PROTOCOL TITLE:
Cognitive Remediation of Cognitive Control in Late-Life Depression

Brief Title:

Cognitive Fitness for Depression in Older Adults

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Supported by:
The National Institutes of Health
NCT04790630

Version 14.0
December 1, 2024

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1 BACKGROUND

Major depression in the elderly or late-life depression (LLD) is both challenging to treat and detrimental to the cognitive functioning of patients. LLD increases the probability of a later dementia diagnosis by 4 to 6 fold. By targeting cognitive processes in treatment, I hope to both find a more effective means to manage LLD, but also demonstrate how top-down processes (e.g., Executive Control Network or ECN connectivity) may be driving depression and cognitive decline in older adults. The conduct of this research will help me attain my training goals of learning how to use MRI and intervention strategies to detect changes in cognitive functions and neural interconnections, and the results of those changes.

It is thought that frontolimbic brain changes result in both depression symptoms and EF weakness in LLD. The ECN is a functionally linked system comprised of the dorsolateral prefrontal, medial frontal, and parietal cortices. The ECN presides over EF and may exert "top-down" control over limbic regions involved in emotional reactivity and regulation (e.g., the Default Mode and Salience Networks). ECN abnormalities may be a key mechanism in LLD, and treating EF weakness in LLD may enhance functioning of the ECN and result in improved emotion regulation and cognition. To test this, we intend to use a computerized cognitive remediation program to increase ECN connectivity and improve cognitive control behavior in LLD, and determine whether these changes are associated with reduced depression and a delay in cognitive decline.

Weakened EF, depression symptoms, and decreased ECN functional connectivity are all independently associated with progression of cognitive decline in older adults. EF weakness and depression symptoms may be the earliest manifestations of mild cognitive impairment (a clinical risk state for later dementia). EF weakness and depression also increase the probability of mild cognitive impairment transitioning to dementia. Using MRI, lower baseline resting state functional connectivity in the ECN, Default Mode, and Salience Networks is associated with cognitive decline in healthy elders, even when controlling for structural changes to the brain (e.g., atrophy and white matter hyperintensities). Together, this suggests the ECN may be an important target against cognitive decline in LLD.

Computerized cognitive remediation programs have been successfully used to improve cognitive abilities in older adults with and without major depression. The long-term impact of this training in LLD remains unclear. There have been no studies testing whether computerized cognitive remediation can both improve depression and delay cognitive decline over the long term in LLD.

To advance understanding of ECN functions and improve clinical outcomes in LLD, 54 older adults with LLD will undergo a 6 week randomized controlled trial contrasting the effects of computerized cognitive remediation targeting EF with an active control group on multiple assessments of cognitive control (ECN connectivity, EF, emotion regulation) and depression measured pre and post treatment. Subjects will undergo clinical follow-up one year later (pilot data suggests this is an adequate period to measure change in EF). We emphasize the inclusion of LLD patients at risk for cognitive decline (i.e., treatment resistant depression, patients with mild cognitive impairment). With this Award, I will acquire expertise in using interventions to modulate neural circuits and associated behaviors in LLD and advance my knowledge of clinical trial design and longitudinal data analysis. The primary aims include:

Aim 1: To determine whether computerized cognitive remediation of EF (CCR-EF) significantly increases ECN within-network connectivity and improves behavior. Hypotheses: Compared to an active control intervention group, LLD patients treated with CCR-EF will show: (1a) improved EF (1b) increased use of emotion regulation, specifically cognitive reappraisal; and (1c) increased ECN functional connectivity using task-based and resting state fMRI after controlling for white matter hyperintensities and global brain atrophy.

Aim 2: To determine whether CCR-EF significantly decreases depression symptoms. Hypothesis 2: Compared to an active control intervention group, LLD patients treated with CCR-EF will exhibit fewer depression symptoms (lower score on the MADRS) over 4-6 weeks.

Aim 3 (exploratory): Explore the extent to which ECN connectivity and behavior change correlates with other neural network and clinical change immediately post-treatment and one year later. Hypothesis: (3a) Pre/Post depression symptom change will correlate with pre/post cognitive control changes; (3b) Pre/Post connectivity changes in the ECN will correlate with connectivity changes in the Default Mode and Salience Networks using task and resting fMRI; (3c) Pre/Post change in cognitive control (e.g., ECN connectivity) will mediate one year change in depression and cognition.

Results of this study will help us understand the mechanisms that contribute to depressed mood and cognitive change in older adults with LLD.

2 GENERAL STUDY DESIGN

The design of this study will be a randomized two-group, pre-post test of CCR-EF and an active control group for older adults with LLD. Subjects will be blinded to group assignment. Treatment will last 6 weeks.

2.1 Study Changes Due to COVID-19

We originally planned for subjects to complete some of the study requirements at home and at our lab at UConn Health. Due to COVID-19, we then decided to administer all study visits and assessments (except the MRI) remotely. Due to the increase in vaccination, desire of participants to come in for in-person visits, and logistics of completing all visits remotely, we are planning to adopt a hybrid model of study visits. This will include a mix of remote and in-person visits.

We will continue to consent subjects remotely if needed or allow them to be consented in person. We will then arrange a visit where participants meet with study personnel to pick up a tablet to complete the intervention (e.g., our office at ASB). During this initial visit, we will complete half of the baseline cognitive evaluation that requires use of an iPad (NIH Toolbox). The remainder of the cognitive evaluation will be completed via webex. Following randomization, subjects will then have an in-person visit with Dr. Manning who will review the intervention procedures with them (this cannot occur prior to the completiton of cognitive testing, as subjects have yet to be randomized to treatment arm). Then, for the next six weeks, all study visits will be remote unless there is a need for an in-person visit (e.g., participant may have difficulty using the tablet). Following treatment, subjects will complete one half of the post-testing remotely, and when subjects return the tablet, they will complete the remianing NIH toolbox post-test in person. Social distancing will be maintained and both the subject and research assistant will wear PPE.

The procedure for consenting remotely is as follows:

- The HIPAA and consent forms will be mailed or emailed to the subject.
- After giving the subject time to read through the consent, study staff will set up a time to consent the subject by phone or Webex
- During the consenting, study staff will go through the HIPAA and consent forms with the subject, answer any questions, and direct the subject to sign the forms.
- Study staff will sign a copy of the consent form at the same time.

- The subject will mail, fax, or email a scanned copy of his/her signed documents back to study staff. The subject may also bring the signed documents when he/she comes to pick up the study materials. In this case the subject would be instructed to place the documents in the trunk of the car so study staff can take them when placing study materials in the trunk.

- Once received, study staff will join the subject's signed consent with the study staff signed consent, make a copy, and send it to the subject.

3 STUDY POPULATION

Following careful telephone screening entailing the Centers for Epidemiological Studies-Depression (CES-D R) scale, as well as other questions pertaining to eligibility, this study will enroll older depressed patients who will engage in cognitive training.

3.1 Inclusion / Exclusion Criteria

Inclusion criteria are: (1) age 60+; (2) ability to read and write in English; (3) must demonstrate adequate hearing (aided or unaided) during conversation; and (4) meet current criteria for major or mild depression (MADRS >=9) despite ongoing treatment. All participants will be under the care of a physician who prescribes medication for depression. No change to medications or treatment is required in order to participate in the current study. Only patients currently treated with therapeutic dosages (confirmed by Dr. Steffens) of a SSRI or SNRI antidepressant for at least 8 weeks will be included. Our experience indicates this is feasible; Dr. Steffens' R01 and the pilot study described above note 50% of LLD patients present as depressed despite being on stable antidepressants. We will ask that patients and their providers have no plan to change medication or dosages for the study duration unless required for clinical reasons. Should a medication change be required for clinical purposes during the course of the study, this will be coded for future analyses.

Exclusion criteria are: (1) active suicidal ideation at enrollment; (2) psychosis; (3) other psychiatric disorders (except personality and generalized anxiety disorders); (4) unstable / serious medical conditions as determined by study physician; (5) substance use disorders in the prior year; (6) diagnosis of dementia (determined by comprehensive neuropsychological assessment as detailed below, see cognitive classification section); (7) neurological disorders that may interfere with interpretation of MRI (e.g., brain injury with LOC > 30 minutes, brain tumors, demyelinating diseases); (8) any metal or bodily object that precludes MRI; and (9) corrected visual acuity < 20/70 or color blindness. We will allow subjects to participate in the brain training intervention who have had mild strokes deemed not to significantly interfere with cognition (based on clinical review). We will also allow those with symptoms of parkinson's disease to participate. See below for details on the protection of human subjects against worsening mood and suicidal ideation.

We will ask participants if they have someone who can be their study partner (e.g., friend, family neighbor) who will complete questionnaires regarding their opinion of the participant's everyday functioning and cognition. If they have someone who can fill this role, the research assistant will call their study partner to obtain their address or email and then either mail or email 2 questionnaires to be completed and sent back. These questionnaires can be completed together in approximately 10 minutes. Participants will not be excluded if they do not have a study partner.

