Title: Connectivity Affecting the Antidepressant Response (CAARE)
Study Protocol

Clinicaltrials.gov Identifier: NCT02332291

NIH Grant: R01 MH102246
NIH Grant Title: Neural Connectivity Affecting the Antidepressant Response: Testing a Lesion Model

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1.0 BACKGROUND:

Individuals with late-life depression (LLD) experience high levels of disability, mortality, and poor responses to antidepressants. Age-related white matter disease is characteristic of LLD and contributes to these poor outcomes (1). Although the underlying mechanisms are not well established, white matter disease may contribute to LLD by adversely affecting cognitive, affective, and default mode networks. This project's primary goals are to characterize whether focal vascular damage to specific white matter tracts: a) affects neural circuit connectivity & function, b) influences clinical presentation, and c) predicts poor response to antidepressants.

The MRI hallmark of 'vascular depression' is significant ischemic white matter lesion (WML) severity (2), a finding associated with poor antidepressant outcomes. Despite observations of diffuse white matter disease in LLD, we propose in our "disconnection hypothesis" (3) that focal damage to fiber tracts negatively affects the function of connected regions, resultantly contributing to cognitive deficits and clinical symptoms such as depression severity and negativity bias. Focal WMLs may also reduce the likelihood of an antidepressant response *when the specific antidepressant used acts on neurotransmitter systems projecting through the damaged fiber tract*. This implies that the effect of tract damage on clinical response may *differ between drugs with different mechanism of action*. We propose that the **cingulum bundle (CB)** and **uncinate fasciculus (UF)** are key tracts in LLD as they are components of cognitive, affective and default mode networks and contain monoamine neurotransmitter projections. Supporting our model, past work implicates CB and UF deficits in LLD (4-7) and our recently published data associates tract damage in the CB with poor antidepressant response (8).

This study has broad *significance* for elucidating how vascular factors influence the occurrence and course of LLD. It provides a scientific opportunity to use a neuroimaging finding of known pathology (WMLs) to examine how circuit deficits adversely affect antidepressant response. Importantly, clinical translation of this work may guide individualized treatment. Knowledge of circuit-response relationships may inform antidepressant selection or the identification of individuals likely to be treatment-refractory. We propose that we may translate this work into clinical use by linking impairment in circuits and tracts with performance on specific cognitive measures. Such measures can then be used as markers of focal tract damage.

2.0 RATIONALE and SPECIFIC AIMS:

In a cohort of 130 depressed elders we will test our **central hypotheses: a) focal CB and UF WMLs disrupt connectivity and function of connected regions and contribute to cognitive deficits and affective symptoms; and b) antidepressants acting on neurotransmitter systems projecting through these tracts will be less effective**. We will examine how novel measures of tract-specific WML volumes are associated with neural connectivity (using resting state fMRI), reactivity to cognitive & affective stimuli (using a fMRI task), & clinical presentation. After MRI, participants will be stratified by WML volume and randomized to blinded escitalopram (5HT) or placebo. Participants who do not remit in this initial phase will then receive open-label bupropion (DA/NE). These drugs affect different neurotransmitter systems with distinct projection pathways. This design will allow us to examine both drug and placebo responses while also testing whether discrete neural circuit deficits differentially affect drug response.

Specific Aim 1: To characterize the effect of cingulum bundle (CB) and uncinate fasciculus (UF) WMLs on

tract connectivity, function of connected regions, and the cognitive and affective presentation of LLD (Fig 1&2).
Hypothesis 1: Greater CB WML volume is associated with a) reduced resting-state connectivity of frontal, temporal, and cingulate regions and b) deficits in attention, memory and processing speed.
Hypothesis 2: Greater UF WML volume is associated with a) reduced resting state functional connectivity between frontocingulate and medial temporal regions, and b) greater depression severity and negativity bias.

Exploratory Hypothesis: Greater CB WML volume is associated with failure of anterior and posterior DMN nodes to deactivate during attentional components of the fMRI task. Greater UF WML volume is associated with greater medial temporal reactivity during affective components of the fMRI task.

Specific Aim 2: To determine whether deficits in tract structural / functional connectivity predict nonremission to antidepressant treatments and if these relationships vary based on antidepressant mechanism of action.
Hypothesis 3: Nonremission to escitalopram will be predicted by: a) greater WML volume in the CB and UF, and b) reduced resting functional connectivity between structures connected by the CB and UF. Greater WML severity and reduced functional connectivity in these tracts will not significantly predict response to placebo.
Hypothesis 4: Nonremission to bupropion will be predicted by a) greater WML volume in the UF but not CB, and b) reduced resting functional connectivity deficits between structures connected by the UF but not CB.

Exploratory Aims: Expl. Aim 1) To determine if specific cognitive measures may serve as markers of focal tract WML damage. **Expl. Aim 2)** To use whole-brain multimodal imaging approaches to examine how connectivity differences in other brain regions may also predict nonremission to antidepressants.

For exploratory analyses, we will also recruit 30 elders with no psychiatric history. Data from this population will help us understand whether our neural and cognitive findings in depression represent differences from what is seen in healthy aging, or whether our observations in depressed elders are within the range of normal aging. This will be important for data interpretation and planning for future projects.

3.0 ANIMAL STUDIES & PREVIOUS HUMAN STUDIES

3.1. Late life depression and vascular disease: Late-life depression (**LLD**) is characterized by poor treatment responses along with increased morbidity, mortality and disability (9,10). A significant body of research supports the role of vascular disease in the pathogenesis of LLD. This informed the "*vascular depression*" hypothesis, which posits that vascular disease, characterized by greater diffuse hyperintense white matter lesion (**WML**) severity on MRI, may predispose to or perpetuate LLD (1-3). Although not all studies agree (11-15), greater WML severity is generally associated with poorer antidepressant response (16-21). In our *disconnection hypothesis* (3), we propose that *the functional and clinical significance of WMLs depends on which neural circuits are disrupted*.

3.2. Circuits in LLD: The uncinate fasciculus (**UF**) and cingulum bundle (**CB**) are critical fiber tracts within functional networks implicated in Major Depressive Disorder (MDD; **Table 1**; Sect A.3). The **UF** is involved in memory and emotional processing (22). It runs within the temporal stem and connects the amygdala and hippocampus with the medial and lateral orbitofrontal cortex (23-28). The **CB** is a pathway superior to the corpus callosum involved in attention, memory, and emotional regulation (29). It contains fibers originating from the cingulate gyrus, thalamus, and frontoparietal areas, projecting to other cingulate regions, the prefrontal cortex, presubiculum, precuneus, amygdala, and hippocampus (26,27,29-31).

Work from our group and others shows that LLD is associated with greater WML severity in discrete tracts including the cingulum bundle (CB) and uncinate fasciculus (UF) (4-7). Similarly, work using diffusion tensor imaging also associates depression with deficits in the UF (7,32-34) and CB (32,34). Similarly, our recently published data demonstrates that greater WML severity in the CB is associated with poor antidepressant response (8). *These data support that damage to the CB and UF contributes to the occurrence and presentation of LLD*.

