Personal Statement:

I grew up in a town called Braintree and have lived in the Boston area my entire life. Braintree is a strange name for a town, and when I was a kid I imagined that somewhere there must be a tree with brains growing out of it. I couldn't wait to find this tree, pick my very own brain from among the branches, and see what it looked like. I was wrong about the tree, but now as a postdoctoral fellow at Mass. General Hospital (MGH) and Brandeis I get to look at brains all the time! 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 aging and 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 in young adults. During my postdoc, I will expand upon my previous training to investigate the neurochemical factors that may preserve cognitive function in the face of AD pathology.

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 with Dr. Jacob Hooker 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 communities. I joined the International Society to Advance Alzheimer's Research and Treatment (ISTAART), attending several of the workshops and seminars they offer. 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 recently won a travel award to attend the NIH-supported *4th Workshop on Research Definitions for Reserve and Resilience in Cognitive Aging & Dementia* in December. Outside of the lab, I've participated in the Walk to End Alzheimer's and I've delivered guest lectures on my research 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. The NIH Loan Repayment Program, would give me the financial freedom I need in order to fully dedicate my time to research. Through the proposed research and training plan, I will establish myself as an expert in the field of multimodal neuroimaging of cognitive aging.

Training and Mentoring Plan:

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 research plan combines multimodal neuroimaging with advanced computational methods to track the cognitive and neural markers of AD in a longitudinal cohort of healthy older adults. I am a newcomer to the field of cognitive aging and Alzheimer's disease, and while I have a lot to learn, I also 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, publishing two first-authored and one co-authored manuscripts. During my postdoctoral fellowship, I will apply my previous quantitative and neuroscientific training to investigate the neurochemical factors that may preserve cognitive function in the face of AD pathology. **Together with Dr. Jacob Hooker (Mentor) and Dr. Anne Berry (Co-Mentor), I have developed a training plan to gain expertise in cognitive aging and AD-relevant research (Goal #1), learn innovative techniques for integrating MRI with PET neuroimaging (Goal #2), and receive training in leading collaborative, interdisciplinary scientific teams (Goals #3)**.

Training Goal #1: **Develop expertise in cognitive and neural changes related to aging and Alzheimer's disease.**

- **Weekly Check-in Meetings** with Dr. Hooker (Mentor) and Dr. Berry (co-Mentor)
- **Weekly Seminars on Cognitive Neuroscience:** BrainMap (MGH), Brown Bag (Brandeis)
- **Monthly Grand Rounds:** Neurology Department, MGH
- **Methodological Training** from postdocs in Dr. Berry's lab (Dr. Jenny Crawford and Dr. Hsiang-Yu Chen) for administering neuropsychological testing to older adults. (The BABS neuropsychological battery includes WASI, CVLT, WMS, MMSE)
- **Journal Clubs:** Alzheimer's Disease (MGH, run by Dr. Julie Price); Cognitive Aging (Brandeis, run by Dr. Jenny Crawford)
- **Workshop:** "Alzheimer's Fast Track" short course (BrightFocus Foundation - 1 week)\
- **Seminar** in Cognitive Aging and Alzheimer's Disease (taught by Dr. Berry at Brandeis).
- **Conferences:** Alzheimer's Association International Conference, Dallas Aging & Cognition, and Human Amyloid Imaging
- Finally, I recently won a **travel award** to attend the NIH-sponsored *4th Workshop on Research Definitions for Reserve and Resilience in Cognitive Aging and Dementia* in December, 2023.

Training Goal #2: **Establish myself as an expert in multimodal neuroimaging studies that incorporate structural and functional MRI with PET data.** *The proposed research will incorporate analysis of [11C]raclopride and [18F]MK6240 PET with functional MR images to measure the effects of dopamine and tau on functional connectivity and memory in aging.*

