Protocol Title:
Dopaminergic Dysfunction in Late-Life Depression (The D3 Study)

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Cover Sheet

Choose ONE option from the following that is applicable to your study
If you are creating a new protocol, select "I am submitting a new protocol." As 5 Year Renewals are no longer required, this option remains for historical purposes.
I am submitting a new protocol

Division & Personnel

Division

What Area Group does the PI belong to?
What Division/Department does the PI belong to?
Neurobiology and Therapeutics of Aging Division
Within the division/department, what Center or group are you affiliated with, if any?
N/A

Unaffiliated Personnel

List investigators, if any, who will be participating in this protocol but are not affiliated with New York State Psychiatric Institute or Columbia University. Provide: Full Name, Degrees and Affiliation.

Jennifer Felger, PhD
Emory University School of Medicine

Procedures

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

✓ Psychiatric Assessment
✓ Neuropsychological Evaluation
✓ Collection of Biological Specimens
✓ Medication Trial
✓ Use of Placebo or Sham Treatment
✓ PET/SPECT Scan
✓ MRI
✓ Use of Investigational Drug or Device
✓ Off-label Use of Drug or Device

Population

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

✓ Medically and Psychiatrically Healthy Subjects
✓ Adults over 50

Research Support/Funding

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

Funding Source #1

Is the PI of the grant/contract the same as the PI of the IRB protocol?
Yes
Select one of the following
The grant/contract application is a pending review or a funding decision
Source of Funding
Federal
Institute/Agency
NIMH
Grant Name

1/2-Dopaminergic Dysfunction in Late-Life Depression (The D3 Study)
Grant Number
R01 MH123660
Select one of the following
Single Site
Business Office
RFMH
Does the grant/contract involve a subcontract?
Yes
Subcontracted?
To
Name institution(s)

Columbia University

Emory University School of Medicine

Study Location

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

Lay Summary of Proposed Research

Lay Summary of Proposed Research
Growing evidence suggests that dopamine contributes to key cognitive, emotional, and motor functions across the lifespan. In Late-Life Depression (LLD), dysfunction in these areas is common, predicts poor outcomes, and manifests as difficulties in motivation and effort along with cognitive and gait impairment. While studies of dopamine function in early and midlife depression primarily focus on individuals' ability to feel pleasure and respond to rewards, they often exclude the cognitive and physical function domains relevant for older adults despite a recognized decline in dopamine function with normal aging. The objectives of this collaborative R01 proposal between Columbia University/New York State Psychiatric Institute and Vanderbilt University Medical Center are to: 1) characterize dopaminergic dysfunction in LLD across cognitive, emotional, and motor domains at several levels of analysis (cellular [PET], circuit [MRI], and behavioral / self-report); and 2) examine the responsivity of dopamine-related circuits and behavior to stimulation with levodopa (L-DOPA). Supported by pilot data, this project builds on our past work demonstrating that dopamine function declines with aging, that dopaminergic dysfunction contributes to deficits in behavior, and that L-DOPA administration improves cognitive and motor performance. The long-term goal of this line of

research is to determine how dopaminergic dysfunction contributes to clinical presentations of LLD, how responsive behavioral symptoms are to modulation of dopamine function, and to identify novel targets for future interventions. Our approach is to enroll 30 psychiatrically healthy elders and 60 depressed elders at Columbia/NYSPI exhibiting either slowed processing speed or slowed gait speed. Participants will undergo thorough clinical evaluations and complete PET imaging measuring different aspects of the brain's dopamine system, neuromelanin-sensitive MRI measurement of long-term dopamine transmission, functional MRI focused on effort-based decision making and reward processing, a comprehensive neurocognitive evaluation, a physical performance evaluation, and measurement of inflammatory markers. To assess responsivity of the dopamine system to modulation, depressed subjects then will be randomized to L-DOPA or placebo for 3 weeks, followed by repeat multimodal MRI and cognitive/behavioral assessments. In a second phase, participants will receive the opposite intervention for an additional 3 weeks followed by clinical and cognitive assessments only. This proposal is significant and innovative, as no prior published study has comprehensively examined dopamine-dependent behaviors in LLD. This will inform treatment approaches focusing on facilitating cognition and movement, reducing the effort cost of voluntary behavior, and promoting behavioral activation.

Background, Significance and Rationale

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A.1. Overview: Late-life depression (LLD) is a source of disability, risk for suicide, and elevated mortality in older adults (1). Differences from younger adult depression include more motivational impairment, cognitive deficits, and motor dysfunction. This triad of symptoms may be associated with age-related or accelerated declines in dopamine circuits that negatively affect the Positive Valence, Cognitive, and Sensorimotor RDoC domains. Better understanding of the molecular, circuit-level, and behavioral manifestations of dopaminergic decline and responsivity of the system to stimulation can inform therapeutics and guide personalized treatment.

A.2. Dopaminergic Circuits: Overview in Depression and Changes with Aging. Depressed patients exhibit motivation deficits, reduced willingness to commit effort to obtain rewarding stimuli (2), impaired reward-based decision making (3), and dysfunctional activation in neural circuits underlying approach behaviors (4). Most studies examining dopamine's role in Major Depressive Disorder (MDD) primarily focus on aspects of reward processing as mediated by mesolimbic dopaminergic projections from the ventral tegmental area (VTA) to nucleus accumbens (NAC), ventral striatum (VS), hippocampus, and amygdala (5). Many data are consistent with a view of dopamine release in NAC influencing motivation and approach responses (6-8), but it has been challenging to precisely specify the nature of dopaminergic disturbances in MDD. Studies of D2/D3 receptor binding using SPECT or PET in MDD are mixed, with some finding receptor upregulation consistent with decreased dopaminergic activity (9-13), while others report no differences compared to controls (14-18). Functional MRI studies using reward tasks in patients with MDD report divergent results, though decreased striatal activation to rewards emerges as a consistent finding in recent meta-analyses (19,20).
As dopaminergic function declines with aging, depressed older adults may be a specifically informative subgroup to test the links between dopamine and MDD. Post-mortem and in vivo neuroimaging studies demonstrate that aging is associated with decreased dopamine receptor binding potential and loss of

dopamine transporters (DAT) (21-23). Decreased dopamine synthesis and release may result from chronic, low-grade inflammation seen with aging (24), referred to as "inflammaging" (25). Declines in dopaminergic function amount to an average dopamine loss of 10% per decade from early adulthood, with some groups exhibiting greater declines (26). DAT PET studies show that 25% of older adults without Parkinson's disease (PD) have a striatal DAT binding threshold ≥3 SD below that of younger subjects (27). Diminished dopaminergic tone has significant cognitive and motor effects in normal aging, including decreased processing speed (28), fine motor dysfunction (29), slowed gait and impaired balance (30,31). As dopamine circuits are implicated in the pathogenesis of MDD across the lifespan and as aging is associated with functionally significant dopaminergic decline, it is intuitive to hypothesize that dopaminergic dysfunction plays an important role in LLD.

A.3. Positive Valence System: Motivation and Effort. Anhedonia is a core symptom of depression across the lifespan and has been proposed as a critical endophenotype with a distinct neurobiology (32,33). Often defined as "loss of pleasure," anhedonia also encompasses diminished interest and anticipation, time spent in activities, and willingness to expend effort for rewards (34,35). Depressed adults exhibit impairment across many of these domains, prominently including deficient reward learning (36,37), reduced reward sensitivity (20,38), and decreased willingness to expend effort (2,39-41). All of these dimensions of reward processing are related to dopaminergic function (42-50). For example, using an amphetamine challenge combined with [18F] fallypride PET, changes in D2/D3 binding potential (BP) in the striatum and ventromedial prefrontal cortex (vmPFC) were associated with willingness to expend effort (48). Individuals with dopaminergic system dysfunction (e.g., those with PD) exhibit reward learning impairments that can be restored by dopamine replacement (51,52), while administration of levodopa (L-DOPA) to individuals performing a probabilistic learning task results in faster reward learning and enhanced VS representations of expected reward (53).

These findings are particularly germane for the treatment of patients with LLD, who are at risk of dopaminergic decline due to advanced age. While fMRI studies using the Monetary Incentive Delay Task (MIDT) suggest that behavioral and neural responses to the anticipation and receipt of rewards are similar between younger and older adults (54,55), aging is associated with greater perceived cost of effort (56) and reduced neural activity in relationship to a reward's subjective value (57,58). Increased fatigability is a common complaint of many elders and predicts functional disability (59-61). In LLD, comorbid fatigability is associated with a doubling of mortality risk (62). We propose that decreased willingness to expend effort for rewards and impaired reward learning may result in older individuals failing to engage in pleasurable goal-directed behavior and becoming more withdrawn and isolated.

A.4. Cognitive Systems: Cognitive Control and Processing Speed. Executive dysfunction and cognitive control deficits are common in LLD and predict poorer acute antidepressant response and higher risk of relapse (63-66). In conjunction with executive deficits, decreased processing speed may be "the core cognitive deficit" in LLD (67,68) as it mediates working memory, verbal reasoning, fluency, and knowledge (69,70). Decreased processing speed is consistently reported in LLD (67,68,71), mediates the effects of depression on daily functioning (72), and places older individuals at risk of dementia (73) and disability (74). In aging adults, dopamine receptor density, DAT availability, and DA synthesis capacity are all associated with cognitive performance on tasks of processing speed, cognitive control, working memory, and episodic memory (75,76). Thus, decreased dopaminergic tone during aging may be an important neurochemical contributor for the cognitive slowing and executive dysfunction observed in LLD.