Figure 1. Uncinate Fasciculus (UF) Model

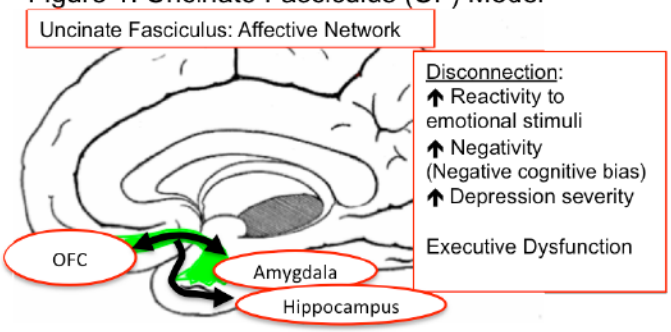
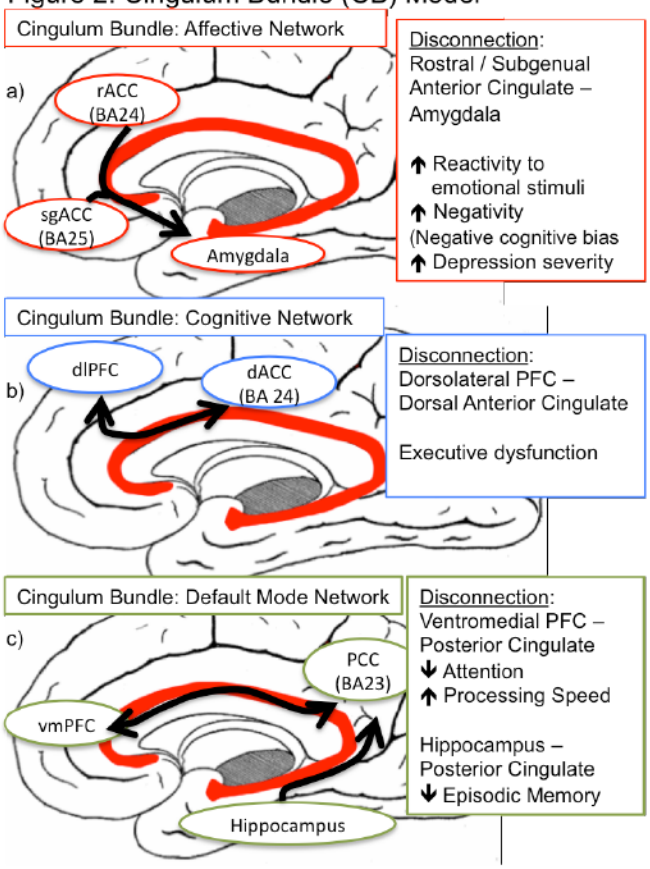


Figure 2. Cingulum Bundle (CB) Model



3.2.a Functional Networks in LLD: Effect of WMLs: Although some well-designed studies have not found altered functional connectivity in LLD (32), others report that LLD is associated with altered connectivity in affective, cognitive, and default mode (**DMN**) networks (35-41). Greater WML severity appears to impair connectivity and function of these networks (41-43). Importantly, some of these studies observed *increased* functional connectivity in LLD. As has been observed in MDD (44), observations of increased connectivity can be related to *deficits* in structural connectivity, particularly if structural deficits occur in regulatory connections.

A recent reports shows that DMN circuit deficits in LLD affect the antidepressant response. Compared with treatment-nonresponsive subjects, antidepressant responders exhibit greater pre-treatment connectivity between the posterior cingulate cortex and medial PFC (45). *This supports our theoretical model (**Fig. 2c**)*.

3.3. Network deficits in late-life depression: A theoretical model: Summarized by Sheline et al. (46), MDD is characterized by altered function of three key networks. These networks have distinct roles with some anatomical overlap (47). The UF and CB are critical fiber tracts within these networks.

3.3.a. The **affective network** (AN) mediates emotional processing and is involved in autonomic and visceral regulation. It consists of the affective division of the anterior cingulate cortex (ACC), along with its connections to the amygdala, entorhinal cortex, nucleus accumbens, and other limbic structures. Altered AN activity in MDD is well documented, including increased reactivity to negative stimuli (48,49).

The UF and CB are involved in the AN (Figures 1 and 2a). Disruption of these tracts affects frontocingulate control over amygdala reactivity. In turn, amygdala hyperactivity is associated with greater depression severity (50) and a negative bias in processing and interpreting emotional stimuli (51,52). We anticipate that WMLs in the UF and CB will contribute to greater amygdala **reactivity to negative emotional stimuli** (reviewed in (49)). Similarly, greater WML severity in these tracts will be associated with greater out-of-scanner **depression severity** and **negativity bias**.

3.3.b. The **cognitive control network** (CCN) consists of frontal and parietal regions, including the dorsolateral prefrontal cortex and dorsal anterior cingulate cortex. The CCN modulates attentional processes and working memory, is involved in decision-making and conflict resolution and is impaired in MDD (38,53). The anterior CB contains connections between dorsal CCN regions (Fig 2b) (54,55). Anterior CB disruption may contribute to decreased connectivity between CCN regions in LLD (38), which is correlated with poor antidepressant response (38). Altered CB microstructure is associated with **executive dysfunction** (34,56), which in LLD is associated with poor treatment response (21,57). However, altered UF microstructure is also associated with executive dysfunction (34,58,59); this may be due to disrupted ventral hippocampus – PFC connectivity (60).

3.3.c. The **default mode network** (DMN) (47,61) is important in self-referential activities and more active at rest (47). The DMN consists of widely distributed elements but is divided into anterior and posterior nodes (61) that often act independently (62). The posterior node includes the posterior cingulate cortex and precuneus while the anterior node includes the anterior cingulate and ventromedial PFC. Reduced functional connectivity between DMN nodes may contribute to difficulties deactivating the DMN during tasks (38,46,63,64).

In MDD, the DMN often does not deactivate during affective and cognitive challenges, contributing to

maladaptive cognitive processes (61,65). In MDD we observe a *dissociation between* anterior and posterior DMN nodes (66) while within-node functional connectivity is increased (38,46,63,64). As reduced functional connectivity is related to altered CB structure (67,68), we propose that WMLs in the CB adjacent to the cingulate gyrus may disrupt communication between DMN nodes. This would impair anterior-posterior connectivity, resulting in difficulty coordinating deactivation of the DMN during tasks (61). This contributes to deficits in **attention** (69,70) and **processing speed** (59,71-73), deficits associated with poor antidepressant response (21,57). *Additionally*, damage to the CB in the region of the hippocampus may have further effects. WMLs in this region may disrupt hippocampus-posterior cingulate connectivity (31,47,74) resulting in poorer episodic memory performance (75-77). This results in **episodic memory deficits** that are also associated with poor LLD antidepressant responses (21) (Figure 2.c).