- **Monthly Seminars:** MGH Chemical Neuroscience Program's Human Imaging Meetings (organized by Dr. Nicole Zürcher)
- **Workshops:** Martinos Center's Pharmacokinetic Modeling Course (1-week) (organized by Dr. Julie Price); Turku PET Center online short course in PET/MRI (1 week)
- **"Green Badge" Certification** (safety training by Grae Alvarez & 20 hours of supervised scanning time) to independently run simultaneous MR/PET scans at MGH.
- **Methodological Training** in MR/PET acquisition and analysis from postdocs and faculty working with Dr. Hooker (including Dr. Tseng (Jane) Chieh-En, Dr. Nicole Zürcher, Dr. Hsiao-Ying (Monica) Wey, and Dr. Jessica Fang-Lu).
- **Conferences:** Organization for Human Brain Mapping; Nuclear Receptor Mapping

Training Goal #3: **Attain proficiency in collaborative scientific leadership, including multi-site research projects and cross-institutional collaborations.** *The proposed research will require intense collaboration across Brandeis University, a small liberal arts university, and MGH, a major research hospital.*

- **Biweekly Seminars:** "Martinnovate" (MGH, focusses on how to build collaborations across academia and industry).
- **Weekly Seminars:** "Science on Tap" (MGH, focusses on presenting your science to broad audiences).
- **Workshops:** Scientific Leadership for Future Faculty (twice monthly for 1 year; MGH Center for Faculty Development); K-Award Workshop (Spring Semester Year 1, MGH Center for Faculty Development 1hr/week)
- **Coursework:** Research Management (Harvard Business School – Fall Semester Year 1, 2hrs/week); Clinical Project Management Certification Program (Fall Semester Year 2, 1hr/week)
- **Mentoring** of graduate and undergraduate students working with Dr. Hooker and Dr. Berry.
- Dr. Hooker (mentor) and Dr. Berry (co-mentor) have agreed to include me in regular meetings with lab managers and clinical research staff to learn the ins-and-outs of lab administration. They have also assured me that I can take any data, analyses, and results that I collect as part of this proposal with me when I eventually start my own lab.

WRITING GOALS

- **Grants:** Currently, I have fellowship proposals under review at the NIA and the Alzheimer's Association. By the end of Year 2, I will use preliminary data from the proposed project to submit an NIH K-award. I will participate in the MGH Center for Faculty Development's workshop on writing K-grants (8 weeks online). Potential topics for the K-award include a longitudinal study of the associations between dopamine and tau on memory, or an investigation into the effects of dopamine and norepinephrine on brain network dynamics and executive functioning in aging and AD.
- **Abstracts:** I will submit abstracts to at least two national/international conferences each year. I will also present my work at local symposia, poster sessions, and invited talks. In November 2023, I will present preliminary results from the proposed work at the Society for Neuroscience meeting in Washington, D.C.
- **Manuscripts:** I recently published a co-authored paper with members of Dr. Berry's lab in *Neurobiology of Aging*, and will continue to co-author additional papers. I aim to publish at least three first-authored manuscripts from the proposed project. Potential paper titles include:
  1. An Investigation of Functional Connectivity Between the Hippocampus and Dorsal Striatum During Reward Memory in Healthy Older Adults
  2. The Effects of Baseline Dopamine D2/3 Receptor Density on Methylphenidate-Induced Improvements in Memory for Rewarding Stimuli in Aging
  3. Interactions between Entorhinal Tau-Burden and Dopamine Enhancement on Reward Memory in Healthy Older Adults.

Prepared by Dr. Hooker & Dr. Berry: I (Dr. Hooker) have been fortunate to supervise many impressive graduate students, and postdoctoral fellows since I began my independent career at MGH in 2009. I have sponsored a total of 5 predoctoral trainees and 32 postdoctoral trainees, including co-sponsorship of two NIH Career Awards. In 2010 I was awarded the Presidential Early Career Award for Scientists and Engineers by President Obama. The citation from the President noted my unique commitment to science mentorship, something I am particularly proud of. On my Google Scholar page, you will see that these days I am usually a middle-author on publications. This is because my current and former trainees typically lead the publication effort as first or last author. Many of my trainees have gone on to secure prestigious roles in academia (Assistant/Associate Professor at Harvard Medical School, the University of Arkansas, Cairo University (Egypt), KU Leuven (Germany), Gonzagga University) and industry (Charles River Analytics, Novartis, Pfizer, Mayo Clinic, Merck).