By increasing the time demands of instrumental tasks and worsening mental fatigability, cognitive slowing may predispose older adults to inactivity. Given the important modulatory roles of cognitive control circuits and hippocampal-striatal connections, dopamine-dependent cognitive deficits also may contribute to impairments in reward learning (77). Conversely, since motivation and effort are critical determinants of cognitive performance, Positive Valence System abnormalities may contribute to cognitive deficits in LLD. Decreased reward sensitivity and reduced motivation impairs performance of Cognitive Systems, particularly cognitive control (78,79) while using rewards as incentives during cognitive tasks leads to improved performance (80,81). Higher levels of motivation and effort are associated with better cognitive task performance in both younger and older adults (82), and in depressed groups (71,79,83,84).

A.5. Sensorimotor Systems: Motor Function. Motor deficits are common with aging, including slowed movement, coordination deficits (85), and difficulties with balance and gait (86). Depressed older adults are at increased risk for such problems (87-89). This may be a bidirectional relationship, where depressive symptoms lead to the development of decreased gait speed while slowed gait speed leads to incident depression (90,91). Decreases in gait speed are associated with falls risk (92), disability (87), hospital admission and all-cause mortality (89,93,94). While LLD and decreased gait speed are each independent risk factors for adverse outcomes, their comorbidity synergistically increases mortality risk in older adults (95).

Decreases in striatal dopamine transmission are associated with decreased motor speed (48), fine motor dysfunction (29), slowed gait and impaired balance (30,31). In healthy adults, lower striatal DAT binding is associated with poorer balance, postural control (30) and decreased gait speed, explaining 23% of the variance in gait (31). Diminished DAT binding is associated with exaggerated slips on a challenging walking course (96) and predicts recurrent falls in elderly subjects (97). These motor impairments reciprocally interact with the reward processing and cognitive deficits reviewed above. Increased incentives are associated with increased exertion on motor tasks (98,99), with motor cortex involved in integrating a reward's subjective value with performance (98). Gait control is mediated by frontal subcortical circuits that also underlie executive functions and attention (100), and over half of cognitively impaired individuals also suffer from gait and postural impairments (101).

A.6. Role of Inflammation. Although chronic, low grade increase of inflammatory markers is a fundamental aging process, its unchecked progression can trigger a deleterious cascade contributing to depression. Higher levels of circulating pro-inflammatory markers including c-reactive protein (CRP), tumor necrosis factor (TNF), and interleukin-6 (IL-6) are consistent immunological abnormalities observed in elders and predict the development of depression (102-104). In the aging brain, this pro-inflammatory shift is characterized by increased numbers of activated and primed microglia and decreases in anti-inflammatory molecules (105). Chronic pro-inflammatory activation may lead to depression through multiple pathways including activation of the hypothalamus–pituitary–adrenal axis, decreased glucocorticoid sensitivity of immune cells, altered CNS neurotransmitter metabolism, and decreased neurogenesis and impaired neuroplasticity. Inflammaging (25) is associated with adverse structural and functional changes in the aging CNS, including increased white matter hyperintensity (WMH) burden and decreased hippocampal volumes (106).

Pro-inflammatory cytokines reduce dopamine transmission by limiting tetrahydrobiopterin (BH4) availability and decreasing dopamine synthesis, impairing vesicular release of dopamine in presynaptic neurons by decreasing expression of vesicular monoamine transporter 2 (VMAT2), increasing dopamine transporter (DAT) reuptake of synaptic neurotransmitter, and decreasing glutamate-dependent dopamine

signaling (107). Higher levels of pro-inflammatory cytokines such as IL-6 are associated with cognitive impairment in elderly people (108,109) and higher risk of significant cognitive decline over 7 years (108). Inflammaging is similarly linked to poorer functional and mobility status, including gait slowing and faster decline in gait speed (110-113).

A.7. Integrative Model. A straightforward model integrating these data is that dopamine dysfunction contributes to alterations or deficits in these systems that combine and reciprocally interact in a pathway leading to behavioral deactivation and frank depressive symptoms (see Fig. 1). The severity of symptoms and specific LLD phenotype may depend on which dopamine circuits are most affected. In the primary pathway evaluated by our Specific Aims, decreased dopaminergic tone with increasing age leads to slowed processing speed with consequent

executive dysfunction and slowed gait speed. Slowing results in increased effort costs, increases fatigability and results in decreased motivation to expend effort for a given reward value. Reward learning deficits secondary to dopaminergic decline compound this problem by impairing the ability of past rewarding experiences to influence future behavior. Alternatively, diminished motivation and effort may instead lead to cognitive deficits in LLD patients, and both reward processing and cognitive control may affect motor function. Our current proposal can examine both our primary hypotheses and alternative pathways in LLD.

A.8. Overall Significance and Integration with NIMH Priorities. First, delineating how dopaminergic dysfunction contributes to LLD will help identify new treatment targets and inform development of novel or repurposed therapeutics. These may include pharmacologic means of restoring normative dopaminergic neurotransmission, such as L-DOPA. However, by linking behavioral features to dysfunction in RDoC Domains, these studies will inform a personalized treatment approach where therapeutic strategies can be deployed depending on the clinical presentation (e.g., behavioral activation psychotherapies for Positive Valence System dysfunction, cognitive remediation for Cognitive Systems impairment, and exercise/physical therapy for Sensorimotor Systems deficits). Second, deepening our understanding of RDoC Domains across multiple levels of analysis in older adults is of major significance. The current iteration of the RDoC matrices has been criticized for neglect of developmental factors (114), including senescence and aging (115). A significant outcome of this project would be to stimulate further study of aging & psychopathology interactions

Specific Aims and Hypotheses

Specific Aims and Hypotheses

The proposed study will enroll 60 elderly depressed outpatients who exhibit evidence of dopaminergic dysfunction, characterized as either slowed processing speed or slowed gait speed. To disentangle depression effects from age-related changes, 30 never-depressed elders also will complete baseline evaluation. Assessments include PET imaging of dopamine synthesis and receptor density, neuromelanin-sensitive MRI (NM-MRI) measurement of nigrostriatal status, task-based MRI focused on effort-based decision making and reward processing, and comprehensive psychiatric, neurocognitive, and physical performance evaluation. Depressed subjects then will be randomized to L-DOPA or placebo for 3 weeks, followed by repeat multimodal MRI and cognitive/behavioral assessments. In a cross-over phase,

participants will receive the opposite intervention for an additional 3 weeks followed by clinical and cognitive assessments only. This mechanistic probe allows us to examine the contributions and interrelationships of dopamine-dependent processes in LLD and evaluate the responsivity of dopamine systems to pharmacological stimulation.

AIM 1: To characterize dopaminergic dysfunction in LLD at molecular, circuit, and behavioral levels. **Hyp 1:** Compared to age- and gender-matched controls on baseline fMRI, LLD subjects will be less willing to expend effort for rewards and exhibit lower prefrontal cortex (PFC) and striatal activation on the Effort Expenditure for Rewards Task (EEfRT). **Hyp 2:** Across all subjects, lower striatal [18F]-FDOPA relative influx rate (Kocc), lower midbrain & striatal [18F]-fallypride binding, and lower NM-MRI signal in the substantia nigra, pars compacta (SNc) will predict lower performance across RDoC domains: Positive Valence (impaired willingness to expend effort, decreased neural activations on the EEfRT), Cognitive (slowed processing speed and executive dysfunction), and Sensorimotor (slowed gait speed). **Hyp 3:** Across all subjects, slowed processing and gait speed likewise will predict lower willingness to expend effort on the EEfRT.

AIM 2: To examine responsivity of dopamine circuits in LLD to stimulation with L-DOPA.
Hyp 1: Compared to placebo, L-DOPA will result in greater normalization of neural activations and improved behavioral performance in Positive Valence, Cognitive, and Sensorimotor domains. **Hyp 2:** Baseline PET and NM-MRI measures will moderate L-DOPA effects. The greatest improvements will be observed in those with the lowest baseline [18F]-FDOPA relative influx rate, [18F]-fallypride binding, and NM-MRI signal.

Exploratory Aims: 1) To investigate associations of baseline proinflammatory markers with dopaminergic function across molecular, circuit, cognitive and behavioral levels of analysis. 2) To evaluate the durability of L-DOPA effects on RDoC domains in the crossover phase.

Description of Subject Population

Sample #1

Specify subject population
Depressed subjects
Number of completers required to accomplish study aims
55
Projected number of subjects who will be enrolled to obtain required number of completers
60
Age range of subject population
60 and older

Sample #2

Specify subject population

Never-depressed elders
Number of completers required to accomplish study aims
30
Projected number of subjects who will be enrolled to obtain required number of completers
30
Age range of subject population
60 and older

Gender, Racial and Ethnic Breakdown
We will recruit participants of all races and ethnic groups, to the extent possible within the local population demographics. We will make efforts to ensure a representative sample by working to boost minority enrollment to maintain sample consistency with population averages.