3.4. Antidepressants with different mechanisms of action: Antidepressant treatment changes brain metabolism (78-82). However, antidepressants with different mechanisms of action have different effects on neural circuit connectivity (83,84) or neural activity during tasks (85,86).

The relationship between neural circuit deficits and the antidepressant response may *depend on the drug's specific mechanism of action.* We hypothesize that tract damage predicts nonresponse to antidepressants that affect neurotransmitter systems projecting through that tract. Serotonergic neurons project widely through the CB (87), but also to the orbitofrontal cortex and medial temporal lobe (88-90), suggesting UF involvement. Noradrenergic projections largely overlap with serotonergic innervation (91), including CB projections (92). In contrast, dopaminergic neurons have discrete pathways (93-96). Dopaminergic mesocortical and mesolimbic fibers may pass through the UF (97), but compared to serotonin or norepinephrine, have less CB projections (98). *Thus drugs affecting serotonin and norepinephrine may require intact connectivity in both the CB and UF, while dopaminergic agents may depend less on the CB.*

4.0 ENTRY CRITERIA

We plan to enroll a cohort of 200 individuals to meet goals of having 130 evaluable subjects. Participants will meet DSM-IV-TR criteria for MDD, single episode, recurrent, or chronic. We will not be enrolling vulnerable populations, specifically pregnant women, children, prisoners, or institutionalized individuals. We also will not enroll subjects incapable of providing their own consent. Should a potential subject present where there is a concern (either by a study clinician or staff member) about their ability to understand study procedures and provide meaningful consent, their cognitive ability and understanding will be evaluated by a study doctor. If there is any concern that the individual may be impaired, they will not be enrolled in the study. The rationale will be provided to the individual as well as his or her family members. Referrals for further evaluation, including urgent or emergent evaluation, will be made as needed and clinically warranted.

Men and women of all races / ethnicities are eligible.

Depressed Cohort:

Inclusion Criteria:

1) Age 60 years or older.
2) Current diagnosis of major depressive disorder (DSM-IV-TR), single episode, recurrent or chronic, without psychotic features, as detected by MINI and clinical exam.
3) Minimum MADRS score ≥ 15.
4) Mini-Mental State Exam ≥ 24.
5) Fluent in English.

Exclusion Criteria:

Diagnostic Issues:

1) Current or past diagnoses of other Axis I psychiatric disorders, except for generalized anxiety disorder (GAD) symptoms occurring during a depressive episode
2) History of alcohol or drug dependence or abuse in the last three years
3) History of developmental disorder or IQ score < 70
4) Presence of acute suicidal ideation, defined as a "yes" response to items 3, 4, or 5 on the C-SSRS
5) Acute grief (< 1 month)

6) Current or past psychosis

Medical Issues:

7) Primary neurological disorder, including but not limited to dementia, stroke, brain tumors, epilepsy, Parkinson's disease, or demyelinating diseases
8) MRI contraindications
9) Any physical or intellectual disability adversely affecting ability to complete assessments
10) Current pregnancy or capable of becoming pregnant (defined as ability to have children [i.e., has not had a hysterectomy or bilateral oophorectomy] and is not clearly postmenopausal [> 1 year of amenorrhea])

Antidepressant Treatment Issues:

11) ECT in last 6 months
12) A failed therapeutic trial of escitalopram in the current depressive episode (defined as at least 6 weeks of treatment at a daily dose of 10mg or higher)
13) Known allergy or hypersensitivity to escitalopram or bupropion
14) Current or planned psychotherapy

We will additionally enroll up to 60 older adults with no history of psychiatric or neurological illness in order to have 40 subjects with MRI data. Data gathered from this cohort will assist us as we interpret data from the depressed cohort. Entry criteria will be similar to those of the depressed cohort, but adjusted to reflect we want to enroll individuals without any history of depression or other psychiatric illness.

Nondepressed Cohort:

Inclusion Criteria:

1) Age 60 years or older.
2) Mini-Mental State Exam ≥ 24.
3) Ability to read and write English.
4) MADRS score ≤ 8

Exclusion Criteria:

Diagnostic Issues:

1) Current or past diagnoses of any Axis I psychiatric disorders
2) Any use of illicit substances (such as marijuana or cocaine) or abuse of prescription medications (such as benzodiazepines or opiates) within the last three months.
3) Presence of acute suicidality
4) Current or past psychosis

Medical Issues:

5) Known primary neurological disorder, including dementia, brain tumors, epilepsy, Parkinson's disease, or demyelinating diseases
6) Chronic untreated medical disorders (including but not limited to hypertension, hyperlipidemia, fibromyalgia, hypothyroidism, or any medical disorder) where treatment is warranted
7) Any physical or intellectual disability affecting completion of assessments
8) MRI contraindications

Antidepressant Treatment Issues:

9) Any history of antidepressant treatment, including antidepressant medications, psychotherapy, or brain stimulation such as ECT. Brief couples / martial counseling, where the focus of treatment was not a psychiatric illness is allowable.

5.0 ENROLLMENT AND CONSENT

We will enroll patients from clinical referrals and response to advertisements. In these cases, potential participants will call our study contact number. We will describe the study to them, including a description of the study entry criteria. Those who continue to be interested will then be scheduled for an evaluation. After scheduling, a study doctor will review their electronic medical record to assure that potential subjects meet entry criteria, however no data will be recorded. Occasionally a clinician may identify a patient who may be

eligible and request that we initiate contact. We will do this, but the referring clinician must first broach the idea of research and secure the patient's agreement to be contacted.

Upon presenting for evaluation, we will obtain formal written consent from all participants. Following policies of the Vanderbilt University Health System Institutional Review Board, written informed consent will be obtained and documented by the study's Research Coordinator before any study-related procedures are performed. The study coordinator will review study procedures and the consent form with each potential participant. A study doctor will be available should any consent-related questions arise. Each individual may take as much time as they like to decide if they do or do not wish to participate.

We will allow that nondepressed participants can be consented and complete the screening visit without coming physically to VUMC. This will be conducted via HIPPA compliant Zoom teleconferencing unless there are technical problems with Zoom, in which case we will use Facetime or other videoconferencing software at the participant's request. An e-consent process will be conducted using a REDCap-based electronic consent form. The consent form has been developed in REDCap, a secure, web-based, HIPAA-compliant, data collection platform with a user management system allowing project owners to grant and control varying levels of access to data collection instruments and data (e.g. read only, de-identified-only data views) for other users.

Potential participants will be initially evaluated using our currently telephone screening approach. If they appear eligible, they will be scheduled for a Zoom meeting. Once that meeting is initialized, the first step will be to obtain e-Consent using the REDCap survey via iPad or other portable electronic device. This link will be emailed to them. A study coordinator will review the consent form while teleconferencing with the participant and answer any questions before the participant signs.

Patient signatures will be obtained using REDCap's 'Signature' field type on the survey. Upon completion of the consent, participants will be able to download a signed copy of the consent form. We will also provide them with a copy of their version of the consent document signed by them and by the consenting study staff member by mailing of a hard copy of the consent.