Including Tom, I currently supervise four postdoctoral fellows, two of whom are co-mentored with other Professors within the Martinos Center's Chemical Neuroscience Program. Outside of research, my main responsibilities are administrative. I am the Director of Radiochemistry at the MGH Martinos Center and the Scientific Director at the MGH Lurie Center for Autism. I have maintained productivity and effective mentoring with this workload for the last decade. Dr. Berry is an Assistant Professor of Neuroscience and Psychology at Brandeis University, where she started her lab in 2019. Currently Dr. Berry supervises three postdoctoral fellows including Tom, and five PhD students. Dr. Hooker and Berry have a strong ongoing collaborative research program and have co-mentored several students, technicians, and research assistants together. Currently, we are co-mentors on an NIA F31 (NRSA) fellowship (F31 AG079515).

We are committed to each meeting with Tom weekly to maintain progress towards his research and professional goals. Tom will regularly present at our lab meetings and we will encourage Tom to submit abstracts/presentations to major meetings including Human Amyloid Imaging, Society for Neuroscience, the Alzheimer's Association International Conference, and the Dallas Aging and Cognition Conference. We will also advise Tom on manuscript preparation and his work will be submitted to top journals in the field. Tom will also submit a K99/R00 award to secure independent funding.

We are highly committed to Tom's career development and his research project. Through collaborations with Dr. Berry, Tom will analyze data collected as part of the Brandeis Aging Brain Study. He will also assist with and receive training on MRI and PET data collection with older adult participants, occurring at the Martinos Center. **The proposed project will leverage data being collected for current NIA projects (NIA R01AG074330, R00AG058748, PI: Dr. Anne Berry, Co-PI: Dr. Hooker).** As a postdoc at the MGH Martinos Center, Tom will have the opportunity to interact with other researchers including several renowned ADRD experts. Already he has met with Dr. Heidi Jacobs and Dr. Brad Dickerson to discuss various aspects of this proposal. He will also have the opportunity to collaborate and interact with other researchers using simultaneous MR/PET neuroimaging including Dr. Nicole Zurcher and Dr. Hsiao-Ying Wey. We have a team of radiochemists, MR/PET technicians, phlebotomists, nurses, and an MD on staff who can interpret EKGs and prescribe methylphenidate that will be used in the proposed research project.

Dopamine, Tau, and Memory in Aging: An Integrative Investigation

Thomas Morin, PhD
Massachusetts General Hospital
November, 2023

SPECIFIC AIMS

Normal aging is associated with both dopamine system dysfunction and the aggregation of hyperphosphorylated tau[1,2]. These alterations in neural systems are broadly considered to arise through independent processes, and are thus studied independently. Dopamine-centric fields propose that age-related declines in memory are mediated through reductions in dopamine (e.g. the "correlative triad" hypothesis[3,4]). Alternatively, advancements in positron emission tomography (PET) imaging have inspired Alzheimer's disease (AD)-centric fields to propose that medial temporal lobe tau pathology is the major driver of reduced memory performance, even in cognitively unimpaired individuals[5]. Evidence from our group suggests there are interactions between age-related neuromodulatory changes and neuropathological changes in predicting memory performance[6,7]. While individuals with a "double hit," meaning reduced dopamine receptors and higher tau burden, will likely show poorest aging trajectories, we find that maintaining or restoring dopamine can produce better-than-expected memory performance given neural losses[7].

Understanding the many factors that influence age-related cognitive decline is essential for predicting who will benefit most from future therapies that may target the dopamine system and/or tau aggregates. The overall objective of this proposal is to study the joint effects of dopamine and tau on episodic memory in cognitive aging. In this proposal, I outline a study using simultaneous MR/PET neuroimaging to investigate the relationship between dopamine availability, tau burden, and memory in aging. We will use [^{11}C]raclopride to measure dopamine D2/3 receptor density and simultaneous fMRI 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]MK-6240 scan to measure tau burden. Our proposal will sample from an existing cohort of subjects participating in a longitudinal study of cognitive aging at Brandeis University. Our central hypothesis is that increased levels of dopamine receptor density are protective in aging, and can stabilize memory performance in the face of tau burden.

