White Matter and Emotional and Cognitive Control in Late-Onset Depression

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OVERVIEW & RESEARCH QUESTION

The primary aim of this project is to use sub-clinical, non-contrast functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) in LOD to examine whether dysfunction of the emotional and cognitive control systems are mechanisms by which aging-related structural and functional abnormalities contribute to the development of LOD and to the persistence of its symptoms.

For our primary hypotheses we will focus on the role of microstructural white matter abnormalities and activation of control structures in the development of LOD.

For our secondary hypotheses, we will focus on the role of microstructural abnormalities, activation of control structures and the persistence of LOD despite treatment with a FDA-approved SSRI antidepressant medication (escitalopram). In addition, we will examine the role of microstructural abnormalities, and activation of reward systems in the presence and persistence of LOD despite treatment with escitalopram.

The aims will be pursued in 70 normal and 70 older adults with LOD. The LOD group will undergo a one-week psychotropic washout phase during which they will complete an MRI session that includes fMRI and diffusion tensor imaging. LOD patients will then receive 12 weeks of escitalopram treatment at the target daily dose of 20 mg.

In addition to testing our hypotheses, the study enables exploratory analyses of the:

1) Role of white matter integrity in the development and persistence of LOD;
2) Relationships of control network and reward system activation after 12 weeks of SSRI

treatment to baseline activation and white matter integrity and persistence of depression at 12 weeks.

We expect this MRI study of LOD to offer novel information about the neural circuitry mechanisms of depression. In addition, the identification of structural and functional impairments of LOD can aid the development of clinical instruments and targeted interventions.

EXPERIMENTAL DESIGN

Participants

The subjects will be divided into two groups each with 70 participants:

- Older adults (aged 60-85 years) with late-onset (>60 years), unipolar, non-psychotic, major depression and without cognitive impairment;
- Normal controls (aged 60-85 years) without psychiatric illness and without cognitive impairment.

We anticipate that approximately 15% of depressed patients will improve and fail to meet the depression severity eligibility criterion after the washout phase and approximately 12% of subjects will have unusable fMRI scans (e.g., excessive motion, claustrophobia, clinically significant abnormalities on MRI). Thus, we anticipate the need to recruit 94 patients and 80 controls to meet our requirements.

Medication: Depressed Subjects

This section pertains only to subjects with depression. Depressed patients will undergo a psychotropic washout phase of one week duration (at the end of which they will have an MRI) followed by 12 weeks of escitalopram treatment at the target daily dose of 20 mg. The washout phase is intended to reduce the impact of prior treatment on brain activation. While a longer psychotropic-free period may be advantageous, concerns about worsening of depression made us limit the washout phase. (Patients on fluoxetine and MAOIs will be excluded from the study because they would require a longer drug-free period.)

Subjects will only be asked to discontinue psychiatric medications (e.g. antidepressants, select sleep agents, and anxiolytics. See exclusion criteria for full description) after it has been ascertained that, in spite of the medication, the subject still has significant depressive symptoms of at least moderate severity, i.e. they meet the diagnostic criteria for a current episode of MDD and are suffering at least a moderate level of depressive symptoms (24-HDRS score > 19). Under the supervision of the study psychiatrist, subjects will be asked to gradually withdraw other psychotropic medications. (Zolpidem for insomnia will be permitted; see exclusion criteria for full description).

In most cases, the washout phase will last one week (7 days). If subjects continue to meet depression severity criteria at the end of this one week period, they will be started on medication.

The washout phase may extend beyond 7 days for the following reasons:

1. If the study psychiatrists believe that it is clinically indicated to lengthen the washout period in order to reduce side effects of removing psychotropic medications. The maximum washout period will be two weeks.
2. On rare occasions when subjects miss their scheduled appointment (due to bad weather, illness, etc.) during which they will begin active medication, every effort will be

made to reschedule this study visit within two-three days, thus extending the washout phase until they come in for the visit;

3. The washout phase may extend beyond 7 days if a subject no longer meets the depression severity cut-off for study inclusion, and the study physician judges that such improvement is transient and based on instability of symptoms during the washout phase, or that symptoms are not covered by the HDRS and are likely to return, the study physician may extend the washout for a maximum of seven additional days. If after that extension the subject meets criteria s/he will be entered into the 12-week active treatment phase of the study. If the subject no longer meets entry criteria the study physician will discuss the subject's symptom improvement and will refer him/her for further evaluation or treatment as clinically indicated.

