Effects of Donepezil HCL on Task-Activated fMRI Brain Activation in Healthy Older Adults at Genetic Risk for Alzheimer's Disease

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Introduction

The neuropathological changes associated with Alzheimer's disease (AD) are thought to begin decades prior to the advent of symptoms. By the time AD is diagnosed, patients have experienced widespread cognitive impairment and extensive brain atrophy. Interventions administered at this stage may be too late to alter the disease trajectory. This recognition has prompted investigators in the field to consider prevention trials involving cognitively intact individuals at genetic risk for AD. The first wave of such prevention trials will focus on persons with the autosomal-dominant mutation variant of AD, since it is possible to determine with certainty that the participant will develop AD. Should these prevention trials identify an agent that effectively alters the disease course during the preclinical phase, the next step will be to enroll cognitively intact elders at risk for the more common, sporadic form of AD.

Prior to conducting a prevention trial in sporadic AD, it is essential to validate biomarkers for purposes of accurately identifying persons at risk for AD during the preclinical phase and for monitoring treatment response since such individuals are by definition asymptomatic. Several candidate biochemical, anatomical, and functional biomarkers have shown promise, but vary in their ease of administration, availability, safety, accuracy, reproducibility, and invasiveness. Among these candidate biomarkers, task-activated functional magnetic resonance imaging (fMRI) is a promising approach that is noninvasive, carries little risk, and offers a high potential for identifying persons who may eventually develop AD. Our fMRI research program has examined brain circuits involved in semantic memory using a famous name recognition test. We have demonstrated that the presence of the apolipoprotein-E (APOE) ε4 allele and a family history of dementia are associated with increased activation in several key AD-related brain regions (e.g., hippocampus, posterior cingulate, temporoparietal junction), suggesting its possible role as a marker for disease risk and progression during the preclinical stage (Seidenberg et al., 2009). This increased activation is believed to serve as a compensatory brain response during the prodromal period. We have shown that genetically at risk elders who do not demonstrate hyperactivation at study entry develop cognitive dysfunction within 18 months of the fMRI scan (Woodard et al., 2010). We have also demonstrated that genetically at-risk elders who exercise regularly demonstrate hyperactivation, where sedentary at-risk elders do not (Smith et al., 2011). We therefore propose to examine the value of task-activated fMRI in monitoring drug intervention effectiveness in persons at genetic risk for AD.

Clinical studies suggest that cholinesterase inhibitors (ChEIs), such as donepezil hydrochloride (HCL), exert a cognitive benefit with chronic use among MCI and AD patients. Some studies also demonstrate a slight treatment benefit for persons who are APOE ε4 carriers. We propose to conduct a 24-week, randomized, double-blind, placebo-controlled, parallel group study of donepezil HCL (Aricept®) in 60 elders who have both AD risk factors, a family history of AD and the presence of one or both APOE ε4 alleles. As noted above, our preliminary analyses indicate that at-risk healthy elders exhibit increased fMRI activation on a semantic memory activation task relative to not at-risk healthy elders and that increased activation is protective against future declines on neuropsychological testing in at-risk elders. For this project, we will extend our preliminary data by using task-activated fMRI as the primary biomarker for assessing treatment efficacy in cognitively intact elders at risk for AD; neuropsychological testing and brain morphometry will serve as secondary endpoints. We hypothesize that changes in fMRI magnitude will demonstrate greater sensitivity to cholinergic modulation than changes on neuropsychological testing. Based on our preliminary longitudinal fMRI data, we also predict that at-risk

elders taking donepezil HCL will maintain or enhance the level of activation in response to a semantic memory activation task; in contrast, at-risk elders taking placebo will experience a decline in their brain activation, indicating a reduction in brain reserve and increased risk for cognitive dysfunction.

For this imaging biomarker validation study, it will also be necessary to include a group of elders who are at low genetic risk for developing AD (no family history and non-carrier of APOE ε4 allele). This group will undergo fMRI scanning and neuropsychological testing at entry and at 24 weeks, but will not receive medication or placebo. The purpose of the low risk group is to serve as a reference for interpreting the fMRI brain activation response. We predict that both the drug and placebo at risk elder groups will display greater activation than the low risk group at baseline. At 24 weeks, the disparity in brain activation between the low risk group and the high risk group taking donepezil HCL will remain stable or increase as compensatory responses are bolstered, whereas the disparity between the low risk group and the high risk group taking placebo will decrease as the compensatory response diminishes.