Aim 1: Define the independent and interactive effects of dopamine and tau pathology on memory in aging. *Hyp. 1:* Tau will moderate the relationship between dopamine and memory. From preliminary data, we predict that individuals with lower levels of tau will show a significant positive relationship between dopamine D2/3 receptor density and memory, but that this relationship 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: Define the best predictors of who will show memory benefits following dopamine enhancement. The Brandeis Aging Brain Study provides us with additional cognitive, behavioral, and biological measures for all participants. We will conduct a partial least squares correlation analysis to determine which brain measures best predict memory benefits following dopamine enhancement. *Hypothesis 3*: We predict that older adults with lower D2/3 receptor density will show the greatest potential for memory improvements following pharmaceutically-induced dopamine enhancement, despite levels of tau. Brain measures will include D2/3 receptor density, endogenous dopamine release, regional tau pathology, regional activation, and functional connectivity. Exploratory analyses will also consider plasma amyloid, plasma tau, neuropsychological measures (e.g., executive function), years of education, and trait anxiety.

The proposed work capitalizes on a unique collaborative training opportunity between interdisciplinary researchers at the MGH Martinos Center for Biomedical Imaging and Brandeis University. Through this project I will gain expertise in cognitive aging and advanced fMRI/PET methodologies, mentor graduate and undergraduate students, publish scientific manuscripts, and apply for independent funding for future follow-up studies, setting me on a path toward independence and significant scientific impact.

Research Strategy:

SIGNIFICANCE

A recent position paper from a working group of Alzheimer's researchers 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[8]. Previously, most research on the dopaminergic system in older adults has not considered AD biomarkers such as neural and plasma markers of tau and amyloid burden. 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.

Tau and Dopamine in Cognitive Aging: The deposition of hyperphosphorylated tau is an inevitable part of aging that occurs years before the onset of disabling AD symptoms[1,2]. In clinically normal older adults, medial temporal lobe tau burden is associated with memory performance[5,9,10]. Normal aging also involves dopamine system decline (striatal dopamine innervation decreases at a rate of 6-10% per decade)[11]. Disruption to the dopamine system is associated with age-related deficits in memory and executive functioning[3,4,12]. Pharmacologically enhancing dopamine in older adults has been shown to improve memory performance and strengthen associated MRI brain measures[13,14]. 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[6,15].

Dopamine, Age, and Functional Connectivity: Memory for rewarding events is modulated by activation of dopamine-rich midbrain regions and the projection of dopaminergic pathways into hippocampal memory systems[16,17]. As a neuromodulator, dopamine tunes activity in target brain regions. Prior studies of older adults suggest that dopamine may have a steadying influence on the dynamics of neural signals in the striatum[18–20]. Additionally, previous work has demonstrated a link between dopamine receptor availability and hippocampal-striatal functional connectivity[12]. Understanding the interacting influences of dopamine receptor availability and tau burden on functional connectivity could offer insight into how memory is preserved in older adults who are resilient to cognitive decline.

Conceptual model and key hypotheses: Based on a proof-of-concept analysis of data from a study at UC Berkeley (see **Fig. 1**), we predict that dopamine release is positively associated with memory performance in older adults, but that this relationship is disrupted in the presence of elevated tau. We predict that the dopaminergic system improves memory by modulating functional connectivity between hippocampal memory systems and striatal reward systems during memory encoding. We predict that tau aggregation dampens this effect by disrupting dopamine's ability to act on hippocampal memory circuits. Successful completion of this research will improve our understanding of who might benefit from future therapies that target the dopamine system in cognitive aging. Additionally, this research may improve our understanding of how the dopamine system is associated with cognitive resilience in healthy older adults.

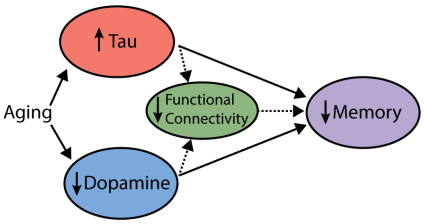


Fig. 1: Aims 1-3 will test our conceptual model that tau burden and dopamine dysfunction are associated with poorer memory in aging. Aim 1 will test the joint effects of tau and dopamine on memory. Aim 2 will test the influence of tau and dopamine on hippocampal-striatal functional connectivity. Aim 3 will determine the factors that best predict memory benefits following pharmaceutically-induced dopamine enhancement.

