outcome is a slower response or even non-response to acute phase therapy or a subsequent relapse/recurrence, we will be able to provide alternate treatment or referrals immediately. There is no benefit to receiving the MRI scans and, because the imaging is performed for research, results are not routinely shared with participants. However, in the event that MRI abnormalities are discovered, subjects will be informed of the finding. Participants experience the indirect benefit of contributing to scientific knowledge.

General Attachments

The following documents are currently attached to this item:

Informed consent form (2019.04.09_ccbtgroups_icfhipaa_v2_feb2019_clean.docx)

Informed consent form (2019.04.09_ccbtgroups_icfhipaa_v2_feb2019_track.docx)

Informed consent form (2019.04.09_healthycontrol_icfhipaa_v2_feb2019_clean.docx)

Informed consent form (2019.04.09_healthycontrol_icfhipaa_v2_feb2019_track.docx)

Additional forms (2019.04.09_scheduleofassessments_ccbtgroup.docx)

Additional forms (2019.04.09_scheduleofassessments_controlgroup.docx)

Cover Letter (2019.04.10_coverletter_modification_832295.doc)