On the basis of previous studies conducted at Columbia/NYSPI's Clinic for Aging, Anxiety, and Mood Disorders (CAAM), it is anticipated that the sample at this site will be composed of approximately 75% Caucasian, 15% African American, and 10% Hispanic subjects. We will make every effort to recruit minority individuals in order to ensure the generalizability of the study's findings to the overall population of individuals with Late-Life Depression (LLD). Given the increased prevalence of depression in women, we do not anticipate difficulty in women representing 60% of our sample. Previous samples in studies conducted in CAAM have been approximately 60% women and 40% men.
Description of subject population
The N=60 Depressed sample will enroll subjects who are 1) aged 60 years old or greater, 2) have DSM5 diagnosis of Major Depressive Disorder (MDD) or Persistent Depressive Disorder, 3) Montgomery-Asberg Depression Rating Scale (MADRS) > 15, 4) decreased processing speed (1 SD below age-adjusted norms on the Digit Symbol Test) OR decreased gait speed (average walking speed on 15' course < 1m/s), and are 5) capable of providing informed consent and adhering to study procedures. Subjects will be excluded for 1) diagnosis of substance abuse or dependence (excluding Tobacco Use Disorder) in the past 12 months, 2) history of psychosis, psychotic disorder, mania, or bipolar disorder, 3) primary neurological disorder, including dementia, stroke, Parkinson's disease, epilepsy, etc., 4) MMSE < 24, 5) MADRS suicide item > 4 or other indication of acute suicidality, 6) current or recent (within the past 2 weeks) treatment with antidepressants, antipsychotics, or mood stabilizers, 7) history of hypersensitivity, allergy, or intolerance to L-DOPA, 8) any physical or intellectual disability adversely affecting ability to complete assessments, 9) acute, severe, or unstable medical illness, 10) mobility limiting osteoarthritis of any lower extremity joints, symptomatic lumbar spine disease, or history of joint replacement / spine surgery that limits mobility, 11) contraindication to MRI scanning, or 12) history of significant radioactivity exposure (nuclear medicine studies or occupational exposure).

The N=30 sample of Never-Depressed Elders will enroll subjects who are 1) aged ≥ 60 years), 2) have MADRS < 8, and are 3) capable of providing consent and adhering to study procedures. Exclusion criteria are identical to the Depressed Subjects, plus: (1) Any history of DSM 5 disorder and (2) family history of MDD in first-degree relative.

Recruitment Procedures

Describe settings where recruitment will occur

Patients will be recruited from around the general New York City/New York area and will present to the Clinic for Aging, Anxiety, and Mood Disorders.

We will be specifically recruiting via advertisements for patients who feel depressed as well as slowed down physically and mentally. Advertisements will include research flyers and brochures posted around CUMC, NAMI website, Facebook advertisements, advertisements in local newspapers and on radio stations, information posted on departmental websites, flyer mailings, pharmacies, Craigslist, ResearchMatch.com, senior community centers, college campuses, and public talks and events. For direct clinical or research referrals, a clinical staff member known to the patient will approach him/her and raise the possibility of study participation. We would also like to implement Columbia University's RecruitMe website as a recruitment method.

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

Recruitment in the Clinic for Aging, Anxiety, and Mood Disorders (CAAM) comes from clinician referrals, response to advertisements (radio, flyer, newspaper, online participant matching websites, Facebook), patients who have finished or are currently enrolled in other protocols in the CAAM, or word of mouth.

If the patient expresses a potential interest in participating, he/she will then be scheduled for a full evaluation with a study clinician. The nature of the study will be thoroughly reviewed with its risks, benefits, and alternatives to participation, and subjects' questions regarding the study will be answered. Subjects will be notified that they may leave the study at any time. Informed consent will be obtained in a private research office. A study clinician will review study procedures and the consent form with each potential participant. Each individual may take as much time as they like to decide if they do or do not wish to participate. The consent form specifies (and the study coordinator emphasizes) that participation is voluntary and withdrawal after signing consent will not affect future care. Subjects will be given a copy of the consent form, and the original will become part of the clinical record.

How will the study be advertised/publicized?

The study will be advertised/publicized through clinician referrals and advertisements, Columbia's RecruitMe website, Research Match website, Facebook, Clinical Connection website, Craigslist website, newspapers, recruitment flyers/brochures and mass mailers at community and senior centers, radio, the National Alliance on Mental Illness NYC Metro Research Studies Website, mass email campaigns from consumer marketing databases, which are compiled using public information, surveys, subscription information, home owner information, and phone directory information, pharmacies, senior community centers, college campuses, and public talks and events.

All web based recruitment procedures have been previously approved by Chris Stanley for all of our approved studies.

Do you have ads/recruitment material requiring review at this time?
Yes
Does this study involve a clinical trial?
Yes
YOU MUST REGISTER AT ClinicalTrials.gov IMMEDIATELY UPON RECEIPT OF IRB APPROVAL AND PRIOR TO ENROLLMENT OF THE FIRST SUBJECT. YOU WILL BE PROVIDED WITH A NCT REGISTRATION NUMBER ON REGISTRATION. PLEASE REVISE THIS SECTION OF THE PROTOCOL SUMMARY FORM TO INCLUDE THE NCT NUMBER AND RE-SUBMIT AS AN AMENDMENT TO THE IRB.

Concurrent Research Studies

Will subjects in this study participate in or be recruited from other studies?
Yes
Describe concurrent research involvement
Subjects who are currently participating in IRBs #7540, #7289R, #7409, #7360, #7489, and/or #7379 and meet the selection criteria for this study will be offered participation. Only an investigator not directly involved with an eligible subject's care will approach the subject to describe this protocol and have an informed consent discussion.

Inclusion/Exclusion Criteria

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

Inclusion criteria	Methods of ascertainment
1. Age 60 years or older	1. Clinical interview
2. DSM5 diagnosis of Major Depressive Disorder (MDD) or Persistent Depressive Disorder (PDD)	2. SCID, clinical interview
3. Montgomery Asberg Depression Rating Scale Score >=15	3. MADRS
4. Decreased processing speed or decreased gait speed	4. 1 SD below age-adjusted norms on Digit Symbol Test (processing speed) or average walking speed on 15 foot course <=1m/s (gait speed)
5. Capable of providing informed consent and adhering to study procedures	5. Clinical interview

6. Alternative standard treatments for MDD or PDD have been discussed and the individual agrees to be involved in an experimental treatment	6. Clinical interview

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

Exclusion criteria	Methods of ascertainment
1. Diagnosis of Substance Use Disorder (excluding Tobacco Use Disorder) in the past 12 months	1. SCID, clinical interview
2. History of psychosis (except brief psychosis associated with transient medical conditions [e.g., delirium, urinary tract infection, etc], psychotic disorder, mania, or bipolar disorder	2. SCID, clinical interview
3. Primary neurological disorder, including dementia, stroke, Parkinson's disease, or epilepsy	3. Medical history, MMSE. PD will be ruled out by satisfying (1) and (2) and (3 or 4) below: (1) patient gives no history of PD during clinical interview, (2) patient's primary doctor gives no history of PD, (3) there are no signs of PD on physical exam in CAAM (e.g., absence of asymmetric resting tremor, decreased arm swing, soft voice, decreased facial expression, difficulty rising from chair, dystonia), (4) if a patient does have one or more signs of possible PD on exam as per (3), then Dr. Kimberly Kwei (study neurologist) will come examine the patient and comment on whether PD can be ruled out or whether PD is possible and patient needs further work up
4. MMSE < 24	4. MMSE
5. MADRS suicide item >4 or other indication of	5, MADRS, clinical judgement, CGI

acute suicidality	
6. Current or recent (within the past 2 weeks) treatment with antidepressants, antipsychotics, or mood stabilizers	6. Clinical interview
7. History of hypersensivity, allergy, or intolerance to LDOPA	7. Clinical interview
8. Any physical or intellectual disability adversely affecting ability to complete assessments	8. Clinical interview
9. Acute, severe, or unstable medical illness	9. Clinical interview, physical exam, medical history
10. Mobility limiting osteoarthritis of any lower extremity joints, symptomatic lumbar spine disease, or history of joint replacement or spine surgery that limits mobility	10. Clinical interview, physical exam, medical history
11. contraindication to MRI scanning	11. MRI Safety Screening Form
12. History of significant radioactivity exposure (nuclear medicine studies or occupational	12. Clinical interview, medical history

exposure)

13. Has a medical condition managed with medication and/or device and the managing physician considers the condition and/or its management a contraindication to the research use of L-DOPA in this participant	**13. Clinical interview, medical history, discussion with participant's clinician**

Inclusion/Exclusion Criteria #2

Name the subject group/sub sample
Never-Depressed Elders
Create or insert table to describe the inclusion criteria and methods to ascertain them

Inclusion criteria	Methods of ascertainment
1. Age 60 years or older	1. Clinical interview
2. MADRS < 8	2. MADRS
3. Capable of providing informed consent and complying with study procedures	3. Clinical interview

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

Never-Depressed Elders will meet all exclusion criteria specified for Depressed Subjects, plus:

Additional Exclusion criteria	Methods of ascertainment
1. Any personal history of DSM5 disorder	1. SCID, clinical interview
2. Family history of MDD in first-degree relative	2. Clinical interview

Waiver of Consent/Authorization

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

Consent Procedures

Is eligibility screening for this study conducted under a different IRB protocol?
Yes
Indicate NYSPI IRB #
6395R
Describe Study Consent Procedures
Following clinical evaluation and screening procedures, a study clinician authorized to obtain patient consent will explain the study procedures along with the attendant risks, benefits, and alternatives, including the anticipated outcome of doing nothing. The study clinician will then leave the room while the potential subject reads the consent form and return to answer any questions the subject has. During the consent discussion, individuals will be offered the option to take the consent home to discuss with family and/or physician prior to signing it. Subjects who wish to participate will sign the consent form, while those who do not wish to participate will receive appropriate referrals.
Indicate which of the following are employed as a part of screening or main study consent procedures
✓ Consent Form

Persons designated to discuss and document consent

Select the names of persons designated to obtain consent/assent
Broft, Allegra, MD
Marcus, Galit
Miller, Jeffrey, MD
Roose, Steven, MD
Rutherford, Bret, MD

