Statement of Commitment (3 Pages Max)

My scientific goal is to understand how neurochemistry modulates age-related changes in cognition and brain activity. I am particularly interested in the potential protective role neuromodulatory systems may play in the earliest stages of Alzheimer's disease. My proposed research combines multimodal neuroimaging with advanced computational methods to track the cognitive and neural markers of AD in a longitudinal cohort of healthy older adults. While I am a newcomer to the field of Alzheimer's disease with much to learn, I believe that I have a lot to offer. I have a strong quantitative background with a Bachelor's degree in Computer Science and a PhD in Computational Neuroscience. During graduate school, I gained extensive experience using functional magnetic resonance imaging (fMRI) to study memory and learning. During my postdoctoral fellowship, I will apply my previous training to investigate the neurochemical factors that may preserve cognitive function in the face of AD pathology. My postdoctoral training, particularly through the proposed project and training plan, will enhance my current skillset and support my long term research goals.

I was first introduced to studies of memory and learning in my undergraduate Cognitive Psychology class at Tufts University, where I was captivated by the way functional neuroimaging offered a "window" into the mind. Determined to learn everything I could, I joined the lab of Dr. Jacob Hooker at the MGH Martinos Center as an undergraduate intern. My primary project was to develop a user-friendly simulation tool for chemists to model pharmacodynamics of potential new radiotracers without the need to write any code themselves. The tool is posted to GitHub so that other PET researchers can take advantage of it. Work on this project contributed to a co-authored review paper on PET neuroimaging (Placzek et al. 2015). I also assisted other lab members with their pharmacokinetic analyses, resulting in two additional co-authored publications (Gilbert et al., 2019; Strebl et al., 2017). My work as an undergraduate in Dr. Hooker's lab taught me important skills in taking a project from start to finish. In my postdoc, I will expand my PET neuroimaging skills beyond pharmacokinetic modeling, learning to also collect and reconstruct data, build custom preprocessing pipelines, and learn to work with new radiotracers for measuring dopamine and tau.

As a doctoral student at Boston University, I used functional magnetic resonance imaging (fMRI) to study how the brain's functional network architecture dynamically reconfigures to support reasoning, learning, and memory. My dissertation research resulted in two first author papers (Morin et al., 2021; Morin et al., 2022), a co-authored paper (Isenburg et al., 2023), and ten poster presentations at local, national, and international conferences (incl. Society for Neuroscience, Organization for Human Brain Mapping, & Cognitive Neuroscience Society). Results from these projects contributed to the scientific understanding of how the brain's temporal dynamics (e.g. functional network flexibility and stability) contribute to learning and memory. As part of the Graduate Program for Neuroscience (GPN) I completed courses in graph theory, network science, advanced statistics, and computational neuroscience that have inspired my computational approaches to fMRI analysis. In my final year of graduate school, I was awarded the Russek Student Achievement Award, a prize given to one student in GPN each year for their scientific and community-building accomplishments. Throughout graduate school, I gained a deep interest in how the brain is able to learn and remember information. During my postdoctoral fellowship, I will extend this expertise to study the neurochemical factors lead to deficits in (or the conservation of) memory and cognition in aging and Alzheimer's disease.

My postdoctoral training, which began in July 2022, involves a unique cross-institutional collaborative mentorship between Dr. Jacob Hooker and Dr. Julie Price at the MGH Martinos Center where I am a Postdoctoral Fellow, and Dr. Anne Berry at Brandeis University where I am a Visiting Scientist. Throughout the first year of my postdoctoral training, I have worked hard to integrate myself into the cognitive aging and Alzheimer's research community. I joined ISTAART, attending several of the workshops and seminars offered by the Neuromodulatory Subcortical Systems (NSS) and Neuroimaging Professional Interest Areas (PIA)s. In January, I was invited to present at ISTAART's Neuromodulatory Subcortical Systems Professional Interest Area (NSS

PIA)'s annual "year in review" webinar. In February, I attended the Dallas Aging and Cognition Conference. Next month I will present preliminary findings from the proposed research in a poster at the Society for Neuroscience Conference. Additionally, I was recently awarded a travel award to attend the 4th Workshop on Research Definitions for Reserve and Resilience in Cognitive Aging & Dementia at the NIH campus in December. Outside of the lab, I've participated in the Walk to End Alzheimer's and I've guest-lectured for Beacon Hill Seminars – a continuing-education program for older adults. Finally, I am a co-author on a manuscript recently accepted in *Neurobiology of Aging* that investigates genetic polymorphisms related to BDNF and amyloid-beta using data from ADNI. Through the proposed research project and training plan, I look forward to establishing myself as an expert in multimodal neuroimaging, developing expertise in cognitive aging and AD, and gaining experience in collaborative, interdisciplinary science.