Strengths and weaknesses in the rigor of prior research: Previously, research has considered dopamine and tau largely in isolation of each other. By considering how protein pathology and neuromodulatory systems interact in the aging brain, we can build a multifactorial explanation of how memory is affected in aging. We will use simultaneous MR/PET and pharmacological administration to measure both between-subjects and within-subjects differences in dopamine and memory performance.

TRAINING POTENTIAL & INNOVATION: The proposed work will leverage 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. Previously I have studied memory and learning in healthy young adults using fMRI. Through this proposal, I will expand my expertise into the field of cognitive aging, learn to integrate fMRI and PET

neuroimaging modalities, and learn to lead interdisciplinary groups in team-based science. I will present this work at local, regional, and international conferences and plan to publish at least three manuscripts from this study (*see Mentorship & Training Plan)*. This work will provide critical proof-of-concept support for how neurochemistry and protein pathology interact to affect memory in older adults, and may suggest a functional mechanism by which cognition is preserved in the pre-clinical stages of AD. In Year 2 of this project, I will use data from this study to submit a K99/R00 proposal. This will help me to transition to an independent faculty position, studying the role of neuromodulators in cognitive aging and disease.

APPROACH: We will use simultaneous [^{11}C]raclopride PET/MRI and administration of methylphenidate to measure dopamine release and hippocampal activity during a reward-memory task in older adults. [^{18}F]MK-6240 PET will be collected in a separate scanning session for assessment of medial temporal lobe tau. Aims 1-3 will use the same dataset. **All experimental procedures involving human subjects are approved by the MGH Institutional Review Board**.

Experimental Design and Methods:

<u>*Participants*</u>: 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). **They will have no contra-indication to MRI or PET imaging, will undergo an electrocardiogram (EKG), and will be screened by a nurse practitioner to ensure that it is safe for them to receive the 20mg methylphenidate medication**. Participants are defined as cognitively normal based on their performance on the BABS neuropsychological battery, which was developed by Dr. Berry (Co-Mentor) in consultation with clinical psychologists. **Currently 45 subjects have completed the [^{11}C]raclopride portion of the study; ten have also completed the [^{18}F]MK-6240 scan.**

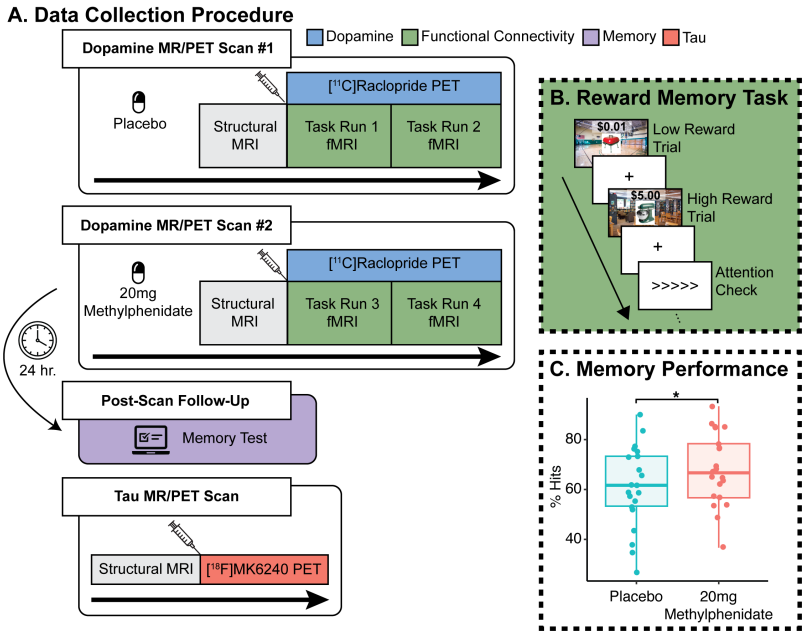


Fig. 2: (A) Participants will complete two dopamine-PET scans (placebo and 20mg methylphenidate), a memory test, and a tau-PET scan. **(B)** Reward memory fMRI task. **(C)** Preliminary data showing improved memory with methylphenidate ($T(20)=4.38$, $p<0.01$)