Type in the name(s) not found in the above list

Study Procedures

Describe the procedures required for this study

Overview

The overarching goal of this project is to characterize the influence of dopaminergic system dysfunction on the clinical presentation of late-life depression (LLD) across multiple Research Domain Criteria (RDoC) domains (Positive Valence Systems, Cognitive Systems, and Sensorimotor Systems) at several levels of analysis (cellular [PET], structure / circuit [MRI], and functional / self-report). This IRB pertains to procedures completed at Columbia/NYSPI. A companion grant in this Collaborative R01 project takes place at Vanderbilt University Medical Center and utilizes similar, but not identical procedures (e.g., the PET scanning at Vanderbilt utilizes a different radiotracer). Thus, we have opted to have separate IRB protocols for this project. At Columbia/NYSPI we will enroll 60 elderly depressed outpatients who exhibit behavioral evidence of dopaminergic dysfunction, defined as either slowed processing speed or slowed gait speed. To disentangle the effects of depression from age-related changes, 30 psychiatrically healthy elders also will complete baseline evaluation. After determination of eligibility, baseline assessments include PET imaging measurements of dopamine synthesis and receptor density, neuromelanin-sensitive MRI measurement of long-term nigrostriatal dopamine transmission, task positive MRI focused on effort-based decision making and reward processing, and a comprehensive psychiatric, neurocognitive, and physical performance evaluation. To examine responsivity of the dopamine system to dopamine supplementation with L-DOPA, the 60 depressed subjects (ONLY) then will be randomized to L-DOPA or placebo for 3 weeks, followed by repeat multimodal MRI, neurocognitive and behavioral assessments. In a cross-over design, participants will then receive the opposite intervention for an additional 3 weeks followed by clinical and cognitive assessments only.

Evaluation

1. Every subject (both potential Depressed participants and Never-Depressed participants) evaluated for this protocol will receive a clinical interview by a psychiatrist or psychologist. A psychiatrist or other qualified physician will see participants to evaluate medical aspects of eligibility, including screening for signs or symptoms of Parkinson's Disease (PD). If there is any concern, they will be referred to the study neurologist (Dr. Kimberly Kwei at Columbia). Additional assessments will be administered by a trained rater (BA, RN, or SW) in CAAM, including the Montgomery Asberg Depression Rating Scale (MADRS) and a SCID performed by a trained rater. Never-Depressed Elders will be selected for participation based on this initial assessment and clinical interview, while potential Depressed subjects will be further assessed as below.

2. If a subject has a diagnosis of Major Depressive Disorder (MDD) or Persistent Depressive Disorder (PDD), he/she will be informed of this and educated about the availability of treatments for depression. If a subject is not interested in depression treatment during the 6-8 weeks of study participation and/or prefers to begin with an experimental treatment for slowing and depression, he/she will be offered participation in the present study provided there is no suicidal ideation present. Based on the extant data supporting the efficacy

of antidepressants for MDD and PDD, they will be informed that antidepressant treatment would be a very reasonable option for their condition. These potential subjects will be offered the option of being referred out for depression treatment, and it will be clarified that L-DOPA is not as yet a treatment for MDD. Thus, all potential participants in this study must state their preference not to be treated with a standard treatment for depression.

3. Next, trained raters (BA, RN, or SW) in CAAM will assess processing speed using the Digit Symbol test from the WAIS-III and the Trail-Making Test Part A. Digit Symbol or Trails A will be used as a selection criterion, with patients included in this study if they score 0.5 SD below the age-adjusted norms on Digit Symbol or Trails A. Patients' gait will be assessed by trained raters as walking speed in m/s on a Gaitrite walkway system. Patients are instructed to walk at their usual or normal speed starting and ending at a point 6 feet prior to and after the walkway course to eliminate acceleration and deceleration effects. Two trials will be completed, and gait speed will be based on the average of 2 trials. Gait speed will be used as a selection criterion, with patients included in this study if they have a gait speed < 1 m/s.

4. If subjects are eligible for the study after review of their processing speed and gait speed and decide to participate by signing informed consent, then they will complete the remainder of the baseline assessment. This includes recording of each subject's chief complaint, referral source, age of onset of mood and/or cognitive decline, number prior depressive episodes, age, sex, marital status, race and ethnicity, years of education, employment status and income, years of education, family history. We also will document medical history, physical exam, urine drug screen, CBC, chemistries and electrolytes, thyroid profile, vitamin B12 and folate levels, urine analysis, and ECG. Vital signs will be measured at baseline and monitored weekly throughout the study. The Cumulative Illness Rating Scale-Geriatric (CIRS-G) will be filled out at baseline to measure chronic medical illness burden. Subjects' current physical pain will be assessed weekly using a 100mm Pain Visual Analog Scale (VAS) and used as a covariate in analyses of gait speed.

5. Additional plasma will be separated and pipetted into tubes to be transferred to Dr. Jennifer Felger's laboratory at Emory University for measurement of baseline markers of inflammatory status, including C-reactive protein (CRP), IL-6, and Tumor Necrosis Factor α (TNFα). The rationale for inflammatory marker measurement is evidence that dopaminergic dysfunction in older adults may be caused by the chronic, low-grade inflammatory process concomitant with aging ("inflammaging"). Pro- inflammatory cytokines such as IL-6 may reduce dopaminergic transmission in multiple ways, including decreasing dopamine synthesis by limiting tetrahydrobiopterin (BH4) availability, impairing vesicular release of dopamine in presynaptic neurons by decreasing expression of vesicular monoamine transporter 2 (VMAT2), increasing DAT reuptake of synaptic neurotransmitter, and decreasing glutamate-dependent dopamine signaling.

6. In the situation where a potential participant is taking medication and/or has a device to stabilize or manage a medical condition, the research physician will, without exception, contact the physician managing the condition to describe the possible research use of L-DOPA, to discuss any possible risks, and to obtain the managing physician's opinion as to whether the participant's condition and/or it's management is a contraindication to the research use of L-DOPA in this participant. This discussion and its outcome will be documented in the research chart.

7. Otherwise eligible subjects who are currently taking an ineffective antidepressant medication (i.e., the individual is symptomatic at a level meeting inclusion criteria) will be offered participation as above after a discussion of the risks, benefits, and alternatives. No patients will be taken off of effective antidepressant medications solely for the purpose of research. Should an individual taking an ineffective antidepressant medication wish to participate and sign consent, their psychiatric care will be taken over by a CAAM study clinician after a discussion with their prescribing physician. Such participants will be tapered off of the ineffective medication as per standard clinical practice (depending on the medication) and be followed closely in CAAM, likely through weekly visits. Should a participant be unable to tolerate the medication taper due to increasing depressive symptoms, they will be withdrawn from the study and entered into the 3 month open treatment period directly. Once participants are washed off of the medication they will proceed with the study assessment described in points 8-10 immediately below. Subjects must be off medication for 2 weeks prior to neuroimaging procedures and beginning the L-DOPA study medication.

8. Other neuropsychological measures completed at baseline include trained study rater (BA, RN, SW) assessment of processing speed using the Pattern and Letter Comparison Tests, broad cognitive evaluation with the NIH Toolbox, and evaluation of executive function via the NIH-EXAMINER battery designed to assess executive functions reliably, comprehensively, and efficiently (154-155). This battery examines working memory, inhibition, set shifting, fluency, insight, planning, social cognition and behavior. We also include the supplemental NIH Toolbox Auditory Verbal Learning (Rey) Test for a robust assessment of episodic memory and allow for classification of amnestic mild cognitive impairment.

9. Domains of function assessed by trained study raters (BA, RN, SW) at baseline include: the Short Physical Performance Battery (SPPB), a performance measure of gait, balance, and lower extremity strength sensitive to meaningful change. The 36-item self-report World Health Organization Disability Assessment Schedule 2.0 (WHODAS2) provides a global measure of disability and 7 domain-specific scores based on the conceptual framework of the International Classification of Functioning, Disability, and Health (ICF). The Falls Efficacy Scale-International will assess subjects' fear of falling weekly using a 16-item scale rating respondents' confidence (1 not at all concerned—4 very concerned) in doing daily tasks without falling.

10. Finally, additional clinical measures include the Antidepressant History Form (ATHF), the Daily Inventory of Stressful Events, the Preceived Stress Scale, and the Duke Social Support Index. Depressive symptoms will be measured with the MADRS in addition to the Inventory of Depressive Symptoms--Self Report (IDS-SR).

MRI Scanning

11. All of the N=60 Depressed subjects and N=30 Never-Depressed subjects will undergo neuroimaging, but the Depressed subjects will undergo a pre-treatment MRI and a post-treatment MRI following Step 1 (3 week duration) of the LDOPA study, whereas Never-Depressed Elders will have a baseline scan only (because they will not participate in below LDOPA study). MRI and PET scanning (see below) may occur on the same day if this can be scheduled (MRI occurring first, followed by PET scan). However, due to the tightness of scheduling for these scanners, it is more likely that the MRI and PET scans will occur on

different days--one day for MRI scan and one day for the PET scan. Typically the MRI scanning day will come before the PET scanning day.

12. MRI of the brain will be acquired using a GE Premier 3.0T System. For PET / fMRI coregistration and region of interest determination we will use a sagittal, whole-brainT1-weighted 3D sequence (MPRAGE) with TR/TI/TE = 2400/ 1000/ 2.22ms, flip angle (FA) 8, field of view (FOV) 240x256, 0.8mm isotropic resolution (no slice gap), and parallel imaging acceleration factor of 2 (Philips SENSE, GE ARC/ASSET). For assessment of white matter hyperintensities (WMH) we will use an axial, whole-brain T2 FLAIR sequence with TR/TI/TE = 9690/2500/91ms, FA 136, FOV 240x256, 0.8x0.8x1.6mm resolution (no slice gap), and parallel acceleration factor of 2.