In some instances the washout phase may be less than one week. The one-week washout phase may be truncated or eliminated if, in the opinion of the study physician and PI, the patient's symptom severity is such that they would not be able to tolerate the full washout phase.

The SSRI escitalopram was selected because it combines an easy to achieve therapeutic dosage with limited drug-drug interactions, safety in overdose, few CNS activation side effects (e.g., restlessness, insomnia, tremor) and a mild withdrawal syndrome. Our research Institute has studied this drug in over 220 depressed elders. Thus, data will be available for secondary analyses of response characteristics. We target 20 mg daily to avoid under-treatment.

Following the drug washout, escitalopram will be started at 10 mg each morning, increased to 15 mg in 1 week, and to 20 mg 1 week later. As its average elimination half-life is 32 hours, steady state kinetics are expected to be achieved before each dose increment so that dose-dependent side effects can be adequately assessed before a higher dose is given. In subjects unable to tolerate 20 mg escitalopram, the dosage will be reduced to 15 or 10 mg. However, subjects unable to tolerate 10 mg/day will be excluded from this protocol, as lower dosages may be of limited efficacy. Based on the Institute's experience, we expect to terminate less than 10% of subjects from the study because of intolerance of escitalopram. In all such cases, Institute clinicians will provide treatment until a referral for community based care can be established.

Depressed subjects will be seen by a study psychiatrist on week 0, 1, 2, 3, 4, 5, 7, 9, 11, 13 and given a 12-week course of treatment with escitalopram. During their visits (15-20 minutes), subjects will meet with a research psychiatrist, who will follow a medication management format (review psychiatric symptoms, medical state, side effects, suicidal ideation, and adherence to treatment). To reduce burden, psychiatrist visits will be scheduled immediately after research assessment sessions, so that information obtained by the research assistant can be shared with the psychiatrist. The "comprehensive assessment" will be completed before termination.

At the completion of the treatment phase of the research study subjects will be referred for continued treatment, if needed, to our clinical services or to a qualified clinician of the subject's choice. If the treating research-study psychiatrist determines it is indicated that a subject remain on escitalopram at termination, we will provide up to 4-weeks of escitalopram, at the study MD's discretion, at no cost to the subject to assist in transitioning to treatment outside of the research study.

Medical Evaluations & Research Assessments: Depressed Subjects

The objective of the initial research assessment is to screen for study eligibility by establishing a diagnosis, gathering basic demographic data and screening for the presence of any significant past or present psychiatric disorders, acute or severe medical problems, or cognitive limitations. Subjects will undergo a physical and neurological examination at our clinic. The examination will be performed and recorded by study psychiatrists. With the subject's consent, the study MD will request results from recent blood tests (SMAC, CBC, TSH). If such test from the previous three months, or more recently in some cases based on clinical judgment of the study MD, the subject will be asked to obtain the tests, either in our laboratory or at their own doctor's office. Patients will be responsible for charges not covered by their insurance for these tests.

Research Assistants (RAs) will administer all study questionnaires in order to minimize misunderstanding and incomplete ratings. All RAs have a minimum of an undergraduate degree and are trained by staff psychologists or psychiatrists proficient in the use of the study instruments. Training involves didactics, reading and discussion of measure administration manuals and study procedure manuals, observation of in-person subject interviews, and credentialing after conduct of in-person subject interviews with a supervisor. Ongoing inter-rater reliability auditing will monitor instrument administration.