Scientific Goals and Training Plan

Training Goal #1: Develop expertise in cognitive and neural changes related to aging and Alzheimer's disease. *Objectives for completion: Participation in seminars, attendance of regular meetings with experts, and completion of proposed research project.*

- Weekly meetings with Dr. Hooker and Dr. Berry. Monthly meetings with Dr. Price.
- Attendance at relevant weekly seminars: BrainMap, Martinnovate (MGH), Brown Bag (Brandeis)
- Training from postdocs in Dr. Berry's lab for administering neuropsychological testing to older adults. (The Brandeis Aging Brain Study neuropsych. battery includes WASI, CVLT, WMS, MMSE)
- Participation in T32 training activities coordinated by Dr. Price (including AD journal club & lecture series)
- "Alzheimer's Fast Track" short course (BrightFocus Foundation – 1 week)
- Attend AAIC, Dallas Aging & Cognition, and Human Amyloid Imaging conferences

Training Goal #2: Establish myself as an expert in multimodal neuroimaging studies that incorporate structural and functional MRI with PET data. *Objectives for completion: Instruction in MR/PET image analysis, completion of the proposed research project, oral presentations, scientific manuscripts, and grant applications*

- The proposed work will incorporate analysis of [^{11}C]raclopride and [^{18}F]MK6240 PET with functional MR images to measure the effects of dopamine and tau on functional connectivity and memory in cognitive aging.
- Attend pharmacokinetic modeling course offered annually by Dr. Price and colleagues. In subsequent years, assist in teaching the course.
- Attend virtual Turku PET Center short course in PET/MRI (1 week).
- Earn "green badge" certification to independently run simultaneous MR/PET scans at MGH.
- Receive training in MR/PET acquisition and analysis from postdocs working with Dr. Hooker/Price.

Training Goal #3: Attain proficiency in collaborative science, including multi-site research projects and cross-institutional collaborations. *Objectives for completion: Formal leadership training at MGH, regular meetings with mentors, participation in seminars, and completion of the proposed research project.*

- Work collaboratively across Brandeis University, a small liberal arts university, and Mass. General Hospital, a major research hospital.
- Attend the biweekly "Martinnovate" seminar series at the MGH Martinos Center, which focusses on how to build scientific collaborations across academia and industry.
- Attend and present at weekly "Science on Tap" seminars at the MGH Martinos Center which focus on presenting your science in an accessible way to broad audiences.
- Attend Scientific Leadership Course (meets twice monthly for 1 year) offered by the MGH Center for Faculty Development to chart a course towards independence and learn how to manage a lab as a professor.
- Enroll in a Research Management course offered through Harvard Business School (1 semester, 2hrs/week) to gain expertise in science leadership and in running a lab.

Statement of Commitment (3 Pages Max)

Activities Planned for this Training Plan

WRITING

- **Grants:** By the end of Year 2, I will use preliminary data from this project to apply for an NIH K-award. I will participate in the MGH workshop on writing K-grants (8 weeks online). This is an important step on the path towards securing independence as an investigator.
- **Abstracts:** I will submit abstracts to at least two national/international conferences each year, including the annual AAIC meeting. I will also present my work at local symposia, poster sessions, and invited talks.
- **Manuscripts:** I will aim to publish at least one first-authored manuscript for each year of the fellowship. I will also co-author manuscripts with other members of Dr. Hooker, Dr. Berry, and Dr. Price's labs.