Sample

Ninety cognitively intact, healthy older adults (60 with and 30 without AD genetic risk factors) will be recruited between the ages of 60 and 80 (inclusive). Candidate participants will undergo comprehensive screening, including review of medical records, standardized telephone screening, and background history questionnaires. The 60 High Risk participants must have a family history of dementia and have one or both APOE ε4 alleles; the 30 Low Risk participants will not have a family history of dementia and not possess an ε4 allele. The Low Risk group will be demographically matched to the High Risk group.

To be *included* in the study, all participants will have

- Normal general cognitive function
- MMSE score ≥ 27
- Logical Memory II subscale Delayed Paragraph A score of ≥ 7
- Geriatric Depression Score < 6,
- Hachinski Score ≤ 4
- Intact activities of daily living
- Visual and auditory acuity adequate for neuropsychological testing
- Women must be two years post-menopausal or surgically sterile
- Stable prescription medication dosages one month prior to testing and participant will agree not to change their medication regimen unless cleared by the study physician

Prospective participants will be *excluded* if they have a history or evidence of: 1) *neurological illnesses/conditions,* such as motor or vocal tics (including a diagnosis of Tourette's syndrome), head trauma with significant loss of consciousness (>30 min), cerebral ischemia, vascular headache, carotid artery disease, cerebral palsy, epilepsy, brain tumor, chronic meningitis, multiple sclerosis, pernicious anemia, normal-pressure hydrocephalus, HIV infection, Mild Cognitive Impairment, Alzheimer's disease, Parkinson's disease, and Huntington's disease; 2) *medical illnesses/conditions* that may affect brain function, such as untreated hypertension (blood pressure > 140/100 mm Hg), insulin-dependent diabetes mellitus, endocrine disorders, renal disease, glaucoma, and chronic obstructive pulmonary disease; 3) *current Axis I psychiatric disturbance* meeting DSM-IV Axis I criteria; 4) *severe depressive symptoms* as indicated by Geriatric Depression Scale (short form) score greater than or equal to 6; 5) *substance abuse or dependence* meeting DSM-IV Axis I criteria; 6) *exclusion criteria specific to MR scanning*: pregnancy, weight inappropriate for height, ferrous objects within the body, low visual acuity, and a history of claustrophobia; 7) use of medications that may affect the hemodynamic response in the scanner; 8) prior history of use of any cholinesterase inhibitor; 9) hypersensitivity to donepezil HCL or other carbamate derivatives or other components of the formulation; 10) currently taking drugs or over-the-counter

preparations that increase cholinergic activity (e.g., sage); 11) body weight below 45 kg; 12) planning to undergo surgery requiring general anesthesia during the treatment period; 13) any unstable or severe cardiovascular disease or asthmatic condition; 14) history of transient ischemic attack or a score of more than 4 on the modified Hachinski ischemic scale 15) Screening laboratory testing indicating any of the following; total bilirubin, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than two times the upper limit of normal; Renal impairment with a serum creatinine (Cr) greater than 1.2 times the upper limit of normal; Hematocrit (Hct) less than 37% for males and less than 32% for females, absolute neutrophil cell count of less than or equal to 1,500/L, or platelet cell count of less than 120,000/L. We will also exclude participants whose high-resolution anatomic MR scans reveal the presence of a structural abnormality.

Research Procedures

Telephone Prescreening

Potential participants will be prescreened over the phone using the Phone Screen questionnaire. If determined to be eligible based on this prescreening, participants will then be scheduled for an in person screening visit. If a prescreened participant enrolls in the research study, the Phone Screen questionnaire will become part of the research record.

Initial Screening Visit (Visit #1)

At the screening visit demographic information will be collected including age, race, years of education, and occupation. The participant's medical history as well as family history of dementia will also be collected. Participants will undergo a neuropsychological battery including the Mini-Mental State Exam, WMS-R Logical Memory, and Geriatric Depression Scale – short form.

All participants will undergo a blood draw for APOE genotyping.

APOE Genotyping

All potential participants will undergo APOE genotyping. If a participant chooses to not undergo APOE genotyping he/she will not be enrolled in the study. If a participant is considered to be ineligible at the screening visit (e.g. low cognitive scores, medical exclusion) his/her blood sample will not be sent for genotyping.