3.1.1 Exclusion Criteria Related to MRI

For subjects who elect to have a MRI, the following conditions are exclusionary criteria for MRI: 1) metal objects in the body (pacemakers, cardiac defibrillator, cochlear/ear implants or implanted hearing

aid, insulin or infusion pump, magnetically-activated implant or device, neurostimulation system or any type of prosthesis, artificial or prosthetic limb; surgical metal; foreign body fragments), 2) prior history of working with metal shavings, 4) injury to the eye that involved metal, and 5) tattoos or permanent makeup/hair extensions/body piercing.

3.2 Study Enrollment Procedures at UConn Health

The study is a single-site prospective cohort study that will be performed at the UConn Health Center on Aging / Department of Psychiatry. Participants will be recruited from a variety of sources as described below. The PI (Manning) and Co-PI (Steffens) are investigators on other foundation and NIH funded studies investigating cognition and depression in older adults. The investigative team has the experience and means to recruit older adults with major depression. The sample will consist of **54** older adults with LLD recruited from the community and via referrals. Based on existing studies, we expect to commence treatment on 3 patients per month for 4.5 years. We allow for an attrition rate of ~10% based on our prior experience with LLD. 80% of subjects will undergo a one-year follow-up in 5 years. A subsample of participants will undergo MRI twice. This study will benefit from established recruitment, assessment, and retention strategies. Our experience with LLD treatment includes an ongoing naturalistic treatment study of 140 LLD who undergo annual cognitive assessments and MRI (Steffens R01MH096725).

Recruitment of subjects will be carried out by several mechanisms, Including:

A) Referral from the psychiatry outpatient clinic, the geriatric medicine clinic at UCHC, and geriatricians in the community. Additional recruitment methods will include community talks where participation in the research study will be offered; distribution of flyers to include community housing, churches, organizations, medical clinics, and community centers; and advertising in newspapers, magazines, UConn Health employee broadcast messages, and other print and electronic media (eg,. Mailer inserts, newspaper, web/online advertisements). The PI and co-investigator will also mention the research study to their clinical patients and other research subjects who appear to meet study criteria. The PI and co-investigator will hand potential subjects a flyer and describe requirements / answer questions regarding participation.

B) Finally, in addition to the methods listed above, we will use the Recruitment and Community Outreach Core of the UConn Center on Aging. The Core provides a centralized infrastructure for the recruitment of older research volunteers from the community. The Core holds a 26,000 name database that has permitted the successful completion of over 50 clinical studies involving older adults. The Core has been managed for over 10 years by Lisa Kenyon-Pesce, MPH, and Dr. Manning previously worked with Ms. Kenyon-Pesce to assist with recruitment of older adults for his Patterson Trust Award. Dr. Manning will work with Ms. Kenyon-Pesce to help maximize recruitment of minority participants.

4 STUDY ASSESSMENTS AND INTERVENTIONS

Table 1: Procedures
1. Phone Screen
2. Consent
3. Pre-treatment assessment
4. Pre-treatment MRI (subsample)
5. Randomization
6. Treatment/assessment (6 wks.)
7. Post-treatment assessment
8. Post-treatment MRI (subsample)
9. Clinical Follow-Up

4.1 Phone Screening

The research assistant / PI will conduct an informational interview and complete the CESD-R over the phone. Individuals who meet study criteria above and score $\geq$ 9 on the CESD-R (suggesting clinically significant depressive symptoms) will be invited to participate.

4.2 Other Procedures

The initial visit will begin with introductions, informed consent, an MRI Safety Screen for those who elect to undergo an MRI, and then follow

the procedures outlined in Table 1 and described below. All assessments and treatment visits will take place at UConn and conducted by the PI or trained research staff.

4.3 Consent

The research assistant / PI will complete the informed consent process with each subject and administer a consent comprehension questionnaire. Should any subject be unable to answer 4/5 questions (so a score of 3 or less), the consent process will be delayed until such time the consent can be reviewed again in the presence of both the subject and a friend/family member of the subject.

4.4 Measures

A summary of proposed measures are presented in Table 2. All subjects will complete a cognitive battery sensitive to subtle cognitive changes (see Table 2).

Baseline exam: Medical comorbidity will be recorded with the geriatric Cumulative Illness Rating Scale (CIRS) and will complete an in-house medical history questionnaire with subjects[3, 4]. Subjects will also complete sections of Duke Depression Evaluation Schedule (DDES)[5] assessing negative history of mania and possible anxiety. Clinicians will ascertain a history of psychosis. Clinical factors obtained pertaining to depression from a medical history questionnaire include age at first episode onset, single vs recurrent episodes, and current episode duration. History and adequacy of prior antidepressant treatment will be measured with the Antidepressant Treatment Form[6]. Prior or current experience with psychotherapy will also be recorded during clinical interview with the study psychiatrist. The Columbia Suicide Severity Rating Scale (C-SSRS) [7] will help ascertain current or prior suicidal ideation or attempts. An

Table 2: Overview of Assessment Measures

Domain	Measures	Pre	TX	Post	Q	1 YR
Biomarkers	TNFR1, TNFR2, IL-6, Beta-amyloid 40 and 42, Tau	X				
Clinical Exam	Medical Questions, DDES, C-SSRS	X				X
Depression	Montgomery Asberg Depression Rating Scale (MADRS), Antidepressant Form (baseline only), Carroll Brief Depression Rating Scale	X	X	X	X	X
Adverse Events	Suicidal Ideation (C-SSRS, MADRS), Other Worsening Symptoms	X	X	X	X	X
CN / MCI Classify	MMSE, Detailed battery (see Table 4), Dementia Severity Rating Scale (DSRS), FAQ, Olfaction from NIH Toolbox	X				X
Cognition: Main Outcomes	TMT AB (and B-A), Flanker Test Toolbox, CVLT Learning	X		X	X	X
Cognition: Exploratory Outcomes	NIH Toolbox Fluid Composite, PCET, PCPT, LNB	X		X		X
Questionnaires: Anhedonia / Apathy	Snaith-Hamilton Pleasure Scale, AMI , AES (will not be done during treatement),	X	X	X	X	X
Questionnaires: ER and Anxiety	ERQ, RRS, GAI	X	X	X	X	X
Questionnaires: Cognition	Memory Complaints	X		X	X	X
Other Questionnaires	NEO-N, AUDIT	X				X
fMRI	Resting State, Go/no-go, Reappraisal	X		X		
sMRI	WMH, Total Brain / Hippocampal Volume	X		X		
Treatment Motivation & Expectancy	Intrinsic Motivation Inventory/ Therapy Evaluation Form (Tx Expectation)	X	X	X		

CIRS=Cumulative Illness Rating; C-SSRS=Columbia Suicide Severity Rating Scale; DDES=Duke Depression Evaluation Scale; DRS=Dementia Rating Scale; ERQ=Emotion Regulation Questionnaire; HAM-A= Hamilton Anxiety Scale; PCET=Penn Conditional Exclusion Test; PCPT=Penn Continuous Performance Test; LNB= Letter N-Back; WMH=White Matter Hyperintensities. Q=Quarterly Post Treatment;

Table 3. Diagnostic Classification Scheme

	Intact Global Cognition	Intact Everyday Functioning	Cognitive Impairment
CN-LLD	Yes	Yes	No
MCI-LLD	Yes	Yes	Yes
Dementia*	No	No	Yes

*** Dementia patients excluded.**

optional blood draw for biomarkers will also be done at baseline.

Cognitive Classification: We will use a comprehensive cognitive battery and informant report to classify patients as cognitively normal (CN), mild cognitive impairment (MCI), or excluded due to dementia. This includes neuropsychological criteria recommended by Jak et al.[8] and informant report with the Dementia Severity Rating Scale (DSRS)[9-11]. The Jak criteria optimize reliability and sensitivity in detecting subtle cognitive weakness by defining "cognitive impairment" as at least two performances 1 SD below normed data in one cognitive domain (normative data will correct for education, age, and, when possible, sex and race). **It should be noted that this value used to defined MCI (-1 SD below mean) is on the low range of normal, so patients with MCI will have mild or very mild cognitive weaknesses. Dementia will be excluded**. Tests include measures from 5 domains as recommended by Jak et al.[8] (see Table 5). DSRS scores ≥ 11 demonstrate high specificity and sensitivity in distinguishing MCI from AD[12] [our sample of LLD patients have an average DSRS of 4.77 ± 4.66[13]]. Generally, patients who exhibit intact global cognitive functioning as determined by age and education Mini-Mental State Exam [MMSE] scores or the equilvanent Telephone Interview for Cognitive Status or TICS) [whereby a MMSE score can be derived), have no "cognitive impairment", and have a DSRS <11 will be considered CN. Participants will generally be considered to have MCI if they have intact global cognition, "cognitive impairment" in at least one cognitive domain, and a DSRS <11. **Patients with significant cognitive impairments, impaired global cognitive functioning, and a DSRS ≥ 11 will be excluded due to dementia (see Table 3).**

We will block randomize group assignment according to the presence of a MCI diagnosis. Exploratory analyses will also examine where MCI status moderates treatment outcome.