The remainder of the screening visit will continue as described below and involve assessments obtained by the study coordinator and a study physician. The only difference will be that the MMSE, typically obtained at the screening visit, will instead be obtained at the baseline visit. Non-depressed participants who complete the screening visit in person will otherwise follow the screening visit plan described below.

This process will not be used for participants enrolled through TVHS.

6.0 ENROLLMENT AND CONSENT PROCESSES SPECIFIC TO VA TENNESSEE VALLEY HEALTH SYSTEM (TVHS)

We also anticipate enrolling patients from the VA TVHS via clinical referrals and responses to advertisements. Only depressed participants will be enrolled from the VA. As with our current plan, we will describe the study purpose and procedures to them, including a description of the study entry criteria. Those who continue to be interested will be scheduled for an evaluation. A study doctor will review their electronic medical record to assure that potential subjects appear to meet entry criteria, however no data will be recorded. Occasionally a clinician may identify a patient who is potentially eligible and request that we initiate contact. We will do this, but the referring clinician must first broach the idea of research and secure the patient's agreement to be contacted.

The initial evaluation and obtaining written informed consent will occur at VUMC. Informed consent will be obtained and documented by a study doctor or the study's Research Coordinator before any study-related procedures are performed. Veterans who receive care at the VA TVHS will be asked to sign both the VUMC informed consent document as well as a separate VA TVHS informed consent document.

7.0. STUDY OVERVIEW

After consent, subjects will be evaluated for eligibility. After standardized clinical and cognitive assessments and MRI, subjects will begin 8-weeks of double-blinded study drug, either escitalopram or placebo. Those who do not remit, defined as a MADRS ≤ 7 at the last assessment, will enter an 8-week open-label trial of bupropion XL. Subjects will be evaluated every two weeks via monthly clinic visits and telephone visits at

intervening two weeks.

Nondepressed participants will only complete the screening and baseline assessments. They will not receive study medication or follow-up assessments.

8.0 STUDY ASSESSMENTS

8.1. Clinical & Cognitive Assessments: These are primarily done at the screening visit or the Biomarker / Testing visit. Measures of depression severity, adverse events, and treatment compliance occur at all visits.

8.1.a. Diagnoses and Symptom Severity: Current and past psychiatric diagnoses will be assessed using the electronic version of the validated Mini-International Neuropsychiatric Interview Plus (**MINI+**) (99,100) & confirmed through a clinical interview which will assess **age of initial onset**. Depression severity will be assessed using the **MADRS** (101) as our primary outcome measure, with an *a priori* definition of remission being MADRS ≤ 7 at the last assessment. The **QIDS-SR$_{16}$** (102-104) is a secondary depression severity measure, included as self-report scales are less susceptible to clinician bias. These measures will be collected every two weeks. Thoughts of suicide will be assessed at study entry by the study physician using the Columbia Suicide Severity Rating Scale (C-SSRS). Safety and the presence of suicidal ideation will be assessed at every contact.

Prior exposure to antidepressants will be assessed with a modified version of the Antidepressant Treatment History Form (**ATHF;** Appendix 3) (105,106). We will use an updated version including current antidepressants and antipsychotics approved for MDD. We will request medical records as needed.

Apathy is assessed with the **Apathy Evaluation Scale** (107). This valid scale uses measures distinct from depressive symptoms (107,108). Childhood trauma history will be assessed using the Childhood Trauma Questionnaire (CTQ).

8.1.b. Medical: All medical comorbidities will be quantified using the **Cumulative Illness Rating Scale** (**CIRS**) (109), which covers all major systems and provides a composite medical morbidity score. Vascular risk will be specifically measured and assessed through the **Framingham Stroke Risk** (Appendix 4) (110). For safety, concomitant medications and vital signs (blood pressure, pulse) will be reviewed at each visit. Disability will be assessed using the WHO-DAS 2.0.

To assure safety for MRI, we carefully screen participants for metal. Working with the Vanderbilt University Institute for Imaging Science, we identify past medical procedures and surgeries that may include metal implants. In these cases, we request medical records to determine if metal was used, and if so, if it is safe for 3Tesla MRI. However, in some cases these records cannot be obtained. In such cases we may obtain an x-ray if there was a question whether there was or was not implanted metal.

We will only obtain an x-ray in cases where a) there is a safety concern about a potential implant or metal; b) medical records for the surgery are not available; and c) participants do not think that metal was involved in the surgery. Thus this procedure will not be needed for the majority of participants. If the x-ray shows there is implanted metal that could be a MRI contraindication, that participant will be withdrawn from the study. Radiation exposure will vary dependent on the area needing to be evaluated.

Based on recommendations from NIH, we formally exclude for current pregnancy. Given the study's minimum eligible age is 60 years, we anticipate all female participants will be postmenopausal (Gold EB, et al. Am J Epidemiol, 153:865-874, 2001). To address this concern, we will ask about the potential for pregnancy and time since the last menstrual period. If a woman presents who is capable of having children (i.e., has not had a hysterectomy or bilateral oophorectomy) and is not clearly postmenopausal (defined as > 1 year of amenorrhea), we will determine she is ineligible and not enroll her in the study. We take this route over requiring use of contraception for safety reasons, given the risks of long-term use of hormonal treatments in older women.

8.1.c. Side Effects / Treatment Compliance: Side effects will be assessed using the Frequency and Intensity of Side Effects Rating / Global Rating of Side Effect Burden (**FISER/GRSEB**) scale (111). Compliance will be assessed with a pill count and the Medication Adherence Questionnaire (**MAQ**) (112).

8.1.d. Other Phenotypic Assessments: We will move beyond traditional diagnostic criteria for a broader examination of specific depressive symptoms. The following assessments will be administered at either the screening or baseline visit, then again after completing each 8-week study drug phase: Insomnia Severity Index (ISI), Ruminative Response Scale (RRS), Penn State Worry Questionnaire (PSWQ), Fatigue Severity Scale (FSS), and the Snaith-Hamilton Pleasure Scale (SHAPS), the PROMIS Applied Cognition Abilities Short

Form, the Type D Scale (DS-14) of negative affect, the Generalized Anxiety Disorder 7 item scale (GAD7) and the Attentional Control Scale. Also, the Perceived Stress Scale (PSS) and the Perceived Social Support/Conflict survey will be administered at the baseline visit.

8.2. Cognitive Assessments: Subjects are excluded for MMSE scores < 24 or a diagnosis of dementia.

Our cognitive domain assessment approach (**Table 1**) is published (21,113). We group the cognitive tasks into rationally motivated domains with reasonable internal consistency by Cronbach's alpha. We will create *Z*-scores for each task measure across participants and to create the domain score, sum the *Z*-scores of the tasks in that domain. Variables in which good performance is represented by lower values rather than higher values will be reverse scored so higher *Z*-scores represent better performance for all variables. This battery covers the range of cognitive deficits associated with poor antidepressant response in LLD (21,57,114).