CAREER DEVELOPMENT

- **Seminars (2-3 hrs/week):** I will attend relevant seminars including the weekly BrainMap and "Martinnovate" Seminars the MGH Martinos Center, and weekly Brandeis Neuroscience Brown Bag talks.
- **Grand Rounds (1hr/month):** I will attend MGH neurology grand rounds once per month to gain a stronger clinical perspective of Alzheimer's disease and related disorders.
- **Hooker Lab Meetings (1hr/week):** I will attend the weekly Hooker lab meetings, as well as our group's monthly section meeting on human-neuroimaging. I will present in lab meeting at least twice per year.
- **Berry Lab Meetings (1 hr/week):** I will also attend the weekly Berry Lab meetings at Brandeis University and present on my research once per year. I will become familiar with the Berry Lab's work on cognitive aging.
- **Training w/ Dr. Price (1 hr/month):** I will attend Price Lab meetings monthly, as well as T32 training activities coordinated by Dr. Price (including AD journal club & lecture series, see *Letter of Support*). I will also attend Dr. Price's annual course in Year 1 (1 week) on Pharmacokinetic Modeling of PET Radiotracers.
- **Conferences:** Locally, I will present annually at MGH Clinical Neuroscience Day and Martinos Summer Symposium. I will attend national/international meetings focused on cognitive aging and Alzheimer's disease including the AAIC, Human Amyloid Imaging meeting, and the Dallas Aging and Cognition Conference.
- **Workshops & Coursework:** During **Year 1**, I will participate in the Brightfocus Foundation's "Alzheimer's Fast Track" short course (1 week), and attend Dr. Berry's "Alzheimer's disease resilience and risk factors" seminar course at Brandeis. In **Year 2**, I will attend Dr. Price's course of Pharmacokinetic Modeling for PET (1 week) and I will participate in a Scientific Leadership Course offered through the MGH Center for Faculty Development (twice monthly for one year). In **Year 3**, I will enroll in a Research Management course offered through Harvard Business School (2hrs/week) to gain expertise in science leadership and in running a lab.
- **Individual Development Plan (IDP):** To ensure that this training plan is achieved, I will generate a formal IDP to be discussed with the mentoring team at least once per year. With the IDP, we will evaluate overall progress, address any unanticipated training issues, and evaluate career goals and progress toward those goals.

Evaluation of Progress: I will meet regularly with my mentors (Dr. Hooker - weekly; Dr. Price - monthly; Dr. Berry - monthly; All Mentors: quarterly), to discuss research milestones, publication drafts, and professional development. Together, we will ensure the research and training plan is effectively carried out. Specific benchmarks include: 1) annual meetings with my mentors and advisors with evaluations of my progress, 2) development of a journal from coursework, lab meetings, seminars, and meetings with my mentors, 3) feedback on research from mentors and advisors, 4) presentation of initial findings at lab meetings, 5) presentation of research findings via conference abstracts/platform presentations (including the annual AAIC meeting) and first-author manuscripts, and 6) submissions to secure independent research funding (e.g. K99).

Area of Research (3 Pages Max)

BACKGROUND & SIGNIFICANCE: In a recent position paper, members of ISTAART's Neuromodulatory Subcortical Systems Professional Interest Area (NSS PIA) expressed the urgent need for research investigating the role of neuromodulators (e.g. dopamine) in Alzheimer's disease (AD). They cited the unique opportunity neuromodulatory systems present as strategic prospects for disease-modifying therapies[1]. Previously, most research on the dopaminergic system in older adults has not considered AD biomarkers such as tau burden and plasma amyloid. In this proposal, I will explicitly examine the relationships among dopamine, AD-pathology, and memory in aging and preclinical AD, years before any significant cognitive deficits are apparent and before tau and amyloid pathology become widespread.

The deposition of hyperphosphorylated tau is an inevitable part of aging that occurs years before the onset of disabling AD symptoms[2,3]. In clinically normal older adults, medial temporal lobe tau burden is associated with memory performance[4–6]. Normal aging also involves dopamine system decline (striatal dopamine innervation decreases at a rate of 6-10% per decade)[7]. Disruption to the dopamine system is associated with age-related deficits in memory and executive functioning[8–10]. Pharmacologically enhancing dopamine in older adults has been shown to improve memory performance and strengthen associated MRI brain measures[11,12]. Although older adults experience both the accumulation of tau and dopamine-system-disruption, some individuals are resilient to cognitive decline. Previous work from our group suggests that the dopamine system is one avenue through which some older adults may maintain intact memory performance, even in the face of tau pathology[13,14].