Depression severity: Depression severity will be measured with the MADRS[14], a 10-item clinician-rated instrument sensitive to treatment response and influenced little by medical illnesses[14, 15]. Scores range from 0-60; scores >15 reflect major depression of at least mild severity[1, 2], and <10 is commonly used to define remission[1]. Dr. Manning or the geriatric psychiatrist will administer the MADRS pre and post treatment, every week during treatment, and at quarterly and one year-follow-up. We will confirm inter-rater reliability before recruitment. During this same time frame, patients will also complete the Brief Carroll Rating Scale and the study psychiatrist will note if a subject has had a change in medication or dosage in the previous week.

Main Cognitive Outcomes: Time to complete Trail Making Part B is the primary cognitive function outcome measure. Weakness on this task of cognitive flexibility remains in older adults even when depression remits[17], and worse TMT B performance in LLD predicts a dementia diagnosis five years later[18]. Secondary analyses will explore the effect of the intervention on the Flanker Test and CVLT Learning (response inhibition and semantic organization). Exploratory analyses will examine the impact of the intervention on other toolbox measures of executive functioning, spatial memory, and processing speed (see Table 6) and computer measures of executive functioning. We will explore variables derived from these tests that further minimize speed demands (e.g., TMT B-A[19]).

Table 4: Cognitive Domains Assessed (Exam Lasts 90-105 minutes)

Memory	Attention	Language	Visuospatial	Executive Functioning
CVLT Trials 1-5 Total, LDFR	WAIS Digit Span	Boston Naming	Clock Drawing to Command and Copy	NIH Toolbox Dimensional Card Sorting Test
WMS-R Logical Memory (Immediate, LDFR)	TMT Part A Completion Time	Letter fluency FAS		TMT Part B Completion Time
NIH Toolbox Picture Sequence Memory Test	NIH Toolbox Processing Speed	Animal Naming	*Constructional Praxis CERAD*	*D-KEFS* Verbal Fluency Switching

Abbreviations: **Long Delay Free Recall (LDFR), California Verbal Learning Test (CVLT), Wechsler Memory Scale – Revised (WMS-R),Wechsler Adult Intelligence Scale, Trail Making Test (TMT), Delis Kaplan Executive Function System (*D-KEFS*)**

Outcome measures are listed below in Table 5, 6, and 7.

We will administer the Trail Making Test (oral and written versions), CVLT Learning, NIH Toolbox, WAIS Digit Span, Verbal Fluency (animal naming, FAS, Switching), and Auditory Consonant Trigrams.cognitive measures at pre-treatment and post-treatment and at one year. See Table 5.

Table 5. Main Cognitive Outcomes Administered Pre and Post Tx and One Year. (Total Admin Time = 10-15 minutes)	
Primary	**TMT-AB (5 min)**
Secondary	**NIH Toolbox Flanker Test / CVLT Learning Trials 1-5 (webex)**

In addition to those measures above in Table 5, we will administer fluid composite measures from the Toolbox. See Table 6.

Table 6. Additional Cognitive Outcomes Measured Pre and Post and One Year (Total Administration Time = 45 minutes)	
Secondary	**NIH Toolbox Fluid Composite (e.g., Dimensional Change Sorting, Flanker Test, Pattern Comparison Processing peed, Picture Sequence Memory), Digit Span (Forward, Backward, Ascending), Oral Trail Making Test, Letter Fluency (FAS), Animal Naming, DKEFS Verbal Fluency Switching, Auditory Consonant Trigrams.**

In addition to those measures mentioned above, we will record cognitive performance post-intervention every three months via telephone. See Table 7.

Table 7. Cognitive Outcomes Measured Quarterly (Total Administration Time = 15 minutes)	
Secondary	**Digit Span (Forward, Backward, Ascending), Oral Trail Making Test, Letter Fluency (FAS), Animal Naming, DKEFS Verbal Fluency Switching, Auditory Consonant Trigrams.**

Listing of all cognitive measures: Besides the TICS/MMSE and the cognitive measures listed in table above, we will also administer the 9-item NIH Toolbox Olfaction Identification Test, thought to be sensitive to early brain changes. For this smell identification task, participants are provided cards which they “scratch and sniff” and identify odors from multiple choice questions. They are also asked to identify whether they find the odor pleasant or unpleasant. We will administer tests of walking speed and grip strength to those subjects who come to an in person visit for MRI .We will also administer a language test from the NIH Toolbox (picture vocabulary) to serve as an estimate of intelligence. The language task from the NIH toolbox will only be measured at baseline.

Alternate forms: Will not be used in the current study as they do not eliminate practice effects and are of questionable equivalence (e.g., the reliability among alternate forms of the Trail Making Test was found to be below .60[20]). Instead, following procedures recommended by Goldberg et al.[21], we will attempt to reduce practice effects and achieve an asymptote in task-familiarity driven-gains by having participants complete the main outcome measure (Trail Making Test) twice in one day in the pre-baseline period of the trial. The intent is to use early repeated exposure to minimize error variance (issues of comprehension of instructions, strategy formation, and inefficient performance.)

Questionnaires: We will also administer self-report questionnaires of habitual reappraisal (Emotion Regulation Questionnaire or ERQ)[22], rumination (the Rumination Responses Scale or RRS), , personality (the NEO-N neuroticism scale), memory complaints (Memory Abilities Scale), childhood trauma (the 10-item Adverse Childhood Experiences Scale or ACES), alcohol use (AUDIT), treatment expectancy (Therapy Evaluation Form), and treatment motivation and engagement (Intrinsic Motivation Inventory or IMI)[32, 33]. The ACES is administered at baseline only. The NEO and AUDIT are administered annually. The Memory Abilities Scale is administered pre-treatment, post-treatment, and at quarterly and one-year follow-up. The ERQ and RRS are administered pre-treatment, middle of treatment, post-treatment, and at quarterly follow-ups. The IMI and Therapy Evaluation Form are administered weekly during treatment (not pre-treatment).

Anxiety / Anhedonia / Apathy: We will measure other symptoms potentially related to depression treatment response – anxiety, apathy, and anhedonia – with the Geriatric Anxiety Index and the Snaith Hamilton Pleasure Scale (SHAPS). We will also administer the AES and AMI. Future analyses may explore whether changes to ECN connectivity following treatment correlates with changes to the DMN and SN and respective clinical correlates (anxiety[24], apathy / anhedonia[25]). These measures will be administered 4 times (pre-treatment, week 3 [except AES], week 7 [post-treatment], quarterly, and annual follow-up).

Informant Report: Study partners will complete the Dementia Severity Rating Scale and Functional Activities Questionnaire (FAQ). These questionnaires can be completed together in ~10 minutes and will be administered annually.

Biomarkers: **There will be an optional blood draw (**approximately 4 – 6 teaspoons of blood**) at the baseline visit.** We will measure an array of protein biomarkers associated with inflammation (e.g., TNFR1, TNFR2, IL-6) as well as biomarkers potentially associated with neurodegeneration and Alzheimer's disease (e.g., beta-amyloid 40 and 42, tau) . These protein biomarkers will be measured using a multiplex assay at Dr. Diniz lab at UCHC. Given the exploratory nature of these analyses, and lack of clear understa**nding of the clinical value of t**hese plasma markers, results will not be shared with participants. We will ask participants for permission to use the blood samples collected from this present study for other future research projects studying mental health, depression, cognition, biomarkers, and genetics in the elderly. If they agree by initialing their preference on the consent, participants' samples could be used for studies going on now as well as studies that are conducted up to 25 years from now.

*For participants enrolled in other studies in the Mood, Cognition and Aging Research program who have been tested within 1 year of this study's baseline visit, we may use the other study's data for assessments that the studies share.

One Year Follow-up: All participants will be re-examined at one year post-treatment using the procedures described above. Intervening treatment history will be recorded.

Note: As of 7/31/2024, subjects enrolled into the study will not be able to complete any follow-up testing timepoints before the study end date. Therefore, study procedures for subjects enrolled after 7/31/2024 will not include the quarterly or One Year Follow-up timepoints.

Beginning in October 2023, an emphasis was placed on using study personnel time to recruit new participants for the project as the project suffered from low recruitment. The goal was to obtain at least one-year follow-up data on participants with an anticipated one-year no-cost extension. However, the one-year NCE was not deemed feasible due to K23 requirements to maintain 75% salary support for the PI. The project is therefore coming to an end and these data will not be collected on participants who are in the follow-up phase of the study as of November 1, 2024.

Study personnel will contact these participants and utilize an IRB-approved script to inform them that they will not have any further follow-up testing visits. The participants will have a chance to ask questions and discuss their available cognitive test results with the PI if they so choose.

Acquisition of Structural and Functional MRI: MRI scans will be performed at UConn Health using the 3T GE magnet. Scanning time lasts ~60 minutes. Dr. Manning and Dr. Lihong Wang will be responsible for data acquisition with the assistance of MRI technicians. T1-weighted, resting-state and task-related fMRI, T2-weighted, fluid-attenuated inversion recovery (FLAIR) and diffusion-tensor images (DTI) will be acquired using parameters described in the Table above. FEAT (FMRI Expert Analysis Tool) Version 5.98, part of the FSL analysis package (FMRIB's Software Library) will be used to conduct standard pre-processing procedures (see Table). During an 8-min resting state scan, participants are instructed to rest and focus on a centered cross.