Using Z-scores increases power but decreases sensitivity. Our primary cognitive outcomes will be the domain scores, but to improve sensitivity we will also examine performance on individual measures, particularly for Exploratory Aim 1.

Table 1. Cognitive Domains & Tasks (21)

Episodic Memory (Alpha = 0.76)
• Word List recall; Logical memory; Constructional praxis; Benton Visual Retention Test
Executive Function (Alpha = 0.73)
• Verbal Fluency; Trail Making Test, Part B; Stroop, color-word interference; Mattis DRS, Initiation-Perseveration subscale; Wisconsin Card Sorting Test
Language Processing (Alpha = 0.62)
• Shipley Vocabulary Test; Boston Naming Test; Stroop, word reading
Processing Speed (Alpha = 0.69)
• Symbol-digit Modality Test; Stroop, color naming; Trail Making Test, Part A
Working Memory (Alpha = 0.68)
• Digit Span, forward; Digit Span, backwards; Ascending Digits

9.0. RANDOMIZATION & STUDY DRUG ADMINISTRATION

9.1. Randomization: After initial assessments, participants are randomized to double-blinded Phase 1 drug assignment (escitalopram or placebo). As our primary interest for Phase 1 is related to escitalopram response, we will allocate participants in a 2:1 drug-to-placebo ratio. Randomization will be conducted by the Vanderbilt Investigational Drug Service. Nondepressed individuals will not be randomized to study drug.

Randomization will be stratified by MRI measures of total cerebral WML volume. Our measurement of total WML volume is automated and available within 24 hours of the scan and subjects will be stratified as "high" or "low" total cerebral WML volume. Based on pilot data, we will use a cutoff of 3.86mL; this is the median 3T WML volume from a cohort of 145 depressed elders analyzed using our WML segmentation method. When we reach 50% enrollment, we will re-assess this cutoff based on study data and adjust if necessary.

If there are delays in scan processing, stratification will be determined using the Coffey-modified Fazekas visual rating scale (2), dichotomizing participants as "high" (2 or 3, confluence of foci) or "low" (0 or 1, absent or punctate foci).

MRI measures will only be used for stratification. They will not guide or determine treatment decisions.

9.2. Phase 1: Blinded Escitalopram or Placebo: We selected escitalopram due to its tolerability, ease of dosing, and lack of effects on dopamine and norepinephrine (115). The Vanderbilt IDS will prepare over-encapsulated escitalopram and matching placebo and maintain the blinded assignment in case of emergencies. Participants will receive one tablet (10mg or placebo) for at least 2 weeks. If tolerated, it can be increased to a target dose of two tablets (20mg) daily at the two-week study contact, but dosing changes will not be made at week 6 or later. For problems with tolerability, the dose can be reduced to the previous level, but not below one tablet daily.

9.3. Transition: After 8 weeks subjects will be assessed for remission (MADRS ≤ 7). Those achieving remission will end their study participation. Those who are not remitted will have their Phase 1 drug tapered over a week to decrease the chance of discontinuation syndrome then progress to Phase 2.

9.4. Phase 2: Bupropion XL: We selected bupropion due to its distinct mechanism of action: a norepinephrine /dopamine reuptake inhibitor with no effect on serotonin (116,117). Bupropion is safe and effective in elderly populations (118-120). Subjects will receive open-label bupropion XL starting at 150mg daily. If tolerated, after 1-2 weeks it will be increased to 300mg daily. The dose may be further increased to the maximum of 450mg daily at week 4; this dose will be reduced if needed for tolerability. Subjects not tolerating the 300mg dose will be withdrawn.

Although bupropion is often used for augmentation (121-123) for Phase 2 we decided to use it as *monotherapy*. This is supported by STAR*D data (124) that found no clear preference for augmentation versus switch strategies (125). This will simplify interpretation of Aim 2 data.

Bupropion xl may be obtained through the Vanderbilt investigational pharmacy and provided to subjects. Alternatively, the study doctor will provide a prescription and they may obtain it through their regular pharmacy. In this case, they will be instructed to save their receipts so they can be reimbursed for their cost.

9.5. End of study medication procedures: For subjects who wish to continue on their end-of-study drug, we will provide prescriptions and assist with follow-up. If they do not wish to continue on study drug, we will make referrals and work with that provider to safely taper the study drug. See Human Subjects for more detail.

9.6. Concomitant treatment: To enhance generalizability, most nonpsychotropic medications will be permitted. Concomitant psychotherapy will not be allowed as it is an effective treatment that contributes to remission through different mechanisms. We allow short-acting hypnotics (eszopicione, zolpidem, or zaleplon) for sleep and lorazepam up to 2mg daily for anxiety. Hypnotics will be discouraged the day of cognitive testing.

9.7 Antidepressant Washout: If potential subjects are currently taking an antidepressant, they may need to come off that antidepressant in order to participate. In order to qualify to have the current antidepressant stopped, participants will need to have continued significant depressive symptomatology (MADRS >= 15) despite taking a therapeutic dose of their current antidepressant for at least 6 weeks. The therapeutic dose will be drug specific, but equivalent to fluoxetine 20mg (such as sertraline 50mg or escitalopram 10mg, for example). Individuals who responded to their antidepressant and do not have this level of depressive symptom severity will not be enrolled in the study and will not be tapered off their medication. The medication taper will occur over 1-3 weeks, dependent on the drug, dose, and duration. They will be assessed with weekly telephone visits during this period to monitor for depression worsening.

9.8. Source of Study Drug: The Vanderbilt Investigational Drug Service will provide study drug for both Phase 1 and Phase 2 for all participants aside from Veterans who receive care at the VA TVHS. Veterans will receive study drug from the VA TVHS Research Pharmacy. The Vanderbilt IDS will coordinate with the VA TVHS Research Pharmacy to assure accuracy in study drug assignment for Phase 1.

10.0 CLOSED - LONG-TERM FOLLOWUP (SUB-STUDY)

The long-term follow-up substudy is now closed. Depressed individuals who were randomized were asked to enter long-term follow-up over the next year. This included only minimal-risk interviews and questionnaires occurring 6-months and 12-months after study exit. This did not affect clinical treatment decisions over this period. The goal of this exploratory sub-study was to gather data on long-term rates of depression relapse. We examined whether neuroimaging measures obtained at baseline or clinical measures obtained throughout the study are related to subsequent rates of relapse over the one-year follow-up period.

10.1. Consent: We discussed this optional sub-study at their final study visit. Those who were agreeable were asked to sign a separate sub-study consent form.

10.2. Procedures: This only involved a telephone interview and completion of study questionnaires at 6- and 12-months after study completion. The telephone interview included an assessment of current medication use with the ATHF and depression severity using the MADRS. During the interview we worked to identify the duration of time they experienced clinically significant depressive symptoms over the interim, particularly for those individuals who remitted through the study but later experienced a relapse of depression. The telephone interview was followed by a completion of study questionnaires assessing depressive symptoms – these are listed in Section 7.1.d above.