13. For the BOLD functional MRI, we will use an axial, whole-brain gradient-echo echoplanar imaging (EPI) sequence: TR/TE = 1000/30ms, FA 45, FOV 220x220, 2.3mm isotropic resolution (no slice gap). Multiband and parallel imaging acceleration factors will be tuned for each scanner to obtain the specified TR/TE/voxel size. The most inferior functional slice will be inferior to the most inferior aspect of the temporal lobes. Prior to functional image acquisition, an axial, whole-brain field map is collected to correct for distortions caused by magnetic field inhomogeneities with TR/TE1/TE2 = 590/4.92/ 7.38ms, FA 60, FOV 220x220, 2.3mm isotropic resolution. We will also collect a pair of single volume spin-echo EPI with opposite phase encoding direction to provide an alternative method for field map computation.

14. Two tasks will be undertaken in the scanner. The first is the Effort Expenditure for Rewards task (EEfRT). On each EEfRT trial, participants decide whether to work harder for a larger reward (high number of finger presses with their pinky), or expend less energy (low number of presses with a dominant index finger) for a lesser reward, with lower rewards being $1 dollar and higher rewards ranging from $1.20 to $5. Participants receive information about the probability of winning on each trial regardless of their pick and one trial from each run is randomly selected for payout. Computational modelling of the EEfRT allows an estimation of the effort level at which people begin to discount rewards, and the rate of discounting once they start discounting. Because these models are more accurate with at least 3 levels of effort, the modified EEfRT offers subjects choices between high and low effort, low and medium effort, and medium and high effort (one third of trials each). The level of effort is manipulated using the number of finger presses and which finger on the nondominant or dominant hand is utilized. The number of button presses (required in a 10s response window) will be calculated as a percentage of each participant's maximum sustained button press rate in order to control for differences in ability level. The response rate (20% index dominant, 50% middle finger nondominant, 80% pinky nondominant) and time span for the responses have been calibrated for this population in order to limit floor effects seen in some participants in past EEfRT studies. Participants will complete three 320-s runs for a total of 60 trials. The following equation will be fit to the data utilizing in-house computational modelling scripts in MATLAB: SV= M -kCp, where SV= subjective value, M = monetary value of the chosen reward, k= the discount rate, C = the effort level of the option, and p determines the inflection point at which participants begin to discount. We will further examine traditional measures of the proportion of high-effort choices made during the session (primary outcome), and the relative influence of reward magnitude on making a high-effort choices (reward magnitude beta derived from a generalized estimating equation (GEE), as a weakening of reward magnitude sensitivity in decision making has been seen in our past studies with depressed patients .

15. The second task is the Monetary Incentive Delay task (MIDT). On each trial, participants are presented with a 2000msec cue indicating that trial's reward value ($0, $1, or $5). After the cue, a 2000-2500 msec delay period ensues as the participant waits for the target. Participants press a button as quickly as possible when the target is visible. After another delay lasting from 950 to 2800 msec, a feedback screen lasting 2500msec appears indicating the outcome ("Hit!" or "Miss!") for each trial, with a brief ISI before the next trial and an average trial length of 8 s. Target duration is continually adjusted during the session based on individual performance to keep success rate at 60%. Participants will complete 96 trials over three five-minute runs, for a total of 32 trials with each cue. Participants receive the money they win from the run with the greatest earnings. We include only gain trials to maximize the number of trials per condition to improve statistical power. This task distinguishes between reward anticipation and notification of reward receipt, and for modeling responses to the presence or absence of reward and responses to the magnitude of rewards. Modeling will use our past approach with the primary contrast being reward anticipation (Potential Win Anticipation > No Change Anticipation) and secondarily reward response (contrast Win Feedback > No Change Feedback). Post-hoc tests will examine the relationship between discounting behavior by reward magnitude and BOLD signal, contrasting responses to the three reward values ($0, $1, or $5.

16. Finally, neuromelanin-sensitive MRI (NM-MRI) will be conducted, which has been successfully implemented by Co-Inv Horga at NYSPI in several studies. NM-MRI consists of 2D gradient echo (GRE) images with magnetization transfer (MT) contrast of the midbrain (2D-GRE-MT, 0.39 mm2 in-plane resolution, 1.5mm slice thickness, 20 slices, FOV=162×200 mm, FA=40°, TR= 260 ms, TE=2.68 ms, MT frequency offset=1200 Hz, AC-PC alignment). To ensure imaging of the substantia nigra (SN), the image stack will be manually positioned by trained research staff according to anatomical landmarks on the high-resolution T1w scan, a protocol that yields excellent test-retest reliability for voxelwise analysis (median ICC=0.91).

17. For all of the MRI procedures, participants are instructed to lie as still as possible within the magnet. The MRI scan is completed in one session, and lasts for a total of approximately 90 minutes, including time for positioning subjects in the scanner. All precautions and protections are given to the participant to ensure that they are as safe and as comfortable as possible. For participants' comfort within the scanner, they lie on a padded table with a pillow to rest their heads on. A blanket is also provided to keep participants warm during the procedure. If the participant appears nervous or anxious, a trained member of the research staff remains with them inside the scanning suite for the duration of the scan. The participant is given a squeeze ball to terminate the scan at any time. If he/she squeezes the ball, he/she will be removed from the scanner immediately. Participants may decline the MRI scans at any time. If the participant chooses not to be scanned, his/her participation in the study will not be affected. Of course, a structural MRI scan would be required to participate in the PET scans. Any subject who cannot have at least a structural MRI scan would not be able to participate in this protocol. All of the MRI procedures are conducted on the 3-Tesla MRI scanner at the New York State Psychiatric Institute. Conducting these procedures will be an accredited Magnetic Resonance Technologist and one member of the research staff (Bachelor's Level or Higher), or Dr Rutherford or Broft, present.

PET Scanning

18. The N=60 Depressed subjects and N=30 Never-Depressed subjects will undergo a single [18F]DOPA PET scan at baseline.

19. PET experiments will be conducted with the mCT scanner in the PET Suite on the R1 level of the Public Health Building. Subjects participating in the study will be escorted on PET scan day by a research staff member to the R1 level of the Public Health Building where the PET scanner is located. A research staff person will stay with the subject throughout the procedure. The preparation of the subject will include the placement of a venous catheter.

20. The radiochemistry laboratory and PET suite staff will be in frequent communication regarding the status of preparation of the research subject (such as placement of venous line) and the progress of the radiotracer synthesis. [18F]-FDOPA will be produced at the on-site radiochemistry facility. After fasting overnight, participants are pretreated with 150 mg of carbidopa 120 minutes prior to [18F]-FDOPA injection to increase brain bioavailability. As scan time approaches, the subject will be placed in a supine position on the camera table and will have vital signs (blood pressure and heart rate) obtained. Each person's head will be positioned, and a headholder will be used to decrease head movement during the scan. Similar to previous studies, participants will be injected with [18F]-FDOPA (maximum dose of 5 mCi). The emission scan will be initiated with injection and data obtained for 90 minutes. At the completion of the scan the IV catheter will be removed, and the subject will be evaluated (including mental status and vital signs) by a study physician. Vital signs will be performed prior to discharge from the PET suite. A new IND application to the FDA is underway by the PI (Dr. Rutherford) to cover the baseline PET scan in this study and will be added to this application when received.

21. PET data will be reconstructed into images using the appropriate reconstruction protocols and filters. PET images will be coregistered to the MRI and regional time activity curves will be measured. Data will be fitted to pharmacokinetic models, and relevant pharmacokinetic parameters, including the percent of receptors engaged by dopamine, will be estimated based on the model fitting procedures.

22. Drs. Miller, Zanderigo, and Lan in the MIND Division at NYSPI are Co-Investigators who will lead analyses of neuroimaging data. In terms of on-site execution of PET and MRI scans, these are supervised by the study PI (Bret Rutherford) and/or Dr. Allegra Broft, who works with the PI as a study clinician and has a research background in PET neuroimaging.

Clinical treatment

23. For the mechanistic probe of dopaminergic functioning using LDOPA, a crossover trial will be conducted. In Step 1, participants will be randomized to initially receive either active L-DOPA or matching placebo based on a block design using R Statistical Software version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria). Participants, physicians and research staff will be blinded to group assignment. The NYSPI Pharmacy will maintain the randomization key for each site and can unblind individual subjects in emergencies. The blind will not be broken until study completion. Following Step 1, participants will have repeat MRI scanning and cognitive/behavioral testing, then undergo a 1 week taper and wash out period before being crossed over to the opposite treatment (Step 2). Repeat cognitive and behavioral testing will occur after Step 2 but there will be no further neuroimaging.

24. Subjects will take active or placebo tablets three times daily (9am, 1pm, 5pm). Those assigned to L-DOPA will begin with a Week 1 L-DOPA daily dosage of 150mg, or 1.5 25mg carbidopa/100mg levodopa

tablets at 9am and placebo tablets at 1pm and 5pm. In Week 2 the L-DOPA daily dose will increase to 300mg (1.5 25mg carbidopa/100mg levodopa tablets at 9am and 5pm, with placebo at 1pm), followed by a Week 3 L-DOPA daily dose of 450mg (1.5 25mg carbidopa/100mg levodopa tablets three times daily). Subjects assigned to placebo will take 1.5 placebo tablets three times daily for three weeks. Individuals will be instructed to maintain the same timing of doses throughout the study. Individuals unable to tolerate an increased dose will have their dosage reduced to the maximum previously tolerated dose.