	T1-weighted imaging	Resting State & Task-related fMRI	3D T2 FLAIR	DTI
Data acquisition parameters	TR/TE=2200/2.8ms Flip angle=13° Matrix=256×256×169 Voxelsize=1×1×1mm³	EPI sequence, FOV=240mm, Flip angle=90°, TR/TE=2000/31ms Matrix=64×64×34 Voxelsize=3.8×3.8×3.75mm³	TR/TE=4500/308ms TI=1800ms, Flip angle=120°, Voxelsize=0.5×0.5×1mm³	EPI sequence, 64 directions, FOV=240mm, Flip angle =78°, TR/TE=4770/125ms, B0=1000 Voxelsize=2×2×2mm³
Imaging measurements	Brain Volume & Voxel-based morphometry	Task activation, ALFF, ICA FC/PPI, graph theory	WMH volume & regional volume	FA, MD, graph theory
Data preprocessing & data analysis programs	Freesurfer & VBM https://surfer.nmr.mgh.harvard.edu/fslwiki	FSL FEAT, DPARSF, Conn, GIFT, Grenta http://rfmri.org/dpabi https://fsl.fmrib.ox.ac.uk/fslwiki	LGA of LST http://www.statistical-modelling.de/lst.html	DTI Studio, BEDPOSTX, Gretna, www.mristudio.org/wiki/user_manual/dtistudio Fsl.fmrib.ox.ac.uk/fsl/fslwiki/FDT

Functional MRI Tasks: Participants will complete three fMRI tasks: 1) a test of response inhibition, 2) a test of reappraisal, and a test of reward sensitivity (of "liking"). Tasks were selected based on their clinical relevance and their ability to reliably probe cognitive control regions and reward regions. Stimuli are presented using E-Prime. The first task is a go/no-go task. Participants are asked to respond as quickly and accurately as possible with a button press when they see the letter X (=go; 412 trials) but refrain from pressing the spacebar when they see the letter K (=no-go; 78 trials). Correct hits are defined as "go" ('X' stimuli) trials that are followed by a button press within 1000 ms of stimulus onset. Correctly rejected "no-go" trials ('K' stimuli) are determined by the absence of a motor response within 1000ms of the no-go stimulus. No-go trials followed by a button press within 1000ms of stimulus onset are false alarms. Based upon Pearlson's prior work with this task[26], correct hits are treated as a baseline condition on which to compare correctly rejected (no-go) events allowing the examination of positively reinforcing events specific to motor inhibition; thus, the comparison of interest will be correct rejections events versus hits, a contrast that reveals activation in the DLPFC, VLPFC, and other ECN regions in healthy adults[26]. The task lasts 8 min.

The second task is a measure of reappraisal in which participants are asked to view emotional information and alter their way of thinking about that information. Participants will be instructed on the use of reappraisal strategies for 20 minutes prior to the MRI. Individuals are trained to imagine that the situation being depicted had a better or different outcome than the one suggested[27, 28]. Alternatively, on attend trials, participants are instructed to maintain their attention to the picture without changing their affective experience. Participants view a sequence of 72 emotionally positive, 72 neutral, and 72 emotionally negative pictures. Each image is presented for 10 seconds. Participants next judge whether the image is positive, negative, or neutral. The task has two 8-minute runs. The primary comparison of interest is "decrease" when presented with a negative image vs "maintain" when presented with a negative image. This contrast allows for comparison of actively attempting to regulate a negative experience with passively viewing a negative experience; as such, activation in the DLPFC and VLPFC, as well as other ECN regions (e.g., posterior parietal) in healthy adults[29].

The third task is a Card Guessing Task (Sensitivity to Reward or Liking) where subjects guess whether the value of the card is higher or lower than 5. The card value then shown and followed by reward (add money), punishment (deduct money), or neutral (no change).

Neuroimaging Data Analysis. Dr. Manning and the imaging analysis team will be blinded to intervention condition. *Task-related fMRI:* We will first conduct whole-brain voxelwise data-analyses to understand whether our hypothesized brain regions/neural pathways are possible treatment targets in LLD. Pre-processing (including slice-timing correction, realignment, co-registration, high frequency filtering, segmentation, normalization, and 8mm^3 kernel smoothness) will be conducted using FSL FEAT. Individual level analysis for each task condition will also be conducted using FSL FEAT FMRIB's Improved Linear Model (FILM).

Within and between network connectivity using Independent Component Analysis (ICA): We will conduct group ICA on the two task-related and the resting state fMRI data to examine functional connectivity within and between ECN, DMN, and SN (including dACC, insula, and amygdala) using the Group ICA for fMRI Toolbox (GIFT) following Calhoun's methodology[30]. Briefly, we will temporally combine all resting-state and task-related data of all subjects followed by a group-level dimensionality reduction using Principal Component analyses. We will then run FastICA to obtain spatially-independent components. We will perform a spatial template matching procedure using the templates of ECN, DMN, and SN provided by Shirer et al.[109] and significant clusters of the amygdala in response to maintaining negative affect to identify components of ECN, DMN and SN. Then we will perform back reconstruction of individual subjects' time courses and spatial maps as outputs. Functional network connectivity (FNC) analyses will be performed using the FNC Toolbox which is an add-on to the GIFT software. The toolbox computes a constrained maximal lag correlation between each pair of networks of interest by calculating Pearson's correlation and constraining the lag between the time courses[31]. In addition to these primary analyses, we will also conduct supplementary ROI-to-voxel PPI analyses to examine treatment changes in regional functional connectivity.

Covariates: *Medical Comorbidity:* Scores on the geriatric Cumulative Illness Rating Scale (CIRS), completed by the study geropsychiatrist will be used as a covariate. *Brain volumes:* T1 imaging total and regional brain volumes (specifically our targeted ROI regions) will be analyzed with Freesurfer and measured using standard procedures. The results will be reviewed and any errors will be corrected manually. *Hyperintensities:* we will use the Lesion Segmentation Tool (LST) program with lesion growth algorithm[93] to segment white matter hyperintensity (WMH) volume from T2 FLAIR images. Total brain and WMH volume will be covariates. We will compare hippocampal and ROI volumes with total brain volume to determine the most influential covariate.

4.5 Interventions

Intervention Computerized Cognitive Remediation of Executive Functioning (CCR-EF): The intervention procedure replicates Morimoto et al.[32, 33]. Participants are asked to complete approximately 28-42 hours of computerized brain training over 4-6 weeks. We are asking participants to complete at an hour a day for everyday. Research staff will be in close weekly contact with participants to provide instruction on accessing the interventions and provide guidance.

Training initially involves 10 hours of processing speed exercises from "Brain HQ", a program that enhances processing of visual and auditory stimuli. We use 3 exercises (auditory tone sweep, visual processing [Double Decision], visual sweep). Following the 8-10 hours of Brain HQ, participants complete 8-10 hours of "Ultimate Word Master" before completing 16-20 hours of "Neurogrow" (formerly called "Catch the Ball").

Ultimate Word Master (UWM) (*Individually titrated training in recognition and initiation of semantic strategy*): Guided by our work suggesting that semantic strategy predicts antidepressant treatment response[3, 4], UWM trains participants to reorganize verbal material. Participants are asked to rearrange multiple, increasingly complex word lists into categories with individually titrated decreases in processing time. Cognitive demands are increased further by including components of "cognitive control"; using previous sort stimuli as proactive interference.

Neurogrow (NG) *(Individually titrated training in visual attention, inhibition of prepotent responses, working memory, cognitive flexibility and dual task performance.* [32, 33]*):* Participants view flower pots on

a screen and are instructed to press the button when the target watering can appears with the target flower. Flowers change from target to foil color (blue, white, pink) at random intervals (1.5-3.5 sec). NG begins at the easiest level (one flower; one can) and the slowest speed (visual attention). The exercise progresses in three ways: Speed, difficulty level, and layered cognitive control functions. After five correct targets, speed increases by 10%; five correct at the fastest speed moves the user to the next level (graduation). If the user becomes "stuck" at the same speed and accuracy level (plateau), NG moves to the next task. The next level begins at 50% of the speed achieved at the previous level. At the most difficult level, a dual-task (divided attention) dimension is added with multiple targets on the screen, each with their own history (working memory) and set (cognitive control function) presented for response from the user. Further working memory demands are increased as visual cues (color/ weather/shape) are systematically and adaptively removed and of rules participants must remember and respond.

Intervention Active Control: Control training will match CCR-EF for training time, audiovisual presentation, and computer use. Our control training follows general physician recommendations for cognitive fitness and is based off of several other CCR studies to keep participants blind to their group assignment[34-36]. Patients in the active control arm will complete three activities according to a standard protocol: 1) play a visuospatially oriented computer game (Myst), 2) watch computer-based educational programs on art, history, literature, and 3) play computer games online through the Brain HQ platform; games include crossword puzzles, soduko, paddleboard, and word search. Participants will complete a total of 32-42 hours of training over 4-6 weeks. Time spent on each task will be evenly divided (15 minutes of each task everday).

Treatment Engagement: We will follow empirically based recommendations[37, 38] to maximize treatment motivation: 1) Make the value of training obvious and personalized to the individual, and 2) Help subjects personalize and gain autonomy over the training. Prior to randomization, the PI will meet with each participant individually, assist the participant in generating goals for participation (e.g., reduce depression, improve concentration), and discuss how (broadly defined) cognitive stimulation can assist in obtaining those goals. During treatment, the PI will meet with participants every week to provide positive reinforcement (by reviewing progress in either treatment arm) and provide psychoeducation on the benefits of cognitive fitness and brain health. Each weekly meeting with the PI lasts 25-45 minutes.