A blood sample will be collected for the APOE genotyping at the first screening visit. The APOE genotyping will be performed by the Cleveland Clinic Genomic Medicine Biorepository lab (GMB) under the direction of Lynn Bekris. However, if participants are also enrolled in the CBH Biobank (14-604) the GMB confirmatory genotyping will be conducted as part of this study and the additional sample will not need to be drawn. If a discrepancy is found between the results, both laboratories will be asked to repeat genotyping.

The results of the APOE genotyping will be stored in the research record and will not be placed in the medical record. If a participant chooses not to receive information on his or her genetic status, participation in the study will be discontinued.

Genetic Counseling

All participants will be required to undergo a genetic counseling session to receive the results of the genetic testing. Test results will not be released to participants over the phone or to a participant's physician. The results of this genetic testing will not be placed in the medical record. During the genetic counseling session, participants will receive a letter stating if they are a carrier of the APOE ε4 allele. The decision to share this information with a physician outside of the study is left to the participant. This genetic counseling will occur at the beginning of the second screening visit.

Laboratory Testing
If a high-risk participant is determined to be eligible based on the screening visit and the genetic testing, blood will be drawn for Comprehensive Metabolic Panel (CMP) and Complete Blood Count (CBC) laboratory testing. The CMP and CBC will be sent to the Cleveland Clinic Main Laboratory. This blood draw will occur at the second screening visit. Participants do not need to fast for this testing. If the CMP or CBC were recently completed within a month for a clinical evaluation or another research project, the results from that testing will be used to confirm eligibility

iPad Application Testing
All participants will be required to complete an iPad application test which will include the Processing Speed Test. This testing will occur at the second screening visit.

Eligibility Confirmatory Cognitive Testing
Participants with borderline MMSE and WMS-R Logical Memory scores at screening visit #1 will receive the Repeatable Battery of the Assessment of Neuropsychological Status (RBANS) at screening visit #2

Electrocardiogram (ECG)
All high-risk participants will undergo a 12-lead ECG at the second screening visit which will be reviewed by the CCF cardiology department to assist the study clinician with determining eligibility. Heart rate will be examined after the participant has been on study drug for four weeks before increasing the dosage to 10mg. Heart rate observance will be used to confirm the absence of any cardiovascular side effect events, most commonly bradycardia. If a participant's heart rate falls below 55bpm, above 110 bpm or experiences a 20 bpm difference from the initial ECG reading, the study clinician will be notified immediately to assess the patient before distribution of 10mg dosage.

Comprehensive Cognitive Battery
Participants in the study will undergo an extensive cognitive battery at the baseline and follow-up visits.

This battery will include:
- Symbol Digit Modalities Test
- Rey Auditory and Verbal Learning Test
- Brief Visuospatial Memory Test – Revised
- Delis Kaplan Executive Function System Verbal Fluency, Sorting, and Trail Making Tests
- Wide Rang Achievement Test-4: Reading
- Wechsler Adult Intelligence Test-IV: Digit Span, Coding, and Block Design
- Judgment Of Line Orientation Test
- Boston Naming Test
- Processing Speed Test (iPad app) (screening visit #2 and follow-up)
- Computerized Stroop, Sternberg, Stop Signal and Paced Finger Tapping tests.
- Measurements of grip strength and finger tapping speed

Self-report measures will include:
- Lawton Activities of Daily Living
- Center for Epidemiologic Studies Depression Scale
- Geriatric Anxiety Scale
- Emotion Regulation Questionnaire
- Toronto Alexithmia Scale
- IQ code

- Satisfaction with Life Scale
- 7-Day Physical Activity Scale
- Stanford Brief Activity Scale
- Prime Screen
- SF-12

Physical Examination
A physical and neurological examination will be performed by a physician at the second screening visit to verify that the participant does not have any of the medical exclusions for this study.