25. Following the three-week Step 1 Phase, there will be a one-week taper period. Subjects will be instructed to decrease their dosage to 1.5 tablets twice daily for 3 days, followed by 1.5 tablets once daily for three days, then discontinue tablets. Subjects will then restart an identical dosing regimen while being crossed over to the opposite treatment assignment for Step 2.

26. At each weekly visit, subjects will meet with a psychiatrist of study physician. Both in our Pilot study and the literature overall, L-DOPA is an extremely well tolerated medication at doses < 600mg, which is substantially less than the doses often reached in the treatment of Parkinson's disease (900-1200mg). L-DOPA has been administered to healthy subjects in single dose studies and found to be well-tolerated. In Parkinson's disease, a recent clinical trial published in the New England Journal of Medicine randomized patients to receive 150mg, 300mg, or 600mg L-DOPA for 40 weeks. No dyskinesias or other neuropsychiatric effects were observed that were greater than the placebo group.

27. Participants will be given the option to receive medication reminders via text messages three times daily (morning 9am, midday 12pm, evening 5pm) adhering to the study medication schedule. Text messages will be automatically sent out by service provider www.remindercall.com. Participants will be able to opt-in and opt-out of this service at any time during the study by either replying "STOP" to any text message or by contacting the study coordinator.
26. At the conclusion of Step 2, participants will undergo another 1 week washout phase and then enter post-protocol open treatment, which will be offered for 3 months. Appropriate medication treatment options for depression will be discussed with each participant, which may include continued off-label use of LDOPA as discussed below.

Assessments

29. Subjects are expected to have a screening/evaluation visit, pre-treatment PET/MRI scanning day(s), and weekly visits during Steps 1 and 2 of the crossover trial (i.e., Weeks 0-3 [Step 1], 4 [taper], 5-8 [Step 2], 9 [taper]). At each clinic visit, depression severity measured using the MADRS and adverse events assessed. The presence of any suicidal thoughts will be assessed at every contact. Vital signs (weight, heart rate, blood pressure) will also be measured.

30. Cognitive assessments will be performed at baseline and after each step of the crossover trial. To obtain a broad assessment of cognitive function, we will administer the NIH Toolbox Cognition Battery that measures 6 ability subdomains and assess episodic memory functioning supplemental NIH Toolbox Auditory Verbal Learning (Rey) Test. Our primary outcome is processing speed, assessed using Coding from the Wechsler Adult Intelligence Scale-IV (WAIS-IV) and the Pattern and Letter Comparison tests (secondary outcomes). To assess executive function, we will supplement the NIH Toolbox with the NIH-

EXAMINER battery, which measures working memory, inhibition, set shifting, fluency, insight, planning, social cognition and behavior (secondary outcomes).

31. Gait will be assessed at baseline and after each step of the crossover trial as both a single and dual tasks (ST, DT) using the GaitRite system (Sparta, NJ), which assesses gait parameters in real time (gait speed, cadence, stride length). For the ST (primary gait outcome), participants are instructed to walk at their usual or normal speed over the 15' walking course. For the DT (secondary outcome), participants are instructed to walk at their usual pace while simultaneously verbally listing as many animals as possible (fluency DT). In addition, a counting DT will be used in which participants are instructed to walk at their usual pace while simultaneously performing serial subtractions by threes starting at 100.

32. Other clinical assessments collected each visit include the CGI Severity and Improvement (provide a clinical assessment of subjects at each visit and help maintain safety by identifying clinical worsening), Inventory of Depressive Symptoms—Self Report (IDS-SR) (provide a self-report measure for depressive symptoms), Structured Pill Count Interview (to assess study medication compliance), and the Treatment Emergent Side Effect Scale (TESS) to monitor side effects associated with medication treatment. We will utilize the Unified Parkinson's Disease Rating Scale (UPDRS) to identify any dyskinesias caused by L-DOPA, although based on our previous studies we are not expecting to observe motor side effects with the L-DOPA doses and duration being used in this study.

End of study procedures

33. Following the 8 week (in total) duration crossover study, endpoint assessments of psychiatric symptoms, cognition, and motor functioning will be made. Once post-treatment research procedures are completed, patients will enter 3 month open treatment period provided free of charge as described below.
You can upload charts or diagrams if any
Figures.pdf
Dosimetry chart for [18F]DOPA.pdf

Criteria for Early Discontinuation

Criteria for Early Discontinuation
The risk of non-response or adverse events to L-DOPA during the study period is addressed by having close clinical follow up of study subjects and stringent withdrawal criteria. These criteria are (1) participant withdraws his or her consent; (2) **significant clinical worsening (in any aspect, including motoric function or depressive symptoms) as defined by a CGI-Improvement scale of 6 (worse) or 7 (much worse) for 2 consecutive visits**; or (3) development of significant side effects or an adverse event. Any subjects meeting any of these criteria will be withdrawn from the study and treated clinically. Furthermore, subjects may be withdrawn if they repeatedly miss scheduled appointments or clinical worsening necessitates more intensive treatment. No treatment is currently available for slowing, so there is not a standard of care treatment to offer patients withdrawn from the study. Thus, withdrawn patients will be followed in the open treatment period, offered appropriate psychiatric treatments if they have any conditions requiring treatment (e.g., depression), and be referred to their internist for close medical follow up.

Blood and other Biological Samples

Please create or insert a table describing the proposed collection of blood or other biological specimens
A 20cc blood sample will be drawn from all depressed (N=60) and healthy (N=30) subjects baseline. General medical tests will be performed as safety screens for Depressed subjects, such as CBC, Chem 7, LFTs, TSH, cholesterol, B12, and folate. Also, plasma samples from all subjects (Depressed and Never-Depressed) will be isolated by centrifugation at 1000 x g for 10 minutes at 4C, aliquoted into siliconized polypropylene tubes and stored at -80C until batch assay. Samples will be shipped to Co-Inv Jennifer Felger's laboratory at Emory University in batches by a staff member at each site who is certified to ship biospecimens using standard procedures for shipping samples on dry ice and with arrival the next day before 10am via Fedex.

Assessment Instruments

Create a table or give a brief description of the instruments that will be used for assessment

Structured Clinical Interview Diagnostic for DSM 5 (SCID): this semi-structured diagnostic interview will allow determination of whether subjects meet selection criteria.

Cumulative Illness Rating Scale-Geriatric (CIRS-G) will be filled out at baseline to measure chronic medical illness burden.

Subjects' current physical pain will be assessed weekly using a 100mm Pain Visual Analog Scale (VAS) and used as a covariate in analyses of gait speed.

MMSE: standard means of assessing global cognition. The SCID, CES-D, and MMSE will be measured at baseline for the purpose of subject selection, while the following measures will be collected weekly throughout the study.

Montgomery Asberg Depression Rating Scale: standard measure of depression severity that measures changes in depressive symptoms.

CGI Severity and Improvement: scales measuring the clinician's view of subjects' global functioning that will provide a clinical assessment of subjects at each visit and help maintain safety by identifying clinical worsening.

Structured Pill Count Interview: assessment of study medication compliance accounting for each dose of prescribed study medication during the study period.

Blind Assessments rate clinician's and patient's guesses as to study drug assignment.

Unified Parkinson's Disease Rating Scale (UPDRS): standardized, reliable, and valid instrument for

assessing the severity of the clinical features of PD; questions 32 and 33 will be used in this study to assess the duration and disability of dyskinesias caused by L-DOPA. While we include this measure, we are not expecting to observe dyskinesias in healthy subjects or at the L-DOPA doses being used in this study. Typically, such L-DOPA side effects emerge only in patients who have had Parkinson's disease for a number of years and then only if the LDOPA dose is raised to 600 mg or more.

Treatment Emergent Side Effect Scale: standardized general checklist used in our clinic for monitoring side effects associated with medication treatment.

Inventory of Depressive Symptoms—Self Report (IDS-SR): rating scale for depressive symptoms based on DSM criteria that has been increasingly used in antidepressant studies due to its equivalent weightings for each item, understandable anchor points, and inclusion of all DSM criteria.

Processing speed will be assessed using the Digit Symbol test from the Wechsler Adult Intelligence Scale-III (WAIS-III) and the Pattern and Letter Comparison tests. These tests are all reliable and valid, with moderate to high loadings on the latent speed factor.

To broadly assess cognitive function, we will administer the NIH Toolbox Cognition Battery, a brief and psychometrically sound set of 7 computerized instruments providing an overall cognitive index from measures of 6 cognitive domains . We also include the supplemental NIH Toolbox Auditory Verbal Learning (Rey) Test for a robust assessment of episodic memory and allow for classification of amnestic mild cognitive impairment.

Executive function will be assessed via the NIH-EXAMINER battery designed to assess executive functions reliably, comprehensively, and efficiently. This battery examines working memory, inhibition, set shifting, fluency, insight, planning, social cognition and behavior.

Gait will be assessed as both a single and dual task (ST, DT) using the GaitRite system (Sparta, NJ), which assesses gait parameters in real time (gait speed, cadence, stride length). For the ST, patients are instructed to walk at their usual or normal speed over the 15' walking course. For the DT, patients are instructed to walk at their usual pace while simultaneously verbally listing as many animals as possible (fluency DT). In addition, a counting DT will be used in which patients are instructed to walk at their usual pace while simultaneously performing serial subtractions by threes starting at 100. Patients will start and end at a point 2 meters from the GaitRite mat to eliminate acceleration and deceleration effects. Each ST and DT will be assessed two times with the average used in the analyses. The ST assessment of walking speed in m/s will be the primary gait outcome measure for this study.

Pittsburgh Fatigability Scale (PFS) will assess mental and physical fatigability.