The PI will use a standardized script to minimize threats to validity when providing reinforcement and use a standardized presentation on cognitive fitness/brain health. Participants will complete the Therapy Evaluation Form, a treatment expectancy questionnaire, and the Intrinsic Motivation Inventory or IMI[32, 33], a treatment motivation and engagement questionnaire. Responses indicating low engagement on the IMI will generate a discussion to increase participant treatment engagement. The PI will always be available for questions when patients undergo training. This and similar methods worked well in maintaining adherence in the UConn pilot (82%), Morimoto pilot (82%)[33], and Morimoto K (91%)[39].

Handling of Worsening Depression, Change in Medication, and Drop Outs: We do not expect many participants to require a change in medication during the 4-6 week trial (e.g., 30/30 subjects remained on the same dosage during a prior study of CCR-EF)[39]. Please see below for details on how worsening mood, SI, and drop-outs will be handled.

5 PROTECTION OF HUMAN SUBJECTS

Human Subjects Involvement, Characteristics, and Design

The primary purpose of this study is to examine whether computerized cognitive remediation of executive functioning (CCR-EF) can improve cognitive control processes (measured with behavioral assessments and MRI) compared to an active control intervention, and determine whether changes to cognitive control are associated with depression symptom and cognitive change in late-life depression (LLD).

We will recruit 54 adults age 60+ with symptomatic unipolar mild or major depression. A subsample of participants will undergo MRI pre and post treatment.

A HIPAA waiver will be obtained from the IRB to collect personal information over the telephone. Following a phone screen, participants will be asked to attend an in-person study visit where they will provide informed consent and undergo: 1) a medical history review with a geriatric psychiatrist, and 2) a structured interview to ascertain relevant psychiatric history (including current and lifetime suicidal behavior). Participants who are not actively suicidal (see exclusion criteria) will then undergo a cognitive evaluation before being randomized to either treatment with CCR-EF or a control intervention for 4-6 weeks. Participants' depression symptoms, potential suicidal ideation, and cognitive functioning will monitored over the course of the 4-6 week trial. We will ask that all participants return for one clinical visit one year later.

Inclusion/Exclusion Criteria

Participants will be 60 years of age or older with the ability to read and write in English and meet current criteria for mild or major depression (MADRS >=9) despite ongoing treatment. Only patients who are currently treated with therapeutic dosages (confirmed by Dr. Steffens) of a SSRI or SNRI antidepressant for at least 8 weeks will be included. We will obtain consent from patients to communicate with their prescribing providers, and also ask that patients and their providers have no plan to change medication or dosages for the duration of the study unless required by significant worsening of clinical symptoms.

Exclusion criteria are: (1) current major depression with psychotic features; (2) active suicidal ideation at the time of enrollment (e.g., 4 or more on the MADRS [meaning suicide is being considered]); (3) bipolar and other psychiatric disorders (except personality disorders and generalized anxiety disorder); (4) alcohol use or other substance use disorders in the prior year; (4) clinical diagnosis of dementia (determined by comprehensive neuropsychological assessment and neurologist consensus); (5) neurological disorders (e.g., stroke, epilepsy, brain injury with LOC > 30 minutes, brain tumors, demyelinating diseases); (6) any metal or bodily object that precludes MRI; and (7) corrected visual acuity < 20/70 or color blindness.

While dementia is an exclusionary criterion, patients with mild cognitive impairment (MCI) will be included.

Rationale for Inclusion/Exclusion Criteria

Emphasis on Persistent Depression Symptoms Despite Treatment:

Our target participant is an adult age 60+ with symptomatic depression symptoms despite adequate treatment with an antidepressant for at least 8 weeks. Only patients who are currently treated with therapeutic dosages (confirmed by Dr. Steffens) of a SSRI or SNRI antidepressant for at least 8 weeks will be included. Specific medications and exact dosages will be recorded for examination of their potential influence on outcomes.

We include only treatment resistant patients for three main reasons:

1. Risk of Cognitive Decline. Patients with persistent depression symptoms despite adequate treatment may have an especially high risk of cognitive decline and neurodegeneration[40, 41].
2. Balanced Research Design. The inclusion of patients already on medications will balance potential pharmacotherapy effects on neuroimaging and clinical outcomes.
3. Gold standard of treatment. All patients enter the study already engaged with a treatment provider and are already taking the gold standard of treatment for major depression (antidepressants).

Why use such a comprehensive approach to defining Mild Cognitive Impairment (MCI)?

We use a comprehensive neuropsychological battery and informant report to classify participants as cognitively normal, mild cognitive impairment, or excluded due to dementia (we exclude dementia as these patients are unlikely to benefit from the cognitive remediation intervention). We elected to use these detail procedures to define MCI rather than screening tests for several reasons:

- This is a sensitive method to detect subtle cognitive weaknesses associated with neurodegeneration and cerebrovascular disease (as evidenced by our pilot data and prior studies).
- This comprehensive approach enables us to characterize cognitive functioning using both continuous outcomes and categorical diagnoses. Stratifying the sample by the presence or absence of MCI will help ensure the treatment arms are balanced in terms of overall cognitive functioning. Using continuous cognitive measures as outcomes will increase our sensitivity in detecting treatment effects.

Why not include only patients with Mild Cognitive Impairment?
Considering computerized cognitive remediation appears to be most effective in patients with cognitive impairment, it could be argued that only patients with MCI should be included in the current study. However, we elected to include patients with and without MCI in the current study. Our rationale for doing so includes:

- Limiting enrollment to only LLD-MCI patients would exclude LLD patients who have subtle cognitive difficulties that do not meet diagnostic criteria for MCI (e.g., impairment on only test of executive functioning). These patients may still benefit from the treatment.
- The use of a large sample (see power analysis for sample size determination) allows for exploratory moderator analyses. It is unclear how exactly MCI status in LLD will influence cognitive remediation treatment. We will be able to answer this question with the proposed study.

6 RECRUITMENT AND INFORMED CONSENT:

All research staff will be CITI certified in Humans Subjects Research training.

Participants will be recruited from various sources (community, prior research studies, Center on Aging) to participate in the study. We will recruit subjects for all groups from other Mood, Cognition, and Aging Research program's studies and with media advertisements (print media such as newspapers and brochures and social media such as Twitter, Facebook, and the Hartford Courant).

We will use a paid service of an advertisement company, Trial Partners (www.trialpartners.co), to improve the exposure of our social media ads to the targeted study population. They work by placing the IRB approved flyers on social media platforms (e.g., Facebook, Instagram, Twitter, Reddit, Snapchat, Google ads, among others), targeting the specific demographic groups target in our study in specific geographical regions (i.e., Connecticut). The company or any of their representatives will not have any direct contact with the potential participants nor serve as intermediaries for any data collection related to the study, including the pre-screening or screening for study eligibility. Potential participants who express interest in the study by responding to the advertised contact information/research registries will complete the pre-screen questions with a research staff over the phone.

Other recruitment methods include advertising this study, along with other studies in the Mood, Cognition, and Aging Research program, in a newsletter that will be mailed to current research subjects and those in the UConn Center on Aging volunteer registry. The newsletter will also be placed in UConn Health clinics and in the community and will be on UConn Health Psychiatry website.

Letters with information about studies in the Mood, Cognition, and Aging Research program, will be mailed from PI's of other UConn Health studies to their subjects who agreed to receive information about other studies.

We will also deliver flyers to UConn Health clinic staff who will hand out flyers when patients check in. If necessary, clinic staff will direct patients who ask for additional information to call research staff listed on

the flyer. We will discuss this recruitment method with clinic managers and have their approval prior to delivering flyers to any clinic staff.

During the recruitment period, a recruitment message to be sent through the UConn Health My Chart patient portal to individuals ages 60 and older who have depression diagnoses. The message will give individuals give the option to select "I'm Interested" or "Decline". If "I'm Interested" is selected, study staff will receive the contact information and call the individual.

Informed consent will take place in a private room. Written informed consent will be obtained from all participants by a trained project staff member in accordance with UCHC IRB guidelines. Participants will be informed that they may take as much time as they wish to make a decision regarding participation. They will be offered ample opportunity to ask questions and seek clarification. Prior to consent is signed, consent comprehension questions will be administered to the participant (to ensure capacity for informed consent and a complete understanding of the study procedures). Upon signing consent, a copy of the consent form will be given to the participants.

Participants will be informed that participation is voluntary, that they may withdraw at any time, and that their refusal to participate will not result in any penalties whatsoever. During the informed consent process, staff will review privacy protections, including information regarding the confidential nature of study participation and that no information about participants will be given to anyone (to the extent permitted by law) without a signed release. The consent process also includes an explanation of the limits of confidentiality—specifically as it relates to mandated reporting of abuse or neglect in vulnerable populations and in regard to suicidal/homicidal ideation.