10.3. Safety: For any participants who are depressed at either assessment, we assured that they were currently receiving treatment for their depression. If so, we encouraged them to let their physician know about their symptoms. If they were not, we provided referral recommendations, including a referral to the Vanderbilt Psychiatry Outpatient Clinics. As we make these referrals at the end of the main study, we did not anticipate that many individuals will be without treatment.

We also assessed for thoughts of death or suicide as part of measuring depression severity with the MADRS. A study physician then assessed the safety of anyone endorsing these thoughts and acted as was clinically indicated. This may have included feedback to the patient's treating psychiatrist or referrals to

intensive outpatient or inpatient hospitalization.

11.0. MRI PROCEDURES

11.1. Image Acquisition: We will image subjects on a 3T Philips Achieva system using a protocol that acquires: A) data to allow automated tissue identification; B) diffusion weighted data; and C) BOLD data at rest and during the emotional dot-probe task. The protocol will acquire T1-weighted (6min), fluid-attenuated inversion recovery (FLAIR; 9min), and diffusion-weighted images (9min). We will assess intrinsic FC (7.5 min, 7700 total frames) while participants focus on a fixated cross. Subjects will then complete the emotional dot-probe task (30 min; Sect. C.9.f). These sequences tally approximately 60 minutes; we budget for a 90-min MRI to allow for the longer time needed to position older adults and to allow a brief break between sequences if needed.

11.2 Functional MRI Task: The emotional pictures dot-probe task is a computerized spatially oriented attention task. The dot probe task contains images taken from the International Affective Picture System (IAPS)-including neutral, positive, and negatively valenced images- and was developed to measure attentional bias toward emotional information. In this task the subject is presented with pairs of pictures presented on the left and right of the screen. Following a picture pair presentation an asterisk appears on either the right or left of the screen. The subject is instructed to indicate the side of the screen on which the asterisk appears via button press, as quickly as possible. The time between when the probe appears and when the subject presses the corresponding key to its location is recorded in milliseconds and used for the calculation of facilitation indices. The primary score from the task is an attentional facilitation index that is calculated separately for the slides of different emotional valence. For the negative facilitation index, it is calculated using the following formula: Facilitation = 1/2 x [(Neutral Only/Probe Up – Negative Up/Probe Up) + (Neutral Only/Probe Down – Negative Down/Probe Down)]. Thus, this index is calculated by subtracting the participant's average response time to probes replacing negative stimuli from their average response time to probes replacing neutral stimuli in the various neutral-neutral picture pairings. This formula controls for potential location effects (participant's tendency to attend to either the right or left location of the screen) by summing latencies for left and right picture locations and taking their average. The facilitation index for positive emotion slides is calculated in the same way. If the spatial location of the probe corresponds to the same spatial location where the participant's attention is allocated then their response to the probes' location will be faster.

11.3. Image Processing: WML Segmentation: WML identification and measurement will be done using the Lesion Segmentation Toolbox (126), implemented through the VBM8 toolbox in SPM8. In native space, each voxel on the T1 image is assigned as gray matter, white matter, or CSF. After bias-correction the FLAIR is coregistered to the T1 image. The toolbox initially creates a conservative binary WML map based on outlier values across the T1 and FLAIR images. Next, a lesion-growth algorithm using Markov Random Fields modeling extends this conservative map to define the extent of the lesions. This lesion map can then be normalized into study-specific space and used to calculate total cerebral WML volume. This process takes approximately 4 hours from the time the images are acquired from the scanner.

11.4 Repeat MRI (SUBSTUDY)

As an optional procedure, we will ask randomized depressed participants to have a repeat MRI after completing Study Phase 1 (the 8-week blinded, placebo-controlled escitalopram phase). MRI procedures will be the same as in the baseline assessment. We will ask participants about participating during enrollment however they may change their mind at any point during study participation. This adds no additional risks to the project.

While the purpose of the overall study is to examine how imaging may serve as a predictor of antidepressant response, the overall Aim of the substudy is to examine how neural network connectivity changes during the course of the 8-week trial. We hypothesize we will observe differences between individuals who do and do not remit during Phase 1, wherein individuals who remit will exhibit post-treatment network connectivity similar to nondepressed elders. We will also examine whether there are differences in the interval change between individuals who remit on active drug and those who remit on placebo.

Data on never-depressed elders will be drawn from a separate study (IRB 130360, Frontal Hypoperfusion Effects on Antidepressant Outcomes in Late-Life Depression, PI: Taylor). We anticipate that results from this substudy will inform the application for this project's competitive renewal.

12.0. POTENTIAL RISKS

1. Interview, emergencies, and possible suicidal ideation. Subjects may experience discomfort during the clinical interview and evaluations when discussing symptoms, life events, and social support. The Project Coordinator will be experienced and skilled in interviewing depressed subjects. Should the subject wish to stop or take a break, the coordinator will allow it. A study doctor will be available as a backup. In addition, should the subject express suicidal ideation at any time during the interview, a study doctor will be contacted immediately to assess the subject and to determine the appropriate course of action. Thoughts of suicide will be taken very seriously. Options for addressing this may include contacting the individual's mental health caregiver, referring for urgent evaluation and treatment, or emergent evaluation and hospitalization. Similar practices will be used for other emergencies, including but not limited to psychosis, homicidal or violent thoughts, or an acute change in a subject's physical status.

2. Unblinding: It is possible that it may be crucial to definitively identify what study drug a participant is receiving to provide optimal care. We will only break the blind if knowledge of the study drug in Phase 1 (escitalopram or placebo) is necessary to provide optimal treatment in an emergency situation. If the emergency situation is an adverse event, this will be recorded and reported as such. Emergency unblinding will be conducted through the Vanderbilt Investigational Drug Service, who is providing study drug and blinding procedures. They have 24-hour access for emergency unblinding.

3. Antidepressant Side Effects: We will formally assess side effects at each planned contact and informally as needed through additional or unscheduled calls. We will attempt to minimize side effects by slow titration and allowance for dose reduction if needed. We will withdraw subjects from the study if they cannot tolerate the lowest dose of 10mg of escitalopram or placebo equivalent during phase 1 or 150mg of bupropion xl during phase 2.