Short Physical Performance Battery (SPPB) provides a performance measure of gait, balance, and lower extremity strength.

The Falls Efficacy Scale-International will assess subjects' fear of falling using a 16-item scale rating respondents' confidence (1 not at all concerned—4 very concerned) in doing daily tasks without falling.

Please attach copies, unless standard instruments are used

Off label and investigational use of drugs/devices

Choose from the following that will be applicable to your study
✓ Drug
✓ Radiolabeled drug/compound
Select the number of drugs used in this study
1

Drug #1

Name of the drug
Sinemet (carbidopa/levodopa)
Manufacturer and other information

We will be using generic carbidopa/levodopa (L-DOPA) 25/100 tablets in this study. We will purchase them through the New York State Psychiatric Institute (NYSPI) pharmacy, using the generic manufacturer recommended. L-DOPA is currently approved by the Food and Drug Administration (FDA) for the treatment of the symptoms of idiopathic Parkinson's disease, post-encephalitic parkinsonism, and symptomatic parkinsonism. This project proposes off-label use of L-DOPA in individuals with significant cognitive/motor slowing.

Approval Status
No IND is required
Choose one of the following options
FDA has determined that IND is not required

Off label and investigational use of radiolabeled drugs/compounds

Radiolabeled Drug/Compound #1

Name of the radiolabeled drug/compound
[18F]DOPA
Manufacturer and other information
[18F]-FDOPA quantifies dopamine synthesis capacity in the striatum, although it is also used for quantification in the cortex. Striatal [18F]-FDOPA uptake has been inversely related to depression severity and cognitive and motor function in PD. Moreover, striatal [18F]-FDOPA uptake was decreased in a group of patients with MDD who exhibited psychomotor retardation and affective flattening as compared to a second MDD cohort characterized by impulsivity and anxiety and a group of healthy volunteers. These data

suggest that this tracer may be sensitive to deficits in dopamine synthesis capacity that we hypothesize to mediate pathological processes in LLD.
Approval Status
IND is approved
IND#
151595
Who holds the IND/IND sponsor?
IND is held by PI/CU Investigator
Rutherford, Bret, MD

Research Related Delay to Treatment

Will research procedures result in a delay to treatment?
Yes
Maximum duration of delay to any treatment
None.
Maximum duration of delay to standard care or treatment of known efficacy
Since patients will be assigned to placebo for one phase of the crossover study and the effects of L-DOPA on depression in this population are currently unknown, there will be an 8-week duration delay to receiving an agent of known efficacy to treat depression posed by subjects' participation in this study.
Treatment to be provided at the end of the study
We will provide 3 months of additional free clinic visits following the end of this project. At the conclusion of the 3 week study, a non-study clinician in our research clinic will be given the data on the subject's response to L-DOPA. This clinician will discuss with each subject on a case-by-case basis the risks and benefits of continuing L-DOPA treatment as well as other treatment options if warranted. Those who have benefited from the treatment and have not had significant side effects may elect to continue receiving LDOPA after receiving an explanation of the potential risks of chronic administration. If they do not want to continue L-DOPA, it will be discontinued after a 3 day step-down withdrawal of the drug. Transferring after-study care to a non-study clinician protects against the development of bias in the study clinicians and offers optimal clinical care to the subjects at the study conclusion.

Clinical Treatment Alternatives

Clinical treatment alternatives
The alternative to participating in this study is to seek treatment outside the research project. Patients who would rather receive treatment elsewhere will be given referrals to appropriate and affordable care.

Risks/Discomforts/Inconveniences

Risks that could be encountered during the study period

1. L-DOPA Side Effects: Side effects will be assessed at each planned visit and as needed through additional or unscheduled contacts. We will attempt to minimize side effects by slow dosage titration and allowance for dose reduction if needed. We will withdraw subjects from the study if they cannot tolerate the lowest dose of carbidopa/levodopa (L-DOPA) 37.5mg/150mg daily. L-DOPA is a well-tolerated medication at the doses we will be using in this study. In healthy controls, the only available studies are single-dose experiments, in which the sole reported side effect has been **nausea**. No serious adverse events or side effects due to an effect on the nigrostriatal dopamine system have been observed in these studies. There are many studies of chronic L-DOPA administration for the treatment of Parkinson's disease (PD), since this drug has been used since the 1960s. Perhaps the most relevant study was a clinical trial published in the New England Journal of Medicine in 2004. In this study 361 patients with PD were randomized to receive 150mg, 300mg, or 600mg L-DOPA for 40 weeks. In the 150mg and 300mg L-DOPA treatment groups, the only side effects observed that were different from placebo were headache and nausea. No dyskinesias or other neuropsychiatric effects were observed that were greater than the placebo group, and this study lasted 40 weeks as opposed to 4 weeks (3 week dose titration, with 1 week taper) in this study.

In our preliminary work at NYSPI, a series of depressed older adult outpatients (N=36 subjects aged 75.3 ± 7.5 years, 44.4% male) were treated with open L-DOPA for three weeks (one week each of 150mg, 300mg, and 450mg). The overall drop-out rate was 8.3%, with 5.6% subjects dropping out due to adverse effects of L-DOPA. Thirty of the total N=36 analyzed subjects reached the final L-DOPA dose of 450mg. **Nausea was the most frequently reported treatment-emergent side effect, and the frequency of subjects reporting nausea decreased over the course of the trial**, from 19.4% of subjects reported for 150mg L-DOPA, to 17.1% for 300mg L-DOPA, and 9.1% for 450mg L-DOPA. The only other side effects reported by more than one subject were insomnia and headache. The emergence of dyskinesias during L-DOPA treatment was evaluated using items 32 and 33 of the UPDRS, and no significant change from baseline was observed on either these items. Mean scores were 0.0 at Week 3 for both items. No significant adverse events (SAEs) attributable to study medication were noted during the project. Since we found the greatest effects on processing/gait speed at 450mg without no decrease in tolerability relative to 150mg and 300mg doses, we selected 450mg as the target dose for the mechanistic probe in the present study. In our pilot work, L-DOPA 450mg was associated with increased dopaminergic availability in the sensorimotor and associative striatum.

a. L-DOPA common side effects: In patients taking L-DOPA for the management of bradykinesia and freezing associated with PD, the most common side effects are dyskinesias (i.e., choreiform, dystonic, and other involuntary movements) and **nausea**.

b. Other L-DOPA side effects: blood pressure changes, orthostasis, anorexia, dyspepsia, constipation, psychotic episodes (e.g., delusions, hallucinations), vivid dreams, and nightmares.

c. Discontinuation Syndrome: A neuroleptic malignant-like syndrome (fever, akinetic crisis, rigidity, autonomic disturbances) has been reported following withdrawal of levodopa in patients with PD.

2. [18F]-FDOPA PET Imaging Specific Risks: Risks associated with [18F]-FDOPA PET scans are (a) radiation exposure, (b) toxicology, (c) venous catheter, and (d) discomfort during scanning. To limit the risks of radiation exposure, participants with radiation exposure in a research study in the previous year will

only be included if the injected dose and dosimetry of the radiotracer are known and the cumulative annual exposure of the previous study and this study is lower than the annual limit for research subjects defined by the FDA (21 CFR 361.1, see below). The critical organ is the bladder for [18F]-FDOPA. The exposure to the critical organs after a single injection of [18F]-FDOPA is below the 21CFR361 single dose limits for research subjects, of 5 rads (50 mGy) for dose-limiting organs and 3 rads (30 mGy) for testes. The total annual dose is also below the limit for research subjects of 15 rads (150 mGy) for dose-limiting organs and 5 rads (50 mGy) for testes. Further protections are that, before scanning, participants are interviewed about past radiation exposure to ensure that limits are not being exceeded. In order to further limit radiation exposure, after the PET scan, participants are asked to empty their bladders following scanning and to drink extra fluids in order to decrease radiation exposure to the bladder wall. Persons exposed to radiation in the work place or to nuclear medicine research procedures during the previous year are excluded from participation.

A low dose attenuation CT scan will be needed before each PET scan acquisition is started. If the subject needs to leave the scanner to use the restroom during the scan, the CT scan will need to be repeated. The effective dose per administration will be 0.044 mGy, so the total potential effective dose per study/protocol will be 0.088 mGy. The total effective dose for all procedures in the study will therefore be 4.71 mGy. These doses are below the dose limits for research studies under FDA 21CFR 361. Since only trace amounts of the radiotracer will be present, the procedure presents no risks in terms of toxicity. L-DOPA is an approved medication for Parkinson Disease at much higher doses. The use of [18F]-FDOPA for PET imaging is approved in the European Union for clinical nuclear medicine use in the field of oncology. Nevertheless, a physician will be present during each injection of the radiotracer in case of an idiosyncratic response.

3. Delay in Antidepressant Treatment Initiation: As specified in the above selection criteria, participants in this study will have a DSM 5 depressive disorder and MADRS $\geq$ 15, but current treatment with antidepressant medication is an exclusion criterion. Otherwise eligible subjects who are currently taking an ineffective antidepressant medication (i.e., the individual is symptomatic at a level meeting inclusion criteria) will be offered participation after a discussion of the risks, benefits, and alternatives. Those wishing to participate will undergo a medication washout following standard clinical practice and be closely followed by study clinicians until they are eligible to begin the study. The maximum duration of delay of treatment for depression with an agent of known efficacy will be 8 weeks. No patients will be taken off of effective antidepressant medications solely for the purpose of research, and patients will be withdrawn from the study and treated if clinically indicated and desired by the patient.