SPECIFIC AIMS & HYPTOHESES: Participants from this study will be recruited from the existing longitudinal Brandeis Aging Brain Study (BABS). We will use [^{11}C]raclopride to measure dopamine D2/3 receptor density and simultaneous functional MRI to measure brain activity during a reward memory task: first after receiving a placebo, and then after receiving a dopamine-enhancing drug (methylphenidate) to measure endogenous dopamine release. Participants will return for a [^{18}F]MK6240 scan to measure tau burden, complete a neuropsychological battery, and provide a blood sample to measure plasma beta-amyloid (see **Fig. 1**).

Aim 1: Define the independent and interactive effects of dopamine and tau pathology on memory in aging. We predict that *(Hyp. 1a)* independently, increased levels of tau, and decreased dopamine D2/3 receptor density will be associated with poorer memory. *(Hyp. 1b)* We predict that low-tau individuals will show a positive relationship between D2/3 receptor density and memory, but that this will be disrupted in the context of high tau.

Aim 2: Establish the effects of dopamine and tau on hippocampal-striatal functional connectivity in aging. We predict that (*Hyp. 2a*) functional connectivity (FC) during reward memory encoding will be increased between hippocampal memory systems and striatal reward systems by pharmaceutically enhancing dopamine via methylphenidate. Additionally, (*Hyp. 2b*) we predict that individuals with the greatest endogenous dopamine release will have the highest levels of hippocampal-striatal FC during memory encoding, when adjusting for individual differences in tau burden.

Aim 3: Determine whether baseline dopamine receptor density affects the potential for memory enhancement. *Hypothesis 3*: We predict that older adults with lower baseline D2/3 receptor density will show the greatest potential for memory improvements following pharmaceutically-induced dopamine enhancement, despite levels of tau. Exploratory follow-up analyses will assess the predictive power of subjects' cognitive (e.g. memory, attention), neuropsychiatric (e.g. depression, anxiety), and lifestyle measures (e.g. sleep, physical activity) on dopamine, tau, and memory, providing preliminary data for future studies.

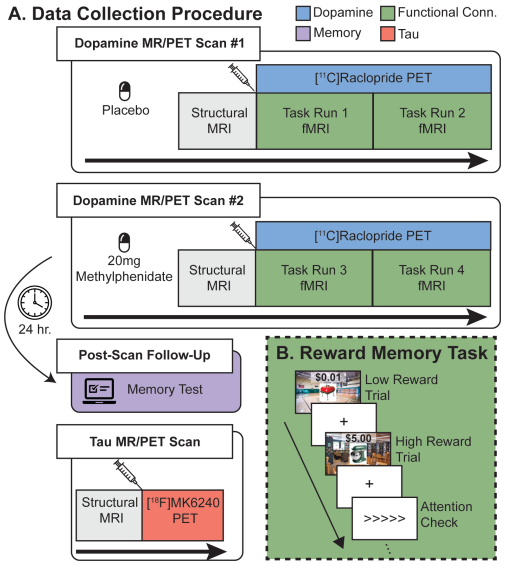

Fig. 1: (A) Participants complete two dopamine-PET scans (placebo and methylphenidate), a memory test, and a tau-PET scan. **(B)** Portion of reward memory encoding fMRI task.

Area of Research (3 Pages Max)

INNOVATION: This project leverages a unique training opportunity and collaboration between interdisciplinary researchers at the MGH Martinos Center for Biomedical Imaging where I am a Postdoctoral Fellow with Dr. Jacob Hooker, and Brandeis University where I am a Visiting Scientist with Dr. Anne Berry. The influences of dopamine and tau on cognitive aging and preclinical AD have mostly been studied independently. We will begin to bridge these subfields by studying the joint influences of tau and dopamine on memory together in the same individuals. We will use simultaneous MR/PET and pharmacological administration of methylphenidate to measure both between- and within-subjects differences in dopamine and memory performance. This work will provide critical evidence for how neurochemistry and protein pathology interact to affect memory in older adults, and may suggest a functional mechanism by which cognitive function is preserved in pre-clinical stages of AD.