We will obtain consent from patients to communicate with their prescribing providers. We will also obtain consent to contact a friend or family member should we be unable to reach a participant. The patients' prescribing providers will be contacted in the event of worsening mood and/or suicidal behavior as described further below. If confidentiality must be broken for mandated reporting reasons, participants will be informed that this will be done. They will be invited to be present when the mandated reporting occurs, whenever possible. For the safety and supervision of the staff, any reports will be done at the lab offices under the supervision of Dr. Steffens. We will create written protocols for handling mandated reporting and clinical emergencies within research contexts, and manualized guidelines and scripts for mandated reporting. Clinical oversight will be provided by PI Dr. Manning and Dr. Steffens.

7 SAFETY

Overview of Potential Risks to Human Subjects

There are risks associated with participation. They include:

- **Worsening Mood.**
  - We are including patients with persistent depression symptoms despite evidence of adequate treatment with antidepressants. Patients may experience a worsening of their mood symptoms.
- **Suicidal Behavior.**
  - Patients' illness (major depression) and clinical characteristics (age, cognitive weakness) increase the likelihood of suicidal ideation and even suicide attempts. The risk of suicide is due to the nature of the population being studied (geriatric depression with potential cognitive weaknesses) not participation in the study
- **Emotional Distress.**

- Consistent with the clinical evaluation process, there may be temporary emotional distress during the interview regarding psychiatric history and depression symptoms.

- **Boredom.**
  - Participants may be bored or frustrated with the intervention procedures or cognitive exam, but there is no physical risk as a result of this treatment / assessment.
- **Claustrophobia.**
  - With MRI, there is a risk of discomfort due to claustrophobia.
- **Loss of Confidentiality.**
  - There is a slight risk of breach of confidentiality of research data.

Protections Against Risks to Human Subjects

- **Worsening Mood.** Worsening depression or anxiety (measured with the MADRS and GAI) in the 6-week trial will result in:
  - Immediate updates to the patient's psychiatric medicine prescriber.
  - Case review by the study team (the study psychiatrist, the PI Dr. Manning [a clinical psychologist], and primary mentor [Dr. Steffens, geriatric psychiatrist]).
  - Significant mood and/or anxiety worsening (as determined by the patient's psychiatric medicine prescriber with input from the study team) will result in appropriate clinical action (e.g., change in medication dosage).
    - For patients who require a change in antidepressant medication or dosage, this will be coded and used as a covariate in data analyses.

- **Suicidal Behavior.** Detection of suicidal ideation will be taken very seriously. Participants will complete: 1) a baseline structured interview regarding current and past suicidal behavior using the Columbia Suicide Severity Rating Scale (C-SSRS) and MADRS, and 2) a weekly structured interview with the MADRS assessing depression symptoms (including potential suicidal ideation). The C-SSRS is designed to distinguish the domains of suicidal ideation and suicidal behavior. Four constructs are measured: 1) Severity of ideation rated on a 5-point ordinal scale in which 1 = wish to be dead, 2 = nonspecific suicidal thoughts, 3 = suicidal thoughts with methods, 4 = suicidal intent, and 5 = suicidal intent with plan, 2) Intensity of ideation subscale comprised of five items (frequency, duration, controllability, deterrents, and reason for ideation); 3) Behavior subscale, which is rated on a nominal scale that includes actual, aborted, and interrupted attempts; preparatory behavior; and non-suicidal self-injurious behavior, and 4) Lethality subscale, which assesses lethality and potential lethality of actual attempts.
  - Active suicidal ideation at baseline is an exclusionary criterion (i.e., score ≥ 2 on the C-SSRS severity of ideation scale, or ≥ 4 or more on the MADRS item #10 [meaning suicide is being considered]). These patients be will referred for more intensive treatment (see below).
  - During the study, the reporting of any suicidal ideation (i.e., score 2 or more on the on the MADRS item #10 [meaning the presence of fleeting suicidal thoughts]) will result in:
    1. Reporting to the patient's psychiatric medicine prescriber.
    2. Case review and formulation of a plan by the study team (study psychiatrist, the PI Dr. Manning, and primary mentor Dr. Steffens). The plan may include ongoing monitoring or more intensive treatment (e.g., hospitalization).
  - We are aware that as the study group ages; it is likely that the risk for suicidal ideation and even for completed suicide will increase. With this in mind, we will maintain a higher level of vigilance for suicidal ideation. Patients with missed appointments will be called within 24 hours by the study staff in order to reschedule and find out the reason for the missed appointment. If the reason for the missed appointment is more serious than the patient forgetting the appointment, having a physical illness, weather-related concerns, or similar reasons, Dr. Manning will ascertain if there has been any exacerbation of depressive

symptoms or new onset of suicidal ideation (see points above for how this will be handled). Should the participant report suicidal ideation to Dr. Manning over the phone that is high-risk (i.e., intent or plan to attempt suicide), Dr. Manning will advise the patient to come into the ER.

- **Psychological harm.** Risks to participants are minimized by placing strong emphasis on building relationships with participants that facilitate open communication. At the beginning of the visit, participants will be informed that they may take a break as needed or skip questions that make them feel uncomfortable or that they wish not to answer for any reason. Ample time for breaks and appropriate snacks will be provided. Dr. Manning's supervision of the research fellow will address how to identify and respond to participant distress and when additional clinical supports may be needed. We will also take substantial effort to ensure that any clinical matters that arise will be handled appropriately. PI Manning, a licensed clinical psychologist with extensive experience conducting clinical assessments with older adults, will also be available to address problems.

All research staff involved in patient contact are experienced research assistants or medical professionals who are regularly involved in clinical care or other clinical-research protocols. The research assistants have been previously trained by Dr. Steffens to work with older adults with major depressive disorder (MDD). This involves educating staff on the symptoms of MDD including symptoms that may contribute to discomfort / emotional distress (e.g., irritability, low frustration tolerance). Staff are all trained to interact with patients in a caring and considerate manner and contact the PI or a study MD to speak with anyone who in the unlikely event experiences more than mild distress during assessments. Should any new staff join the study they too will undergo the same training.

- **Potential Risks of Phlebotomy** include some mild discomfort. In addition, about 0.5% of people develop a bruise larger than the size of a quarter at the needle site, and about 2% report dizziness after the blood is drawn. The risk of infection is rare, significantly less than 1%.

- **Confidentiality.** The research data files will not contain identifying information about the participants. Data protection measures used in this study are rigorous (see Sources of Materials section below). Each participant will be assigned a unique identification number that will be included on the questionnaires, biomarker samples, and electronic data files. Only authorized research staff will have access to the password-protected file linking the participants' identity with the anonymous code, which will be kept electronically on a secure network in the UConn Health Department of Psychiatry.

  Biomarkers samples (plasma, buffy coat) will be processed and stored at the lab of Dr. Breno Diniz, M.D., Associate Professor in the Center on Aging. Dr. Diniz's lab is located on the third floor of the main hospital building. The biomarkers samples will be stripped of any personal identification and they will identified by the participant ID number. The data generated by the laboratory analysis (values for the individual biomarkers and the SASP index) will also only include the participant ID.

- **Claustrophobia.** We will explain the risk of claustrophobia in advance, and encourage MRI participation in only those patients who do not report experiencing claustrophobia.

Incidental Findings (including MRI)

It is possible that subjects will present with laboratory abnormalities or vital sign irregularities needing further evaluation. MRI brain scans are reviewed formally by a radiologist at UConn Health. Rarely, incidental findings are found on brain MRI scans and in this age group include small benign tumors (e.g., meningiomas) and lacunar infarcts. We will discuss these findings with subjects immediately following receipt from Radiology. In this instance, Dr. Steffens (primary mentor and geriatric psychiatrist) will telephone participants. With the subject's permission, he may discuss results with a subject's family member. Dr. Steffens will also seek permission to provide these results to the subject's

primary care provider. He may also suggest that the subject seek further evaluation with a neurologist. If the subject chooses to pursue such an evaluation, permission will be obtained to provide the specialist with results of the MRI.

Patients not enrolled due to acute medical or psychiatric reasons:
All patients will have a medical provider who follows the patient for psychiatric care (i.e., prescribes antidepressants). In addition, all participants will undergo a medical examination and review of medical history with a study physician or APRN. We will exclude individuals who are medically unstable or who are in the midst of a serious/life-threatening illness, e.g., undergoing treatment for cancer or another acute condition. In this instance:

- The patient's psychiatric medicine prescriber will be alerted. In discussion with this provider, the study psychiatrist (or treatment provider) will make an appropriate referral. Following medical stabilization, and should they continue to meet eligibility, the patient will be invited to participate.

Patients who do not meet eligibility requirements due to psychiatric reasons (e.g., depression symptoms not meeting criteria for major depression, history of mania) will be referred back to their psychiatric medicine prescriber. The provider will be alerted as to the patient's continued symptom reporting. Additional suggestions for treatment will be offered.

Active suicidal ideation at baseline is an exclusionary criterion (i.e., score ≥ 2 on the C-SSRS severity of ideation scale, or ≥ 4 or more on the MADRS [meaning suicide is being considered]). In the event of active suicidal ideation detected at the baseline assessment, the following will occur:

1. Reporting to the patient's psychiatric medicine prescriber. In conjunction with the patient's provider, the study team (study psychiatrist, the PI Dr. Manning, and primary mentor Dr. Steffens) may recommend more intensive treatment (e.g., hospitalization).