   We describe below some of the more common or particularly concerning side effects. There is always the potential for the development of rare, unanticipated side effects. In general, we will carefully assess subjects with new complaints to determine if they may be related to study drug and if there is a need for closer monitoring or change in study drug dosing.

   a. Escitalopram common side effects: Although generally well tolerated, escitalopram does carry risk of side effects. These include: dermatological (rash), gastrointestinal (dry mouth, nausea, diarrhea, constipation), neurological (dizziness, vivid dreams), systemic (fatigue, somnolence or insomnia, appetite change, weight loss/gain, sweating), and sexual dysfunction.
   b. Bupropion common side effects: Likewise, bupropion is generally well tolerated. Common side effects include: dermatological (rash), gastrointestinal (nausea, diarrhea, constipation, dry mouth), neurological (dizziness, headache, tinnitus, tremor, vivid dreams), psychiatric (anxiety, agitation), or systemic (insomnia, appetite and/or weight loss, sweating). There are also rare risks of seizures or Stevens-Johnson syndrome, which we address through our entry criteria.

   c. Suicide risk: Antidepressant-induced suicidality is an important concern and one that has resulted in a black-box warning on antidepressants by the FDA. We will both inform subjects of this potential risk and monitor for suicidality at each contact. Should any possible suicidality be detected, a study doctor will assess that individual and act accordingly (see Item 1 above).
   d. Discontinuation Syndrome: Discontinuation syndrome, seen with abrupt cessation of antidepressant drugs, may cause a variety of neurological (dizziness, vertigo, insomnia, tremor, paresthesias), gastrointestinal (nausea, abdominal cramping), systemic (lethargy, flu-like symptoms) and psychiatric symptoms (irritability, anxiety, dysphoria). We will provide a medication taper for individuals who wish to stop escitalopram at the study's end.

4. Risk of Placebo: The primary concern with use of placebo is that individuals receiving placebo will fail to improve or worsen over the course of the placebo period. We minimize this risk by using a shorter study (8

weeks in contrast to 10 or 12 weeks) and use of withdrawal criteria, including worsening depression ("stopping rules" – see Section 12 below). We further minimize this risk by an unequal allocation of subjects in phase 1 to escitalopram or placebo in a 2:1 ratio. Such an approach is feasible as we are not testing for drug efficacy but examining neural predictors of remission, which we hypothesize would differ between escitalopram and placebo.

5. Antidepressant Medications: End of Study Procedures: During the course of the study we will work with study subjects to identify providers who will continue their care at the end of the study. For those subjects who wish to continue on their end-of-study drug, we will provide prescriptions, two free visits, and assist with arranging follow-up clinic visits with their provider. If they do not wish to continue on study drug, we will also refer to clinical providers, but also work to slowly discontinue the study drug to avoid discontinuation effects.

6. Magnetic Resonance Imaging. Although this procedure is generally low-risk, there are particular concerns. Individuals will be screened for the presence of implanted metal (including but not limited to medical devices, shrapnel, tattoos or permanent makeup); those who screen positive will be excluded from the study. Claustrophobia is also an issue for many potential subjects. During the MRI, subjects will have voice contact with a radiology technician, and may request the scan be stopped at any time.

7. Incidental Findings: Magnetic Resonance Imaging: Another risk is the occurrence of incidental findings on MRI. All scans are reviewed at time of acquisition and concerning findings are discussed with an attending neuroradiologist. Should any concerning findings be seen, a study doctor will convey these findings to the subject along with recommendations for further evaluation, and facilitate referrals for such evaluation and treatment.

8. Breach of confidentiality: There is the potential risk of breach of confidentiality of clinical, genetic, and laboratory information. The PI, Dr. Taylor, has extensive experience as a clinical investigator dealing with such sensitive information, and as a previous member of an Institutional Review Board has experience assuring that data is adequately protected. Safeguards to protect confidentiality include locked records and firewalls around password-protected electronic data, and all study data being coded, with the key linking the code with a subject's identity being kept in a separate, locked file.

13.0. ADVERSE EVENT REPORTING:

We define an adverse event as any adverse change in health or development of a side effect occurring in a study participant after enrollment. These may be expected events (known drug effects, as detailed in the consent form, safety monitoring plan, or package insert) or unexpected events. We define a serious adverse event as any event that results in hospitalization, disability or permanent damage, is life threatening, results in death, or any other serious event that does not fit these outcomes, but require urgent medical intervention.

We will carefully monitor adverse events throughout the study. Subjects will be assessed for safety, medication tolerability, and unanticipated problems at each contact. Emergency contact information will be

provided to each subject for urgent, unanticipated problems. All adverse events will be reviewed by Dr. Taylor at least weekly. All AEs, regardless of being judged as related or non-related, will be summarized and included in the annual IRB continuing review. All SAEs will be reported to the Vanderbilt IRB and VA TVHS IRB within 7 working days. Dr. Taylor will have responsibility for this reporting requirement. Additionally, working in collaboration with the IRB, he will assure that reportable adverse events are also reported to NIH.

As this study will use FDA approved antidepressant medications, is not a multi-site clinical trial, and is not a Phase III clinical trial, we will not establish a formal DSMB for this study. As Phase 1 is placebo-controlled and blinded, we did consider initiation of a DSMB but in conjunction with NIH program officers ultimately decided it was not necessary due to the long history of experience with escitalopram, its overall tolerability, and excellent safety profile. Per NIH request, prior to initiating enrollment we have named Dr. Ronald Cowan as the independent safety monitor. He will review all safety events in a blinded format every 6 months while subjects

are participating in the study. If, after reviewing the blinded data, he is concerned about adverse event rates, he may request unblinded data. In addition to other reporting requirements, he will also review any serious adverse events (SAEs) within 7 days. Dr. Cowan's conclusions after each data review will be provided to the Vanderbilt IRB and VA TVHS IRB with each continuing review.

14.0. STUDY WITHDRAW / DISCONTINUATION

Participants may withdraw from the study at any time. If participants leave the study early, we will recommend a medication taper and clinical referrals for further care.

A participant will be withdrawn from the study if:

1) The participant withdraws his or her consent
2) The PI considers it is in the best interest of the patient for him or her to stop study participation
3) In the PI's judgment, the participant's depressive symptoms have worsened significantly since study drug initiation
4) The patient develops suicidal ideation where he or she should be referred for regular clinical care for safety
5) The patient is lost to follow-up

If a participant develops worsening depression (but not suicidality) or intolerable adverse events during blinded Phase 1, the subject does not have to be withdrawn but can instead proceed to open-label Phase 2. Otherwise, participants will be referred for clinical treatment. We will offer two free visits when they finish the study and will discuss further treatment options.

15.0 STATISTICAL CONSIDERATIONS

For **Aim 1**, inter-correlation matrices and scatter plots will be used to assess and visualize the patterns of association among the tract WML values and respective fMRI connectivity values. Multivariate analysis will be conducted using canonical correlation. Canonical correlation can accommodate more than one variable on both the independent and dependent sides of the general linear modeling equation and those variables may be either metric or nonmetric. In canonical analysis, the solution depends both on correlations among the variables in each set and on correlations among variables between sets. In a simultaneous process, underlying canonical variates (or factor loadings) comprising the WML values on the independent side will be constructed in such a way to maximize the correlations with canonical variates of the fMRI values on the dependent side. The same assumptions as those underlying multiple linear regression apply. Evaluations of normality, linearity, and homoscedasticity will be conducted, as will tests of multicollinearity and singularity of the underlying correlation matrices. Simple bivariate correlations and scatterplots will assist with describing and visually the patterns of association, canonical correlation will control for the inter-correlations among the WML and fMRI values will maximizing the correlation between the two sets. Covariates of *age, sex, and vascular risk* will be included with the WML measures. Effects of *MADRS and total brain WML volume* will also be examined. We will use a similar approach to examine how WML values are associated with clinical presentation. For Hypothesis 1, attention, memory, and processing speed scores will be on the dependent side. For Hyp. 2, BRISC and baseline MADRS scores will be on the dependent side.