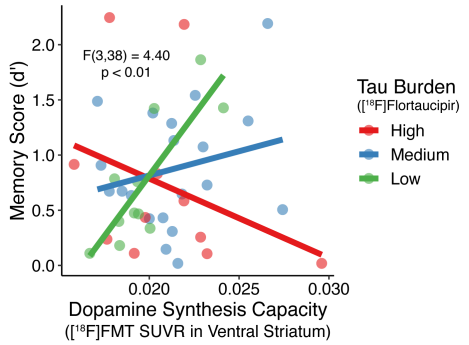

Fig. 2: Proof-of-concept data from a UC Berkeley study demonstrating that participants with low-tau (green) show a significant association between dopamine synthesis capacity and reward-memory, but that this relationship is disrupted in high-tau individuals (red). (*Provided by Dr. Berry.*)

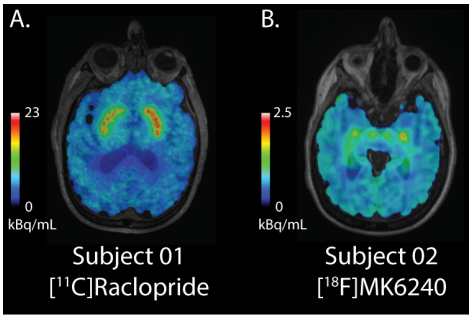

Fig. 3: Two healthy older adult participants from the proposed study. Preprocessed **(A)** [^{11}C]raclopride showing dopamine D2/3 receptor density **(B)** [^{18}F]MK6240 tau PET data.

PREVIOUS WORK: Proof-of-concept data from a UC Berkeley study demonstrates that there is a positive relationship between baseline dopamine *synthesis capacity* and memory score on a similar reward-memory task (see **Fig 2**, *data provided by Dr. Berry*). In the proposed research, we will expand upon this preliminary finding by (1) administering methylphenidate to pharmaceutically enhance dopamine, (2) measuring *endogenous dopamine release* instead of synthesis capacity, (3) using a 2nd-generation tau-PET tracer ([^{18}F]MK6240), and (4) collecting simultaneous fMRI to measure task-related changes in brain activity associated with dopamine release and tau burden.

METHODS: *Participants*: 45 cognitively unimpaired older adults with normal vision (ages 60-80, 50% female) will be recruited from the ongoing longitudinal Brandeis Aging Brain Study (BABS). Four full-time Brandeis staff members from Dr. Berry's lab will handle recruitment, scheduling, transportation and data collection of participants. The applicant will assist with data collection occasionally and will lead data analysis efforts. They will have no contra-indication to MRI or PET imaging, and will undergo an electrocardiogram (EKG) to ensure that it is safe for them to receive the 20mg methylphenidate medication (see *Recruitment Plan*). BABS participants also complete a comprehensive neuropsychological battery including measures of cognition, neuropsychiatric symptoms, and lifestyle factors (see *Data Sharing Plan* for a list of measures). **Currently, 40 subjects have completed the two dopamine MR/PET scans and the follow-up memory test. Five of these subjects also completed the tau-PET scan.** I have constructed reusable preprocessing pipelines to analyze the imaging data (example imaging data is shown in **Fig. 3**). Preliminary behavioral data that was analyzed from the first 21 participants suggests increased memory for high reward items presented during the methylphenidate session vs. placebo ($T(20) = 4.38$, $p = 0.01$).

***Reward-Memory Task*:** During each of the two simultaneous dopamine-PET/MRI scans (one with placebo, one with methylphenidate), participants will complete a reward-memory task in which they view items and are instructed to remember as many as possible. For each correctly remembered item, participants will receive a monetary reward. Items will appear in one of two contexts (indicated by a background photo): a high-reward context (library) worth $5.00 and a low-reward context (gymnasium) worth 1¢. 24-hours later participants

complete a memory test outside of the scanner, and are scored for hits, correct rejections, misses, and false alarms. Memory scores will be compared across the high/low-reward contexts and the placebo/methylphenidate scans.