<u>*Study Design:*</u> Simultaneous MR/PET brain images will be collected at the MGH Martinos Center to measure brain activity and dopamine D2/3 receptor binding potential (with [^{11}C]raclopride) during a reward-memory task. Participants will complete a two-scan protocol on the same day: first with placebo, followed by a second scan after oral administration of methylphenidate (20 mg), which increases synaptic dopamine concentrations by blocking dopamine re-uptake. The tau-PET scan (using [^{18}F]MK-6240) will be completed in a separate session no more than one year after the initial session. (**Fig. 2a**)

<u>*Reward-Memory Task*</u>: 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 are instructed to view and remember as many items as possible. Participants will receive a monetary reward corresponding to the value of the items they correctly remember. Items will appear in one of two contexts (indicated by a background photo): a high-reward context (library) worth $5.00 and a low-reward context (gymnasium) worth 1¢. 24-hours later during a follow-up session outside the scanner, participants complete a memory test. Memory will be scored for correct recognition (hits), false alarms, and correct context memory. We will compare memory scores within subjects across the high and low-reward contexts and during the placebo and methylphenidate scans. Preliminary data (**Fig. 2c**) shows that methylphenidate administration is associated with improved correct recognition (% hits) for the stimuli across all contexts ($T(20)=4.38$, $p < 0.01$).

MRI Acquisition: During the first scanning session, we will acquire high-resolution structural (MPRAGE) and FLAIR scans to examine brain anatomy. Then, T2* weighted EPI (TR=2.4s, TE=37ms, flip angle=45°) BOLD images will be collected during the reward memory task. FLAIR scans will be reviewed by a qualified radiologist for potential participant exclusion due to large white matter hyperintensities.

PET Acquisition: 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[21] (see **Fig. 3**). **Methylphenidate is used only as a methodological tool for optimizing measurement of dopamine release. It is implemented solely for methodological and not clinical purposes. All eligible participants are administered methylphenidate and undergo the same PET scanning procedures.** For each scan, participants will receive a bolus injection of approximately 10mCi of [^{11}C]raclopride administered to the antecubital vein. Non-displaceable binding potential will be quantified using the simplified reference tissue model (cerebellar gray reference region)[22]. Endogenous dopamine release is defined as percent change in binding potential between the two scans. Analyses will focus on dorsal caudate ROIs which are implicated in reward memory[23,24]. **[^{18}F]MK6240 PET** will be used to measure tau in Braak I MTL regions (entorhinal cortex, hippocampus). Compared to [^{18}F]Flortaucipir (a first-generation tau tracer), [^{18}F]MK-6240 shows increased dynamic range in Standardized Uptake Value Ratio (SUVR), reduced off-target binding in choroid plexus, and improved quantification of early tau (Braak I regions) in cognitively unimpaired older adults[25,26]. Analysis will follow POINTER neuroimaging ancillary protocols (SUVR 90-110 min.)[27]. Data will be partial volume corrected using the Rousset geometric transfer matrix method.[28]

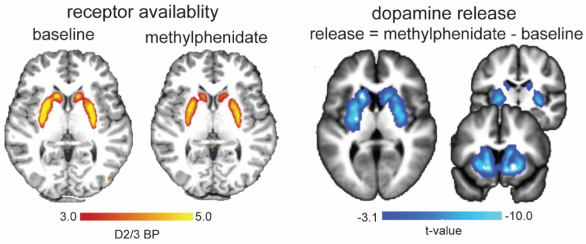


Fig. 3: Dopamine D2/3 Receptor availability is measured with [^{11}C]raclopride (left). Dopamine release is quantified by comparing placebo and methylphenidate scans (right) (Berry et al., 2018).