For the fMRI emotional dot-probe task, we will examine how WMLs are associated with ROI activation(Exploratory Hyp). Specifically, we will examine how CB measures are associated with activity in DMN and CCN regions during the task's attentional component and how UF measures are associated with amygdala activity during the affective component. In this analysis WML measures will be on the "independent" side of the canonical correlation while fMRI activation values will be "dependent" side.

We will use a similar approach for Exploratory Aim 1, where we examine how cognitive test performance may serve as a marker of WML tract damage. Including the previous covariates plus education, cognitive test results will be on the independent side with tract WML values on the dependent side.

Data from nondepressed elders will be integrated into the above analyses. We will test for group differences in the neuroimaging and cognitive measures described above. We will also include a group variable (depressed or not depressed) in analyses.

Aim 2 examines how tract measures predict remission. Following our previous approach (21), our definition of remission is MADRS ≤ 7. Secondarily, we will examine drug response (50% improvement on MADRS). Remission / response status for subjects with missing data will be estimated via multiple imputation

method assuming that dropouts are missing at random.

We will use two regression models to test for mediation while adjusting for baseline MADRS, age, sex, and vascular risk. To assess indirect effects of tract WML and FC measures as mediator variables, we will regress a potential mediator on a tract-based measure (an explanatory variable of interest). We will fit another model in which antidepressant remission or nonremission serves as outcome variable, and the potential mediator and tract-derived measure serve as covariates. The second model can be either logistic or linear regression model depending on the nature of outcome. The product of two beta coefficients corresponding to the tract-based measure in the first model and to the mediation variable in the second model will be assessed by constructing bootstrapped 95% confidence intervals (CI); statistically significant difference from zero implies that the relationship between the outcome and explanatory variable is mediated by the variable in question (127,128).

This approach will slightly differ for each study phase. For Phase 1, models will include drug arm (placebo or escitalopram). To examine for differences in how tract impairment affects remission in each arm, we will test for interactions between drug assignment and tract integrity (WML & FC). We will explore significant interactions in individual models. For subjects entering Phase 2, we will test for differences in tract integrity (WML & FC) between those originally assigned to escitalopram and placebo. If differences are observed, in models we will control for original Phase 1 cohort assignment. In exploratory models, we will use similar approaches to test for the additional effect of cognitive domain function (Table 5) on remission. We will also use this approach for Exploratory Aim 2 when we examine the effect of connectivity deficits in other tracts.

Importantly, the relationship between connectivity and antidepressant response may not be linear. It is possible that a 'threshold' must be crossed in order for tract connectivity deficits to influence response (3). To properly take into account nonlinear effect of a continuous predictor variable (e.g., WML, FC) on response variable (e.g., remission or nonremission) in the models, we will employ restricted cubic splines of the predictor. Statistical significance of the nonlinear terms via F-test implies that the relationship between the two measures of interest can be nonlinear.

15.1. Sample Size and Statistical Power:

Aim 1: From our published report (129) correlations of the FC of the PFC with the amygdala and the hippocampus were in the range of 0.52 to 0.55. A sample of 130 subjects, will have > 90% statistical power for associations >= 0.30 (two-tailed alpha = 0.05). However, our primary approach to the analysis of Aim 1 will use canonical correlation with no known powering algorithms; sample size and effect estimates are used to guide the appropriateness. Using the multiple regression approach (single dependent) as a conservative estimate, a sample size of 130 achieves 83% statistical power to detect an R^2 as small as 0.06 (standardized beta = 0.20, 6% shared variance) attributed to the association of WML with a significance level (alpha) of 0.05 after adjusting for other proposed covariates. These calculations assume that the variables for which we are adjusting have an R^2 of 0.10 (10%) (130). We suspect that the control variables will have a higher inter-correlation value, thus increasing our power for testing the effect of a single variable.

Table 2. Aim 2 Power Estimates

Region	Low WML	High WML	Power ($\alpha = 0.05$)
Baseline MADRS			
• UF, R	21.0 (12.2)	29.5 (3.0)	0.98
• ATR, R	17.4 (8.6)	29.7 (9.0)	1.00
3-Month MADRS			
• Ant. CB, L	8.8 (7.0)	14.8 (5.8)	0.99
• Post. CB, R	7.7 (7.6)	14.6 (7.8)	0.99
• Post. CB, L	5.2 (2.9)	16.0 (7.6)	1.00

Aim 2: The study includes a placebo arm to identify effects specific to an active depressant while having a comparable number of subjects receiving each active drug. Powering the study for Phase 1, Table 2 presents estimates for our proposed sample size using unadjusted effects of low vs. high WML values on the respective outcomes of interest found in our preliminary data. The logistic regression approach allows for the testing of effects adjusted for known covariates. Using this approach, assuming a base non-remittance rate of 0.36 (36%), a sample size of 130 will enable us to detect a log hazard ratio as small as 0.45 for a specific measure. We conservatively included an assumption that covariates would account to up to 10% share of the effect on nonremission. If that value is less, our statistical power will increase for the same hazard ratio. Using high vs. low tract WML volume as an example, after controlling for other effects, our sample will enable us to detect an effect on the likelihood of non-remittance of at least 25% (high WML vs. low WML, 0.45 / 0.36 = 1.25 or 25% increase). Continuous as well as nonlinear operationalization of effects will be examined.

16.0 PRIVACY AND CONFIDENTIALITY

Confidentiality Procedures: As the PI, Dr. Taylor will assure all procedures protecting study data designed to guard subject confidentiality conform to the Vanderbilt Human Research Protection Program requirements. Additionally, the Vanderbilt IRB must approve all procedures and safety precautions before the study can begin. All non-electronic data (clinical evaluations, paper assessments) will be stored securely in locked offices or laboratories accessible only by study staff. All electronic data will be stored in secured servers with limited access. RedCAP will be used for data management.

Further, all information that could potentially directly identify a subject is removed from all study data. This includes MRI data, electronic and paper assessments. Direct identifiers will be replaced with a unique four-digit code. The key to linking the code to subject identity will be kept separately from study data, in a locked file in password-protected computer in Dr. Taylor's office. Only study staff involved in clinical recruitment and assessment will have access to individually identifiable private information. All other study staff, including image analysts, will be blinded to subject identity and will only have access to the coded identifier.

Privacy Procedures: Informed consent and all study procedures will occur in private research offices and private research examination rooms.

17.0 FOLLOW-UP AND RECORDS RETENTION:

Study records will be maintained for at least six years after the study is closed with the IRB. After that time, study data may be destroyed or anonymized, meaning all links to direct identifiers will be destroyed. Any study data in the medical record will be kept indefinitely.

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