***MRI*:** High-resolution structural (MPRAGE) scans will be collected to examine brain anatomy and T2* weighted EPI (TR=2.4s, TE=37ms, flip angle=45*) BOLD images will be collected to measure brain activity during memory encoding. MRI data will be preprocessed using fMRIPrep[15]. Seed-based functional connectivity will be calculated as the Fisher-Z transformed Pearson correlation in fMRI signal between subject specific hippocampal and striatal regions of interest (ROI). I have extensive experience analyzing functional connectivity data[16,17].

***PET*:** Two **[^{11}C]raclopride PET** scans (following oral placebo and 20mg methylphenidate administration) will be collected to measure baseline striatal D2/3 receptor density and endogenous dopamine release, as previously described[18]. Endogenous dopamine release is defined as percent change in binding potential between the two scans. Non-displaceable binding potential will be quantified using the simplified reference tissue model (cerebellar gray reference region)[19]. Analyses will focus on dorsal caudate ROIs which are implicated in reward memory[20,21]. **[^{18}F]MK6240 PET** will be used to measure tau in Braak I MTL regions (entorhinal cortex, hippocampus). This 2nd-generation tau tracer has reduced off-target binding and increased dynamic range, allowing us to quantify individual differences at a finer scale than was possible with 1st generation tracers[22,23]. Tau-PET data will be analyzed using Standardized Uptake Value Ratio (90-110 minutes, cerebellar gray reference region) as previously described[24,25]. PET data will be reconstructed/preprocessed using SPM and in-house scripts. Results will be compared both with and without partial volume correction (geometric transfer matrix method[26]). Dr. Price will provide training in PET image analysis and kinetic modeling.

***Blood Plasma Amyloid-β*:**Blood samples from BABS participants are processed by the Alzheimer's Clinical and Translational Research Unit at MGH. Aβ42/40 ratios will be calculated from Euroimmun ELISA assays and APOE genotype will be determined. Aβ42/40 and APOE genotype will be considered in secondary analyses[27,28].

Statistical Analyses: Aims 1 and 2 will employ linear mixed effects modeling to investigate the main effects of and interaction between dopamine and tau on memory scores (Aim 1) and hippocampal-striatal FC (Aim 2). In line with previous work from Dr. Berry's lab, models will include a covariate for time-lag between tau and dopamine scans[13,29]. Aim 3 will employ multiple regression to determine the if baseline D2/3 receptor density is associated methylphenidate-induced improvements in memory performance. ***Power*:** Using the UC Berkeley dataset from Fig. 1, we estimate medium to large effect sizes ($f^2 > 0.18$). To reach 80% power with α=.05, our sample size (n=45) is sufficient to detect interaction effects exceeding $F > 3.25$, (G*Power v3.1) which is in line with what we are expecting based on the preliminary data.

Potential Pitfalls & Alternatives: We predict that subjects with greater dopamine release will show better memory scores than would be expected, given their tau burden in Braak I regions. However, noteworthy work in animal models suggests that reduced dopamine clearance is associated with increased tau phosphorylation[30,31]. When interpreting our results, we will consider the possibility that increased dopamine release is associated with increased tau burden. If Secondary analyses will consider plasma levels of Aβ42/40 and APOE genotype in addition to tau burden. While brain-based PET measures of amyloid (e.g. using PiB) would be ideal, it is impractical given the time period of this project.

Feasibility: This proposal will leverage existing data supported by R01AG074330 and R00AG058748 (PI: Berry, Co-PI: Hooker). Currently 40 subjects have completed the [^{11}C]raclopride portion of the study, and five have also completed the [^{18}F]MK-6240 scan. Dr. Berry has experience using [^{11}C]raclopride in combination with methylphenidate to measure endogenous dopamine release[18]. Dr. Hooker and Dr. Price have experience using [^{18}F]MK6240 to measure tau burden[25,32]. I have extensive training in functional MRI and memory research[16,17,33].

Timeline: Data collection will be completed by the end of Year 1. Submission of a K99 application will occur during Year 2. Data analysis and manuscript preparation/submission will occur throughout the 3 years.

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