Three comprehensive assessments will be conducted at Baseline, week 7, and week 13. Additional brief assessments will be performed at weeks 0, 2, 3, 4, 5, 9 and 11 of treatment principally for monitoring depressive symptoms and antidepressant side effects and adherence. Subjects who exit the study prior to completion, will be invited to have a "comprehensive assessment" before termination.

Study Schedule: Depressed Subjects

-	Week 0	Week 1*	Week 2	Week 3	Week 4	Week 5	Week 7	Week 9	Week 11	Week 13
Entry	~~X~~									
MD Visit	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~
Study Drug		**<---------- Medication ----------**								**>**
Brief Assessment	~~X~~		~~X~~	~~X~~	~~X~~	~~X~~		~~X~~	~~X~~	
Long Assessment		~~X~~					~~X~~			~~X~~
MRI		~~X~~								**Optional**

***Note:** Week 1 is the medication start-date, and is considered the primary baseline assessment. .

Baseline Comprehensive Assessment (~3 hours):

- ***Demographic data (5 min):*** Data on age, gender, race, religion, living conditions, marital status, occupation, and education will be collected.
- ***Medical Evaluation (30 min):*** Physical examination will be performed by psychiatrists. Blood tests (SMAC, CBC, TSH) and ECG will be obtained. A psychiatrist will quantify medical burden with the Cumulative Illness Rating Scale, modified for geriatrics (CIRS-G). Additionally, a research assistant will administer the Charlson Comorbidity Index (CCI) (Charlson et al., 1987). Information obtained from the CCI will be used to quantify medical co-morbidity. This approach reduces patient burden and bias towards illness under-reporting.
- ***Diagnosis (~60 min):*** A study psychiatrist will interview each subject. In addition, the SCID-R, as rated by a trained research assistant, will be used for diagnosis. DSM-IV

diagnoses will be assigned during the research team's daily morning meeting by consensus of two geriatric psychiatrists after reviewing the SCID-R and Baseline Assessment data and examining the psychiatrist's report.

- ***History of Treatment (15 min):*** Patients with any exposure to citalopram or escitalopram during the current depressive episode will be excluded because retrospective assessment of treatment adequacy, adherence, tolerability, and response is difficult. This decision intends to protect our subjects who have been exposed to a potentially ineffective or not tolerated treatment. We will record the dosage and duration of treatment with each psychotropic used during the index episode, and in subjects with recurrent depression, during the last inter-episode interval. We will classify the intensity of antidepressant treatment according to the criteria of the Longitudinal Interval Follow-Up Evaluation. We will also use the Treatment Intensity Index modified by the Institute of Geriatric Psychiatry for depressed elderly patients. Thus we will be able to study the impact of prior psychotropic use on control systems.
- ***Substance Abuse (5 min.):*** The CAGE questionnaire will be administered to screen for alcohol dependence, and records will be reviewed for tranquilizer and analgesic use. Subjects with addiction disorders by SCID-R/DSM-IV will be excluded.
- ***Severity of Depression (15 min.):*** We will use the Montgomery Asberg Depression Rating Scale (MADRS) as the primary depression outcome because it is influenced little by physical symptoms and is sensitive to change. We will use the Scale of Suicidal Ideation (SSI) and a suicidality severity subscale (GRIM) to assess suicide risk.
- ***Side Effects (5 min):*** We will use the UKU, which includes SSRI side effects.
- ***Functional Status (20 min):*** The World Health Organization Assessment Schedule II (WHODAS II), 36-item will be used. This instrument is compatible with the international classification system, is cross-culturally applicable, and has high test-retest reliability. The ADL and IADL scales (~5 min) of the Philadelphia Multiphasic Assessment Inventory (Lawton, Moss et al. 1982) will be used as most of our disability studies were based on this instrument.
- ***Clinical Features of Depression (15 min):*** In order to explore how brain activity and white matter integrity are related to clinical features of the illness we will administer a brief battery of self-report measures. **Anhedonia:** We will use the Snaith-Hamilton Pleasure Scale (SHAPS), a brief measure of hedonic capacity and anhedonia. Anhedonic symptoms, as measured by the SHAPS, are associated with activation in frontolimbic circuitry in major depression[108]. **Apathy:** We will use the Apathy Evaluation Scale (AES). **Anxiety:** We will use the Clinical Anxiety Scale (CAS)[111], which is derived from the Hamilton Anxiety Scale. **Rumination:** We will use the Response Style Questionnaire (RSQ)(Nolen-Hoeksema et al.) to measure rumination. This scale yields two subscales, brooding and pondering. Behavior Disturbances: We will use the Frontal Systems Behavior Scale (FrSBe) (Stout et al. 2003) to assess behavior disturbances associated with damage to the frontal-subcortical brain circuits. Negativity Bias: We will use the Brain Resource Inventory of Social Cognition (BRISC), a self-report measure that assesses the attributional bias toward perceiving and expecting negative events and outcomes, to examine negativity bias.