fMRI Scanning Session
All participants will undergo a functional magnetic resonance imaging (fMRI) exam at the baseline and follow-up study visits. The MRI will be conducted in the Mellen Imaging Center in a 3.0 T Siemens Trio scanner. This exam will include high resolution anatomical imaging, task-activated fMRI, resting state fMRI, and diffusion tensor imaging (DTI). The Famous Name Recognition (FNR) task will be used for the task-activated fMRI. The entire imaging exam will last approximately one hour. A bite bar will be used to limit motion artifacts in the imaging data. The bite bar apparatus consists of a plastic platform that is placed over the head coil. Prior to placing the coil and platform over the participant's head, a dental impression is taken using dental impression compound. The impression is mounted to a plastic plate that is then passed through the coil, placed into the participant's mouth and bolted to the platform. The process takes around 5 minutes to perform and does not compromise the participant's safety within the scanner. There is a quick release mechanism that allows the bite bar to be removed in seconds in the event of emergency. The participant is asked to bite firmly on the bite bar during periods when the scanner is on and acquiring images. When the scanner is off, the participant is instructed to relax. Some participants will have a sensitive gag reflex that will prevent them from comfortably using this device. The bite bar will not be used in these participants.

Dispensing of Study Drug (High Risk group only)
The High Risk participants will be randomly assigned to either treatment or placebo groups, using a double-blind procedure under the supervision of the unblinded P.I. At the end of Day 1, participants will receive a four-week supply of 5mg donepezil HCL capsules or identical placebo. After the first four weeks (Week 4), participants will then receive a 4 week supply of 10 mg capsules, or identical placebo. Participants will be dispensed a 4 week supply of 10mg donepezil HCL capsules or identical placebo at the Week 8, 12, 16, and 20 visits. Participants will be instructed to take one capsule per day at the same time each day.

Safety, side effect tolerability, and compliance will be assessed at each study visit. Participants will be encouraged to contact the Treating Physician if they have any questions or experience any adverse events. Participants unable to tolerate the higher dose due to side effects will be placed back on the 5mg dosage for the remainder of the study. Participants unable to tolerate the initial dose will be discontinued from the study and replaced. The study treating physician will monitor adverse events as well as drug tolerability.

The study drug and placebo will be stored and dispensed by the Investigational Drug Service (IDS) through the CCF Pharmacy. The IDS will be responsible for the study randomization and will provide the randomization information to the unblinded P.I. and study treating physician.

Donepezil HCL is approved by the FDA for clinical use in patients with AD. This drug is not approved for the treatment of preclinical AD. As such, donepezil HCL is considered an "off label" drug for the treatment of this at-risk population. An IND Exemption request has been submitted to the FDA.

Compensation
Participants will receive $20 for the first screening visit and $10 for the genetic counseling session. Eligible High Risk participants will receive an additional $10 for completing the additional blood draw and ECG at the second screening visit. $50 for the baseline visit, and $75 for the follow-up visit. High Risk participants will receive $20 for each of the five visits during the treatment period. Low Risk participants will receive a total of $155 for completing the study. High Risk participants will receive a total of $265 for completing the study. Stipends will be given as cash at the study visit. If cash is unavailable a check will be mailed to the address provided by the participant.

7T Add-on Pilot Study
The purpose of the 7T add-on study is to better understand the brain mechanisms underlying the unique protective effect of physical activity (PA) on cognitively intact older adults possessing an APOE e4 allele using state-of-the-art 7T MR imaging. We hypothesize that the beneficial effects of PA counteract the negative consequences of possessing an e4 allele in cognitively intact, healthy elders. Specifically, we hypothesize that physically active carriers will demonstrate less atrophy, increased brain activation in memory regions, better functional and structural connectivity, and less white matter lesions than sedentary carriers; the effects of PA will be less pronounced in non-carriers For this add-on study, a subset of 20 cognitively intact, healthy elders between the ages of 60 and 75 will participate. Half will be e3/e4 heterozygotes (carriers); the remaining half e3/e3 homozygotes (non-carriers). PA levels will be derived from a validated self-report questionnaire (SBAS): half will have engaged in moderate PA (high PA) and half will be sedentary (low PA). Thus there will be 4 groups (n=5 each): high PA carriers, low PA carriers, high PA non-carriers, and low PA non-carriers. Participants will undergo ultra-high spatial resolution anatomical imaging, susceptibility weighted imaging, diffusion tensor imaging [HARDI], and T2-weighted imaging [FLAIR]).

Potential Risks and Participant Safety
There are no known risks associated with magnetic resonance imaging.