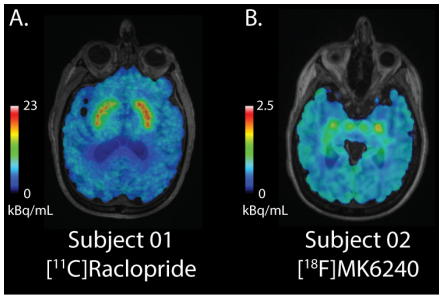
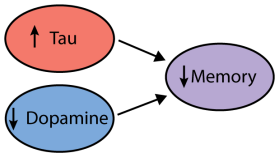


Fig. 4: Two healthy older adult participants from the proposed study. Preprocessed **(A)** [11C]raclopride showing dopamine D2/3 receptor density & **(B)** [18F]MK6240 tau PET.

Blood plasma amyloid-β a ptau181: To measure blood plasma amyloid-β and ptau181, blood samples are acquired from participants in the Brandeis Aging Brain Study. These samples are processed by the Alzheimer's Clinical & Translational Research Unit at Massachusetts General Hospital, and is supported by Dr. Anne Berry's R01AG074330 (Dr. Hooker, Co-PI). Aβ42/40 ratios will be calculated from Aβ42 and Aβ40 levels obtained from Euroimmun ELISA assays. Lower Aβ42/40 ratios have been associated with greater cortical amyloid as measured by PET, steeper cognitive decline, and increased risk of developing AD later on[29,30]. Recent work suggests that levels of ptau181 are also associated with cortical amyloid[31]. Aims 1-3 will account for Aβ42/40 status a ptau181 levels in secondary analyses.

Aim 1: Define the independent and interactive effects of dopamine and tau on memory in aging.

Rationale: Normal aging is associated with dopamine-system dysfunction and the aggregation of phosphorylated tau in the medial temporal lobe. Most previous work examining the effects of tau and dopamine on cognitive aging have considered the two variables independently. The objective of this aim is to examine the interactive effects of tau and dopamine on reward-memory in aging. We will test the working hypothesis that low-tau individuals show a strong relationship between dopamine and memory, but that this relationship is disrupted in the context of higher tau.



Proof-of-Concept Data: We analyzed pre-existing data from a UC Berkeley study using [^{18}F]Fluoro-m-tyrosine and [^{18}F]Flortaucipir PET datasets to examine the relationship between dopamine synthesis capacity and tau burden in participants from the Berkeley Aging Cohort Study (n=42) (*Data courtesy of Dr. Anne Berry: Co-Mentor*). These data demonstrate that low-tau individuals (green) show a positive relationship between dopamine-synthesis capacity and memory, but that this relationship is disrupted in individuals with higher levels of entorhinal tau (red) $F(3,38) = 4.40$, $p < 0.01$ (**Fig. 5**). **Our proposed study expands upon this result by measuring *endogenous dopamine release* (using**

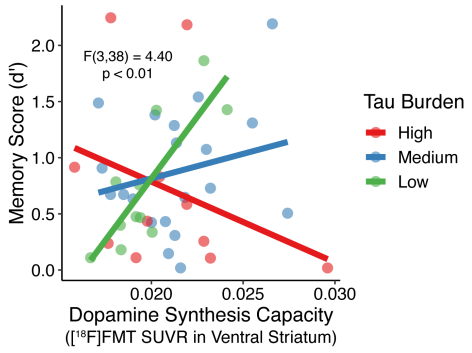


Fig. 5: Proof-of-concept data from a UC Berkeley study demonstrating that participants with low-tau (green) show a significant association between dopamine synthesis capacity and reward memory, but that this relationship is disrupted in high-tau individuals (red). (*Provided by Dr. Berry*)

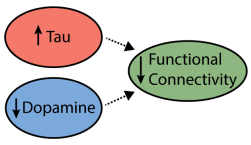
[^{11}C]raclopride and methylphenidate) rather than dopamine synthesis-capacity. We will also use the second-generation radiotracer [^{18}F]MK-6240 to measure tau. This tracer boasts approximately twice the dynamic range in SUVRs compared to [^{18}F]Flortaucipir, which will allow us to more accurately detect early tau (Braak I regions) in cognitively normal older adults[25–27,32,33].