Patients who are actively suicidal at baseline will be given the chance to participate once their suicidal ideation has subsided (should they continue to meet other criteria).

Drop Outs or Non-Compliance
We have maintained a high adherence rate (82%) for our pilot study. This is similar to other studies using this intervention (81-92%). We therefore do not expect a significant drop-out rate. We will record the reasons that any participant leaves treatment or the larger study.

- For participants who leave or are non-compliant with treatment (meaning they are not presenting to complete the interventions), with their permission we will ask them to complete subsequent assessments and recommend additional treatment as appropriate (see above).
- For participants who leave the study, their data will be retained and used in intent-to-treat analyses.

Recommendations for Patients Following Participation
Participants' mood and cognitive findings will be reviewed with participants and will be sent to their clinical providers to help with continued care. Appropriate treatment recommendations will also be discussed. This will occur immediately post-treatment and at one-year follow-up.

8 SOURCES OF MATERIALS

Research data will be obtained from LLD participants. Structural and functional MRI data will be obtained. All other data will be obtained from self-report, interview, and cognitive testing. This will include protected health information (PHI), including the participant's psychiatric and medical history. Confidentiality of study participants will be protected by utilizing the following methods to secure all records and clinical data. All research data will be coded with an ID number in place of subject names and stored securely, separate from files containing identifying information. Information linking participant identifying information with IDs, and any other electronic files containing identifiable information, will be stored on the Psychiatry Department's secure server in a password-protected log,

with access limited to key research staff. Hard copies of assessment data, identified only by code number, will be stored securely in locked offices and/or filing cabinets located in the Department of Psychiatry accessible only to members of the study team. Consent forms, which contain patients' names, will be kept in a locked cabinet in a locked office. Participants' identities will not be revealed in the presentation or publication of any result from this project. All project staff will be educated about the importance of strictly protecting participants' rights to confidentiality.

The cognitive testing program used for this study ("NIH Toolbox") calculates age-based outcome scores using participants' DOB. To maintain confidentiality, we will only enter the participants' age, not the DOB, to be used for these calculations. Research staff deleted all DOB's in the program. Going forward the PI will check the program and verify that no DOB's have been entered and only participants' ages are used.

9 POTENTIAL BENEFITS TO SUBJECTS

The overall benefit is an increase in understanding of the clinical and biologic mechanisms of depression in late life. The studies themselves in some subjects may uncover potential medical problems of relevance to their treatment. Access to geriatric psychiatrists and psychologists will benefit depressed subjects. The risks to the subjects, as discussed above, are minimal.

10 IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

This study will determine whether a novel behavioral treatment can modify mechanisms thought to be important in perpetuating major depression in the elderly. The study may also lead to additional knowledge about the pathophysiologic processes in late-life depression and how those processes relate to depression symptoms. This knowledge will inform our treatment of late-life depression and potentially identify new treatment targets.

11 DATA AND SAFETY MONITORING PLAN

The study will employ a Data and Safety Monitoring Board (DSMB). The DSMB will review the protocol for any major concern prior to implementation. During the trial, the DSMB will review the cumulative study data to evaluate overall study operations, safety, and scientific validity and integrity of the trial.

Items to be reviewed by the DSMB include:

- Interim/cumulative data for evidence of study-related adverse events;
- Interim/cumulative data for evidence of efficacy according to pre-established statistical guidelines, if appropriate;
- Data quality, completeness, and timeliness;
- Adequacy of compliance with goals for recruitment and retention, including those related to the participation of women and minorities;
- Adherence to the protocol;
- Factors that might affect the study outcome or compromise the confidentiality of the trial data (such as protocol violations, unmasking, etc.); and,
- Factors external to the study such as scientific or therapeutic developments that may impact participant safety or the ethics of the study.

Frequency of DSMB meetings:

- One initial meeting prior to the start of the trial.

- Thereafter, the DSMB will meet twice a year.

DSMB members will consist of experts in geriatrics, clinical trials, and biostatistics. No member of the DSMB will have direct involvement in the conduct of the study. Members will include:

- George Kuchel, M.D., FRCP, AGSF; Professor and Travelers Chair in Geriatrics and Gerontology, University of Connecticut School of Medicine, and Director, UConn Center on Aging
- Jonathan M. Covault, M.D., Ph.D; Professor of Psychiatry, University of Connecticut School of Medicine
- Grace Chan, Ph.D., Assistant Professor of Psychiatry, University of Connecticut School of Medicine

The DSMB will conclude each review with their recommendations to the PI, Dr. Steffens, and (the NIMH if needed) as to whether the study should continue without change, be modified, or be terminated.

Additional Safety Monitoring:

- In addition to the review by the DSMB, Dr. Manning and Dr. Steffens will review aggregate data on enrollment and adverse events at least monthly to assure there are no side effects occurring more frequently or more severely than would be expected. We will follow the UCHC IRB policy for Prompt Reporting of Problems or Adverse Events to the IRB and also assure that reportable adverse events are reported to NIH.

- Dr. Manning will provide the NIMH with a summary report on the DSM plan (including DSMB recommendations) with the annual progress report. This report will include participant demographics, expected versus actual recruitment rates, summary of any quality assurance or regulatory issues, summary of adverse events (AEs) or serious adverse events (SAEs) which may have occurred, and any changes in the protocol as a result of these issues.

- The PI will meet with the post-doctoral research fellow and study psychiatrist (as well as any other staff) on a weekly basis. Additionally, Dr. Manning will be available at any time to identify and solve problems in the study's implementation, as well as advice on adverse events experienced by participants during the study.

- We will carefully monitor adverse events throughout the study. Subjects will be assessed for safety and unanticipated problems at each study visit. Symptom severity will be assessed biweekly. All AEs occurring during the study will be collected, documented, and reported to the PI. The PI (supported by Dr. Steffens) will follow all AEs to the point of a satisfactory resolution. A study participant may be withdrawn from the study if the PI and Dr. Steffens determines it is the best decision in order to protect the safety of the participant. All AE's will be assessed to determine if they meet criteria for an SAE. Serious adverse events (SAEs), as defined by the FDA, will be systematically evaluated at each clinic visit. Any SAE, whether or not related to study protocol, will be reported to the IRB and to NIMH within the 3 days of our receipt of information.

12 STATISTICAL DESIGN AND POWER

Randomization: A list of computer-generated random assignments of subjects will be generated using the PLAN procedure in SAS, with permuted blocks of varying sizes unknown to the clinicians**.**

Sample Size and Power: Power for this study is primarily based on the ability of cognitive remediation to improve executive functioning (EF) in older depressed adults. EF will be primarily operationalized as performance on a test of cognitive flexibility / processing speed, the Trail Making Test part B. Based on normative Trail Making Test B data provided by Tombaugh[119] for 336 non-depressed person aged 75-89, we determined that a conservative estimate of the mean for the Trail Making Test B score was 139 seconds (SD=56.3). This score is roughly comparable to that reported by Ashendorf et al.[120] for 200 persons with mild cognitive impairment. While effect sizes from adequately powered cognitive remediation exercises on Trail Making B scores are not available, Smith et al.[114] reported that cognitive training did have an effect on processing speed, a major component of Trail Making B, with an effect size of d= 0.87. Assuming an SD=56 and effect size conservatively estimated at 0.50, a sample size of 128 (64 per condition) would provide 80% power to detect a group difference of 28 using a two-sample t-test with a two-sided alpha of 0.05.

Estimated power for the neuroimaging analyses is based on the ability of cognitive remediation to increase Executive Control Network activation during go/no-go and reappraisal tasks from baseline to post-treatment. It proved challenging to obtain appropriate data in the literature from which to calculate effect sizes for these go/no-go and reappraisal tasks pre and post treatment. We therefore used pre and post treatment data from a pilot study (PI Wang) on 26 non-depressed older adults (mean age = 73.3, SD = 6.7) who underwent an intensive 6-week exercise program. Participants completed a challenging cognitive probe in the scanner (face-name memory task). Power analysis using these data was completed with fmripower software developed by Mumford and Nichols[121] with the DLPFC as the region of interest (ROI). It was determined that a sample size of 80 (40 per condition) would provide 80% power to detect a statistically significant difference from pre to post using a paired t-test with an alpha of 0.05. Considering the obvious differences in interventions, sample, and tasks, these analyses serve only as an estimate and we cannot rule out being underpowered. However, the estimated sample size of 40 per condition is slightly larger than published studies who have found significant increases in DLPFC activation during reappraisal tasks post cognitive behavioral therapy intervention (e.g., Goldin et. al[122]).

Statistical Analysis: This two-arm RCT will initially assess treatment effects using basic tests (e.g., two-group t-test; Wilcoxon rank sum test) depending on whether outcomes can be assumed to be approximately normally distributed. We will assess distributions of outcome and covariate data. As the subjects are randomized, we can expect an even distribution of individual characteristics (e.g., age, gender, depression severity, age of depression onset etc.) across groups. We will block randomize by the presence of MCI to ensure equal sampling of this important variable. We will adjust for any unusual distribution in the second phase of analysis. The primary evaluation endpoint will be at 6 weeks.