All dosages of donepezil HCL proposed for use in the study (including the titration procedure) are recommended by the manufacturer, approved by the FDA, and are commonly used in medical practice in the United States. The most common side effects (with the proportion of patients in the controlled clinical trial titrated to 10mg/day over a six week period who experienced the symptom in parentheses) include nausea (6%), diarrhea (9%), insomnia (6%), fatigue (3%), vomiting (5%), muscle cramps (3%), and anorexia/decreased appetite (3%). At present, the only known contraindication to the use of donepezil HCL is hypersensitivity to the drug or to piperidine derivatives. Prospective participants will be screened for pre-diagnosed contraindications and cautionary conditions for donepezil HCL treatment (see exclusions above). Weight will be monitored during treatment; participants whose weight drops below 50kg will stop treatment and be replaced in the trial. Participants will also be advised to inform their physicians of their participation in this trial. If a safety concern is identified or a participant reports intolerable side effects, a safety visit will be scheduled with the study treating physician. The physician will determine if it is safe for the participant to continue in the study at the current dosage, if the dosage should be lowered back to 5mg, or if the participant should discontinue the study medication and be removed from the study.

Possible risks also include: minor bruising or discomfort from the blood draw, the invasion of privacy from the review of medical records, and discomfort and fatigue associated with neuropsychological testing. Rest periods or breaks will be offered to the participants.

There is a possible risk of psychological harm (anxiety, depression) after learning the results of genetic testing. All participants will be required to undergo genetic counseling with Dr. Rao or one of the study physicians. All physicians involved in this study specialize in dementia and are qualified to provide genetic counseling for APOE status.

Data Analysis

Analysis of the data will be conducted by the study team under the direction of Dr. Rao. Residualized change scores will be computed for each of the three principal outcome measures (fMRI, neuropsychological testing, anatomical MRI). Groups (placebo vs. donepezil HCL) will be compared on each of these residualized change scores. It is expected that group differences will be greater for fMRI than for neuropsychological or anatomical MRI change scores. A hierarchical regression will then be used to investigate other potential predictors (e.g., AD family history) that may account for additional variance in treatment response beyond group membership.

Imaging data analysis will be conducted by the study team at the Cleveland Clinic as well as Sally Durgerian at the Medical College of Wisconsin (MCW). Functional images will be generated and analyzed using the Analysis of Functional NeuroImages (AFNI) software. Both voxel-wise and ROI analyses will be applied to the analysis of the fMRI data.

Power Analysis and Sample Size

Calculations of the number of participants can be made from preliminary longitudinal fMRI data comparing High vs. Low Risk elders. For the posterior cingulate, the mean change in the AUC (Famous minus Unfamiliar Names) from baseline to follow-up was -0.55 percent signal change for the High Risk group and +0.20 percent signal change for the Low Risk group (pooled SD = 0.86). Assuming power = 0.80 and a two-tailed $\alpha = 0.05$, a sample size of 22 is required. Thus, assuming that the treated group performs similarly to the Low Risk group, we have enough power to discriminate treated (n=30) versus placebo (n=30) groups using fMRI as the primary outcome measure.

Data Management

All participants will be assigned a unique study-specific ID when enrolled. Data will be stored in a password protected database (REDCap) with access restricted to the P.I. and designated study staff. Paper study records will be stored in a locked file cabinet with access restricted to the P.I. and designated study staff. Imaging data will be stored on password protected servers behind the CCF firewall. A Data Use Agreement has been put in place to allow Ms. Durgerian at MCW access to this imaging data.

Data shared with co-investigators at other institutions (Marquette University, Rosalind Franklin University, Medical College of Wisconsin, and Wayne State University) will be de-identified. No PHI will be shared with these collaborators without prior approval from the IRB.

Adverse Events and Data Monitoring

Dr. Jeffrey Cummings and Dr. Charles Bernick (non-study staff) will review study reports and will submit a data and safety monitoring report to the IRB every six months. Dr. Rao, with the assistance of the treating physician, will be responsible for monitoring participant safety and adverse events as these events occur. Adverse events will be reported to the IRB as required. If deemed appropriate, serious adverse events will also be reported to the FDA and drug manufacturer.

Consent

A copy of the current informed consent form will be mailed to the participant in advance so that there is adequate time to review the document. After arrival at the first visit, the document will be reviewed and any participant questions will be answered. After detailed explanation of the study and its potential risks,

informed consent will be obtained by a member of the study team prior to the start of any study related activity. The informed consent process will be documented in the participant's medical record. A copy of the signed informed consent document will be provided to the participant and the original document will be stored in the research record.

References

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