1. ***Clinical Neuropsychological Battery (75 min.):*** This battery is not comprehensive as it was designed to minimize burden while enabling us to generate hypotheses about control networks and cognitive functions. The Wechsler Test of Adult Reading (WTAR) will be used to estimate an individual's level of intellectual functioning before the onset of injury or illness (in our case, major depression). *Overall cognitive dysfunction*: Mattis Dementia Rating Scale (DRS). Simple auditory *attention* will be evaluated with the

Digits Forward portion of the Digit Span from the Wechsler Adult Intelligence Test (WAIS-IV). *Working memory* will be evaluated with Digits Backward from the WAIS-IV. *Verbal memory* will be evaluated with the Hopkins Verbal Learning Test -Revised, which has alternative forms and norms for geriatric patients. *Processing speed* will be assessed with the Stroop Word and Trails A. Language functions will be assessed with the Controlled Oral Word Association test (COWAT). The Controlled Oral Word Association Test (COWAT) evaluates the spontaneous production of words under restricted search conditions (verbal association and fluency). *Executive functions* will be assessed with the Stroop Color/Word, Iowa Gambling Task, Wisconsin Card Sort (WCST) and Trails B. We will explore the relationship of control networks to executive functions and use attention/working memory, verbal memory, and processing speed to examine specificity. The **Trait Task is a computerized** task involves the presentation of normed (positive and negative) trait descriptors on the computer screen one at a time. The subjects are instructed to as quickly as possible select a response that indicates whether or not each descriptor describes themselves. The endorsement of more negative words as being self- descriptive may reflect a "negativity bias" and is expected to be associated with poorer antidepressant response.

When MCI is suspected we will use an expanded test battery during screening.

- ***Social Support (5 min.):*** Among the various existing social support measures, the Duke Social Support Index was selected because major depression is associated with low subjective social support in elderly medical patients (Krishnan, Hays et al. 1997). The Index yields scores on 5 categories: subjective social support, social interaction, instrumental social support, social networks, and satisfaction with relationships.

Brief Follow-up Assessments (60 min; weeks: 0, 2, 3, 4, 5, 9, 11):
The purpose of these assessments is to evaluate the severity of depression, functional status, the presence of side effects, adherence to escitalopram, and pulse and blood pressure. We will rely on both patient and caregiver reports, pill counts, and plasma levels, as each offers varying degrees of reliability. The HDRS, MDRS, GDS, along with UKU items related to SSRI side effects, a fall questionnaire, and the 12-item WHODAS II, (described above, in Comprehensive Assessment) will be administered. At each visit, changes in medical condition, and the use of all non-study medications (prescription, over the counter, and alternative), will be recorded on a rating form.

We will provide logs so that patients and caregivers can record daily medication use. We will draw blood on week 7 and 13 and escitalopram plasma levels will be assayed. Nonlinear-mixed effects modeling will be used to determine concentration ranges consistent with acceptable adherence. Subjects with acceptable drug logs and pill counts but plasma concentrations

outside the range associated with adherence will be re-interviewed and excluded from the main analyses if non-adherence is established.