A number of precautions have been taken to safely maintain participants antidepressant-free for the duration of the proposed study. First, our selection criteria exclude individuals who are judged to be at high risk of suicide (MADRS suicide item > 4). Second, we have stringent criteria for early discontinuation and initiation of appropriate open clinical treatment. These criteria are (1) participant withdraws his or her consent; (2) significant clinical worsening in the judgment of the study clinician; (3) a CGI-Improvement rating of 6 (worse) or 7 (much worse) for 2 consecutive visits, or (4) development of significant side effects or an adverse event. Any subjects meeting any of these criteria will be withdrawn from the study and treated as clinically indicated. Furthermore, subjects may be withdrawn if they repeatedly miss scheduled appointments or clinical worsening necessitates more intensive treatment. Finally, following the study,

subjects are offered state-of-the-art clinical visits at no cost to them or their insurer for 3 months, although they will be responsible for the cost of any antidepressant medications.
4. Interview, emergencies, and possible suicidal ideation. Subjects may experience discomfort during the clinical interview and evaluations when discussing symptoms and current life events. The study coordinators are experienced and skilled in interviewing depressed subjects. Half-way through the initial assessment, the coordinator will ask the subject if they would like to take a break, and this will be provided if desired. A study clinician will be available during all aspects of the assessment if there are any questions or problems. In addition, should the subject express suicidal ideation at any time during the interview, the study clinician will be contacted immediately to assess the subject and to determine the appropriate course of action. Options for addressing suicidal ideation will include contacting the individual's mental health caregiver, referring for urgent (same day) evaluation and treatment in an outpatient clinic, or emergency room 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.

5. L-DOPA treatment—End of Study Procedures: We will provide up to 3 months of additional free clinic visits following the end of this project to facilitate the return to clinical care. A non-study clinician in our research clinic will be given the data on each subject's response to L-DOPA. This clinician will discuss with each subject on a case-by-case basis the risks and benefits of continuing L-DOPA treatment as well as other options for the treatment of depression. Those who have benefited from the treatment and have not had significant side effects may elect to continue receiving L-DOPA after receiving an explanation of the potential risks of chronic administration. If they do not want to continue L-DOPA, it will be discontinued after a 3-day step-down withdrawal of the drug. Transferring after-study care to a non-study clinician protects against the development of bias in the study clinicians and offers optimal clinical care to the subjects at the study conclusion.

6. Gait speed assessment: During the gait speed assessment and other physical performance measures, patients may feel unsteady and their risk of falls may increase. To mitigate these risks, patients are accompanied by research coordinators and/or doctors during each of the performance-based assessments (including the gait assessment, balance test, and chair stand, the latter two components of the Short Physical Performance Battery). Coordinators walk slightly behind and alongside the patients during the gait assessment, providing support for the patients should they become unsteady during the procedure.

7. Breach of confidentiality: There is the potential risk of breach of confidentiality of clinical and laboratory information. PIs Rutherford and Taylor have extensive experience as clinical investigators in dealing with sensitive information and 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. Please refer to Human Subjects section 3.3 for a discussion of data management, security, and monitoring.

8. PET and MR scanner environments. The physical confinement and isolation produced by the scanner could cause mild to moderate emotional distress, although in our extensive past experience, subjects generally have tolerated the procedures well. To protect against this risk, subjects will be acclimated to the MRI and its noise with training sessions in a mock scanner on the morning of the scan. Relaxation training will be used to help calm anxious subjects and to reduce motion. Frequent praise and reminders to remain still, along with an inflation pillow and taping of the subject's forehead, will help to acquire motion-free

images. In the past dozen years, our groups at Columbia/NYSPI and Vanderbilt have acquired superb, motion-free structural and functional scans in 1000s of adults affected by a variety of neuropsychiatric illnesses. All subjects will be able to communicate directly with technologists and study staff to report any emotional or physical distress during the scanning procedure. If they wish, the scan will be terminated immediately, and the subject will be removed from the scanner.

9. 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 they may request the scan be stopped at any time.

10. 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, the site PI will convey these findings to the subject along with recommendations for further evaluation, and facilitate referrals for such evaluation and treatment.
11. Risks of blood draw: When obtaining a 20 cc blood sample, patients can experience side effects that include pain, fainting, bruising, light-headedness, and, on rare occasions, infection. The staff will take every precaution to avoid these difficulties. The staff members are all certified at the hospital to be drawing blood from patients and are instructed to keep the comfort and welfare of our patients as their primary priority.

Describe procedures for minimizing risks

1. Side effects will be assessed at each planned visit and if needed through additional or unscheduled contacts. We will attempt to minimize side effects by slow dosage titration and allowance for dose reduction if needed. We will withdraw subjects from the study if they cannot tolerate the lowest dose of carbidopa/levodopa (L-DOPA) 37.5mg/150mg daily.

2. The dose of radiation will be approved by the JRSC, as we will submit an application to cover [18F]DOPA scanning. All scans will be done in the presence of medical supervision and trained nursing staff in an imaging center specifically designed to support imaging studies. In the event of serious medical complications, the PET scan facilities have immediate access to a consultation with specialized medical units at New York Presbyterian Hospital. Preparation of radiopharmaceuticals and performance of PET scans will be by radiochemists, physicians, and technologists of the Department of Radiology at Columbia. These professionals are qualified by training and experience in the safe use and handling of radiopharmaceuticals. Subjects will be asked about their previous radiation exposure and those who have had research exposure within the past year will be excluded if their cumulative annual exposure (including the present study) exceeds FDA limits. The information on the previous radiation exposure of study subjects will be notified to the study doctor.

3. In terms of [18F]DOPA pharmacologic effects, we do not anticipate any pharmacological effects from the radiotracer used in the proposed studies. As with any drug, the possibility of idiosyncratic reaction exists and is mentioned in the consent forms. A physician is present at each experiment.

4. The staff will take every precaution to avoid difficulties with gait speed assessments. Patients are accompanied by research coordinators and/or doctors during the test of gait speed. Coordinators walk slightly behind and alongside the patients during the gait assessment, providing support for the patients should they become unsteady during the procedure.

5. Dr. Rutherford has extensive experience as a clinical investigator in dealing with sensitive information and 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.

6. The study coordinators are experienced and skilled in interviewing subjects with a variety of mental health issues. Half-way through the initial assessment, the coordinator will ask the subject if they would like to take a break, and this will be provided if desired. A study clinician will be available during all aspects of the assessment if there are any questions or problems. In addition, should the subject express suicidal ideation at any time during the interview, the study clinician will be contacted immediately to assess the subject and to determine the appropriate course of action. Options for addressing suicidal ideation will include contacting the individual's mental health caregiver, referring for urgent (same day) evaluation and treatment in an outpatient clinic, or emergency room 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.

7. To minimize MRI risks, each subject will fill out the MRI Safety Questionnaire before the study. Only subjects who fulfill the criteria by this questionnaire will be eligible for the study. In addition, subjects will remove all metal (watch, hair pins, jewelry) before entering the MRI room. If the subject has any metallic prostheses/implants they will be excluded from the study. If a subject becomes anxious during the scan they can request that the MRI scan be stopped.

8. Risks of bruising, clotting, and infection during IV placement and blood draw will be minimized by having venipuncture performed by trained and experienced personnel under sterile conditions. To avoid injury due to fainting, the antecubital vein catheter will be inserted when the subjects are recumbent.

Methods to Protect Confidentiality

Describe methods to protect confidentiality

All records of the participating subjects will be kept in a locked room with access provided only to staff members. Patients' names will be linked with code numbers in a password protected file to which only the research assistant has access. Only these code numbers will appear on all pill bottles and paper measures collected during study. All data collected will be kept confidential and used for professional purposes only. Publications using these data will be done in a manner that protects the subjects' anonymity. All electronically stored data will be accessible by password known only to the principal investigator and research assistants for the study.

The data obtained for this study and biospecimens could be used for future research studies or may be distributed to another investigator for future research studies, however all information **including biospecimens** will be de-identified **and will not include whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen).** Biospecimens will not be used for commercial profit. Clinically relevant research results, including individual research results may be available to participants at their request but such request will be granted under the discretion of the study doctor. Participants may be contacted in the future by the study team for future studies.

Data shared with the National Institute of Mental Health Data Archive (NDA) will maintain patient confidentiality by ensuring exclusion of all 18 identifiers (outlined by HIPAA) prior to data sharing.

Will the study be conducted under a certificate of confidentiality?
Yes, we have already received a Certificate of Confidentiality

Direct Benefits to Subjects

Direct Benefits to Subjects
There is no direct benefit to subjects. If L-DOPA treatment is effective in ameliorating slowing, subjects may experience improved quality of life and decreased of falls and other sequelae of slowing.

Compensation and/or Reimbursement

Will compensation or reimbursement for expenses be offered to subjects?
Yes
Please describe and indicate total amount and schedule of payment(s).
Include justification for compensation amounts and indicate if there are bonus payments.

All subjects who complete a screening visit will be reimbursed $35.

Eligible depressed subjects (N=60), will be reimbursed $150 for cognitive/motor assessment sessions, **paid cash at the end of each visit.**
$100 per MRI (2 MRI scan), and $200 per [18F]-FDOPA PET scan. This equates to $585 per depressed participant. T**his money will be paid in 1 lump sum payment at the end of the study. Payments typically require 1-3 weeks to process and will be mailed in the form of a check.**

Eligible Non-depressed control subjects (N=30) will be reimbursed $50 for cognitive/motor assessment session, **paid cash at the end of each visit**.
$100 for MRI (1 MRI), and $200 for [18F]-FDOPA PET scan. This equates to $385 per control participant. **This money will be paid in 1 lump sum payment at the end of the study. Payments typically require 1-3 weeks to process and will be mailed in the form of a check.**

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