Statistical Analysis Specific to MRI: For group level data analysis, whole-brain voxel based analysis of covariance (ANCOVA) with time (pre, post intervention) by group (CCR-EF vs. active control) by contrasts (no-go vs. go, decrease vs maintain negative affect, decrease vs maintain positive affect etc.) will be conducted using FSL FEAT with mixed effects. The significance level will be set at $P<0.05$, FDR correction for multiple comparison. White matter hyperintensities, total brain volume (or the region of interest volume that had the most influential effect), medical comorbidities, and other possible variables (e.g., age) will be used as covariates. Similar ANCOVA analyses (time by group) will be conducted on resting state ALFF and on the networks of interest (time by group by network FC [ECN, DMN, SN, ECN-DMN, ECN-SN, DMN-SN] during task and during resting state.

Planned analyses:

Aim1a, 1b: To present findings adjusted for covariates (e.g., age) that could influence response to treatment, we will use longitudinal models which will include baseline, week 3 and week 6 measures. The main effects of group (i.e., CCR-EF vs active control condition) and time, plus the group by time

interaction will form the core of the models. A significant interaction would indicate, presumably according to the main hypothesis, that those in the CCR-EF group are performing better on Trail Making B (Aim1a) and reporting higher reappraisal usage on the Emotion Regulation Questionnaire (Aim1b) over time, and that the differences are too large to be observable by chance. These advanced statistical models are generally considered general linear mixed models (GLMMs) that model continuous or bivariate outcomes using maximum likelihood approaches (e.g. MIXED procedure in SAS) or GEE approaches (e.g., GENMOD procedure), respectively. These methods require specifying a distribution, a link function, and a model for the covariance structure (e.g., AR-1). The models produce predicted adjusted mean differences for continuous outcomes (e.g., cognitive function) and estimated odds ratios for binary outcomes. For example, we could report odds ratios (and 95% CL) indicating the extent to CCR-EF group subject were more or less likely to report lower rates of depression, relative to the active control group.

Aim1c: For only two time points (e.g., Executive Control Network functional connectivity data collected at baseline and 6 weeks), the model simplifies to a traditional analysis of covariance (ANCOVA). We will extract mean functional connectivity within ECN, DMN, SN, and between ECN and DMN, between ECN and SN, as well as between DMN-SN in response to “decrease” vs. “maintain” negative affect contrast and “no-go” vs. “go” contrast and conduct ANCOVA to examine between-group (CCR-EF, active control) differences in baseline and post-treatment. Separate ANCOVAs (adjusting for multiple comparisons) will be run for each region of interest: dorsolateral prefrontal cortex and inferior parietal cortex of ECN, ventromedial prefrontal cortex and posterior cingulate cortex of DMN, and dorsal anterior cingulate, right insula, and amygdala of SN activation as well as connectivity among these regions changes during reappraisal and go/no-go will also be analyzed. All models will adjust for the presence of white matter hyperintensities and global or regional brain volume. Significance level will be set at $p<0.05$ with FDR correction.

Aim2: To present findings adjusted for covariates (e.g., age) that could influence response to depression treatment measured with the MADRS, we will use longitudinal models that will include 4 time points (baseline, week 2, week 4, week 6). The main effects of group (i.e., CCR-EF vs active control condition) and time, plus the (group x time) interaction will form the core of the models. A significant interaction effect would indicate, presumably according to the main hypothesis, that those in the CCR-EF group are reporting a more significant decline in depression symptoms (measured with the MADRS) over time, relative to their counterparts randomized to the active control condition.

Exploratory Aim: We will begin by examining the correlations among change scores from pre to post for our outcome measures. We will also fit statistical models (GLMMs and mediation models) to explore the association between change in cognitive control behaviors (e.g., Trail Making Part B, ERQ reappraisal), change in ECN connectivity, and change in depression symptoms and cognition immediately post-treatment and one year later, as well as potential group differences in the magnitude of change.

Other considerations: As we mentioned earlier, although we will use network-based connectivity results as the primary outcomes supplemented by ROI-based analysis, similar analyses will also be conducted using whole-brain voxelwise analyses. The amplitude of low-frequency fluctuation (ALFF) will also be computed to examine therapeutic differences in resting state activity. In addition, changes in cortical and subcortical volumes will also be measured using FreeSurfer program and white matter integrity changes will be examined using FSL TBSS to explore CCR-EF on brain volume and white matter integrity.

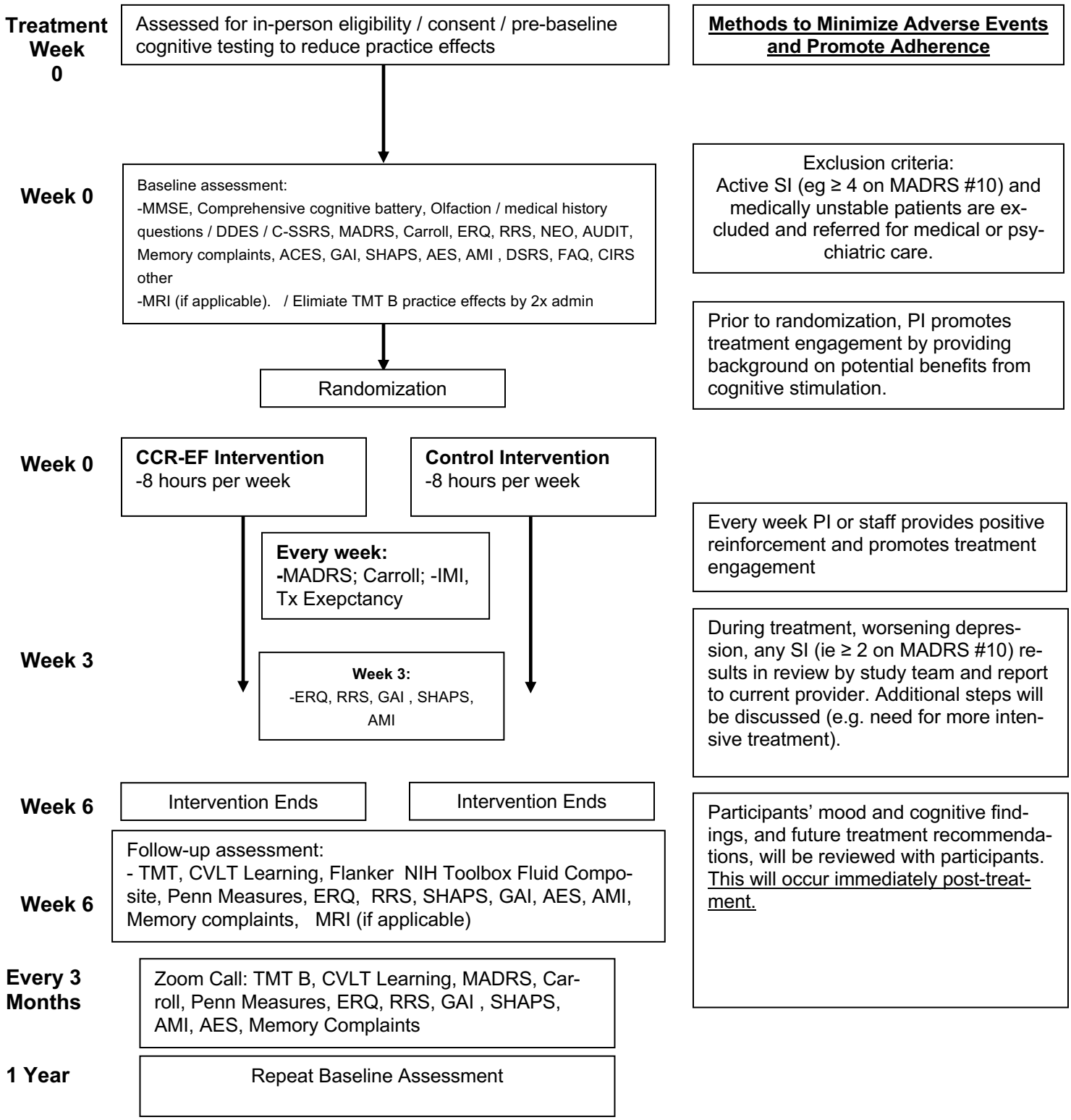
13 TIMETABLE:

Treatment Timeline "Cognitive Remediation of Cognitive Control in Late-Life Depression"

138 older adults with late-life depression will be enrolled (allowing for adequate power with 10% attrition). Recruitment will begin three months after the project begins and will end six months into Year 5. We plan to recruit 3 subjects per month. 80% of subjects will complete a one-year follow-up.

	Year 1		Year 2		Year 3		Year 4		Year 5	
Task	**1-6**	**7-12**	**1-6**	**7-12**	**1-6**	**7-12**	**1-6**	**7-12**	**1-6**	**7-12**
Study start up										
Participant enrollment										
Treatment										
MRI acquisition and processing										
One Year Follow-up										
Data management / keying/cleaning										
Preliminary data analysis										
Manuscripts (based on this study)										
R01 preparation										

Progress through the Randomized Controlled Trial
54 Targeted Recruitment (older adults with LLD on stable doses of antidepressants)



14 DISSEMINATION

Scientific findings will be presented at conferences and submitted for publication in peer-reviewed articles.

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