Comprehensive Follow-up Assessments (week 7: ~1.5 hr and week 13: ~2.5 hrs):
The purpose of these assessments is to provide information on the outcomes of interest after a month and a half of treatment (at Week 7 when patients are expected to show signs of improvement) and at the end of the study. The instruments used in the Baseline Comprehensive Assessment will be used to assess: depression severity, suicidal ideation, adherence to escitalopram, side effects, and functional status. To minimize practice effects, cognitive tests will not be performed at the Week 7 assessment. Subjects exiting early will be invited to have a comprehensive assessment at exit.

Please note that all study measure are validated and published. We will seek IRB approval before use of any new, co-investigator developed measures.

Medical Evaluations & Research Assessments: Control Subjects

As with depressed subjects, the objective of the initial research assessment for control subjects is to screen for study eligibility by establishing a diagnosis, gathering basic demographic data and screening for the presence of any significant past or present psychiatric disorders, acute or severe medical problems, or cognitive limitations. A neuropsychologist will supervise the interview. After the clinical and cognitive screening, it may be determined that the subject is ineligible for participation. If this occurs, the study neuropsychologist will inform the subject of his/her exclusion and provide a referral for follow-up care if indicated.

Study Schedule: Control Subjects

-	Week 0	Week 1*	Week 2	Week 3	Week 4	Week 5	Week 7	Week 8	Week 11	Week 13
Entry	~~X~~									
Ph.D. Visit	~~X~~									
Study Drug										
Brief Assessment										
Long Assessment		~~X~~					~~X~~			~~X~~
MRI		~~X~~								**Optional**

***Note:** For controls, Week 1 is considered the primary baseline assessment.

Control subjects who are eligible for participation after the baseline visit will be asked to return for two additional follow-up assessments at 7 weeks and then again 13 weeks after the baseline visit. These two follow-up visits are intended to collect clinical and cognitive follow-up data, and will be compared to LOD subject data after a month and a half of medication treatment (when the LOD subjects are expected to show signs of improvement), and at the end of the study. In order to minimize practice effects, the neuropsychological assessments will be performed at the baseline and week 13 assessment only. The week 7 assessment should last approximately 1.5 hours while the week 13 assessment will last approximately 2.5 hours. We will not draw blood from Control subjects as part of this protocol.

MRI Scanning Sessions

Overview: Sub-clinical, non-contrast fMRI will be performed at the Nathan Kline Institute (NKI) in Orangeburg, NY at the end of the placebo phase for depressed subjects or after enrollment for

non-depressed controls. Each trip to the NKI will last approximately 2.5 hours which includes consent, preparation for the scan, a brief practice session, and the scan itself. The MRI is limited to a scan of the head. The scanning procedure itself lasts approximately 60 to 90 minutes during which time the subject's head and upper body will be immobile and rest in the scanning apparatus. Travel arrangements will be made by the Cornell research team and, when needed, the subjects will be escorted to NKI by a research assistant and/or the study PI.

MRI Acquisition: MRI will be performed at the Center of Advanced Brain Imaging (CABI) at NKI. Scanning will be done on a 3T Siemens Tim Trio (Erlangen, Germany) housed at the CABI of NKI. First, a sagittal localizer will be used to orient the 3D volume scan. A FLAIR sequence will be acquired to quantify WMH and to screen for structural abnormalities. High resolution images will be acquired using a 3D T1-weighted rapid gradient echo for co-registration with the fMRI and DTI. Prior to fMRI acquisition, the operator will electronically shim the field to minimize inhomogeneities. BOLD images will be acquired in a single-shot multi-slice EPI with a TR of 2000, a TE of 30 ms, and flip-angle of 80 degrees. Each of the volumes will consist of 34 slices, which allows for whole brain coverage. Each of 4 BOLD acquisitions runs (2 Cognitive/Emotional Conflict runs and 3 Probabilistic Reversal Learning runs) will last 7 minutes. A field-mapping scan will be acquired that consists of 34 slices to be used for examination/correction for susceptibility induced geometric distortions in our EPI data. Diffusion tensor scans will be acquired in an axial plane parallel to the AC-PC plane with a pulsed gradient, double spin echo EPI method. Diffusion will be measured along 64 noncollinear directions. A field map will be acquired to match the parameters of the DTI and will be used to correct susceptibility induced distortions using FSL's Prelude and Fugue programs.

MRI Tasks: Subjects will practice each task outside of the scanner. Head motion will be minimized using the Siemens head-holder. Visual stimuli will be presented via a back-projection zoom to a LCD screen mounted at the rear of the bore. Responses to tasks will be collected using a 2-button response pad. Participants' vision will be corrected by non-magnetic glasses.

Each subject will participate in two sets of MRI tasks:

- During the Emotional/Cognitive Control Task, face stimuli are paired with the superimposed words "HAPPY" or "SAD" to produce emotionally congruent and incongruent stimuli, and subjects are instructed to categorize the facial expressions as happy or sad while ignoring task-irrelevant word stimuli (e.g. Word "HAPPY" on a sad face).
- During the Probabilistic Reversal Learning Task, subjects will choose between two colored triangles and receive feedback on their choices. They will be instructed to choose the color that is correct the majority of the time, to stick with it even when it is occasionally wrong, and to only switch to the other color when they are sure that the rule has changed.

Responses consist of manual button presses on a key pad using the middle and the index finger of the right hand. The order of tasks is counterbalanced across subjects. For the Emotional/Cognitive Control Task, subjects are instructed to respond to each face as quickly and accurately as possible. The Emotional/Cognitive Control Tasks is presented in an event-related design. Each trial consists of a face on a black background, depicting either a happy or a sad face (10 male, 10 female). The Emotional/Cognitive Control Task consists of two runs of 80 trials. Stimuli are presented for 1250 ms, with a varying interstimulus interval (ISI) of 2750 – 4750 ms (mean ISI = 3750 ms), during which a white central fixation cross is displayed. Stimuli are counterbalanced, with equal numbers of congruent–congruent, congruent–incongruent, incongruent–congruent, and incongruent–incongruent stimulus sequences. Gender and facial

expression are counterbalanced across responses and trials. For the Probabilistic Reversal Learning Task, each trial consists of a blue and a yellow triangle against a black background. Subjects are instructed to choose the “correct” color and given positive feedback in the form of a green smiley face when they are correct, and given negative feedback in the form a red sad face when they are incorrect. Twelve times per block, the “correct” color reverses. The number of trials between reversals varies between 8 and 15 (mean reversals = 12). Stimuli are presented for a maximum of 2500ms. The feedback is presented for 500ms, and the ISI is 3000ms.

Sub-clinical Examination: The MRI scan that is part of this research study is not a clinical MRI examination and is not intended to provide any benefit to study participants in diagnosing brain abnormalities.

Since NKI is conducting all of this study’s MRI scans, we will follow NKI over-read policy on sub-clinical research scans. A radiologist will review all of the MRIs performed at Nathan Kline Institute. If the radiologist detects an abnormality, it is then the responsibility of the Principal Investigator (PI) to directly contact the research participant and provide appropriately sensitive notification of a possible clinically significant finding and to recommend that the patient follow up with their private physician. Under the patient confidentiality guidelines, no personal information will be given to the specialist. If the specialist recommends a follow-up, he/she will contact the Principal Investigator identifying the subject by using the unique, study-assigned ID. The study PI or designate will then contact the research participant. The initial contact may be verbal (telephone or in-person) followed by a notification letter describing the nature of the finding and the kind of follow-up that is recommended. If requested, a copy of the images (on a CD) can be mailed to the participant or picked up in-person. The decision as to whether to proceed with further examination lies with the participant.

Transfer of MRI Scanning Results: After the NKI technician completes the MRI scan, he/she will burn the reading onto a CD identified with the subject’s unique study ID number. The CD will not have any other identifying information. The study co-investigator who is present during the scan will bring the CD back to our research institute in White Plains and place it in a locked file cabinet in the PI’s locked office. For analysis, data from the reading will be uploaded to our ITS-maintained secure, password protected server with access available only to study co-investigators.