Research Design & Hypothesis Testing: Baseline dopamine D2/3 receptor density will be measured as [^{11}C]raclopride binding potential in the dorsal striatum during the placebo scan (scan 1)[12]. Tau burden will be measured as [^{18}F]MK6240 SUVR in entorhinal cortex and hippocampus. Memory will be measured as the difference between correct hits and false alarms (d') on the memory test. A generalized linear regression model will quantify the association between memory scores and (1) baseline dopamine D2/3 receptor density, (2) entorhinal tau burden, and (3) the interaction between dopamine D2/3 receptor density and entorhinal tau burden. **An adjusted model will also be considered which accounts for age, sex, years of education, elapsed time between [^{11}C]raclopride and [^{18}F]MK6240 scans, and plasma Aβ42/40 and ptau181**. Hypothesis 1 predicts a significant interaction effect whereby individuals with low tau burden will show a significant relationship between dopamine D2/3 receptor expression and memory scores, but that this relationship will be disrupted in high-tau individuals. Graphical summaries and residual analyses will be performed to assess modeling assumptions (e.g., linearity, normality of residuals). Model results will be submitted to statistical significance testing including correction for multiple comparisons.

Alternative Approaches: Other health factors may obscure the predicted relationship with memory scores. Secondary analysis will consider the influence of lifestyle factors including sleep (PSQI)[34], physical activity (CHAMPS)[35], and cognitive reserve proxies (LEQ)[36], which are collected during BABS neuropsychological testing. Aim 3 will examine the relative influence of brain measures on memory scores in greater detail using a partial least squares correlation (PLSC) analysis. Finally, some participants may not qualify for the methylphenidate administration (i.e., due to EKG contraindication). These participants will be included in between-subject analyses of baseline D2/3 receptor density, tau burden and memory.

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.

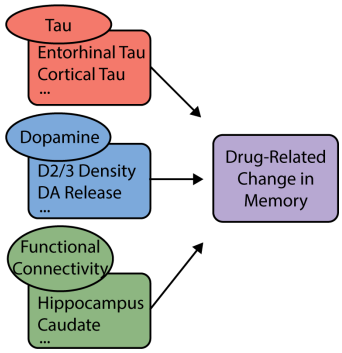


Research Design & Hypothesis Testing: Seed-to-seed functional connectivity analysis will assess the correlation in brain activity (BOLD signal) during pre- and post-task resting state as well as high- and low-reward memory encoding conditions of the task. Resting state functional connectivity will be calculated as the Pearson correlation between mean BOLD signal timecourses across all voxels in each region of interest (dorsal caudate and hippocampus). Task-based functional connectivity will also be calculated as the Pearson correlation of BOLD signal residuals between seed regions during specific task conditions, after regressing out primarily task-based signal (see Hearne et al. 2017 and Morin et al. 2023 for methodology). Prior to calculating functional connectivity, BOLD images will undergo standard preprocessing with fMRIPrep, standard denoising (including regressors for head motion, mean white matter signal, mean CSF signal, scrubbing of high motion timepoints), and bandpass filtering to isolate low-frequency fluctuations in the signal that are most likely to be related to spontaneous hemodynamic fluctuations. The applicant has extensive previous experience conducting functional connectivity analyses with fMRI data[37,38]. Hyp 2a. predicts that functional connectivity between hippocampal memory systems and striatal reward systems will be stronger during the methylphenidate scan compared to the placebo scan. Hyp. 2b. predicts that increases in functional connectivity will be related to dopamine release (calculated as the percent change in [^{11}C]Raclopride binding potential between placebo and methylphenidate scans), but that this relationship will be attenuated in the context of increased tau burden. **Follow-up analyses will also consider age, sex, and years of education, and plasma measures of tau and amyloid-β**.

Alternative Approaches: We are investigating the relationship between dopamine release and functional connectivity because of prior work suggesting that dopamine may have a steadying influence on the dynamics of neural signals in the striatum[18–20]. Additionally, previous work has demonstrated a link between dopamine receptor availability and hippocampal-striatal functional connectivity[12]. We will also investigate univariate amplitude of BOLD signal, which is modulated by dopaminergic pharmaceuticals and reward-memory tasks[39,40]. Finally, it is possible that dopamine modulates functional connectivity in many brain regions beyond the striatum and hippocampus. We will employ graph theory methods to investigate the whole-brain functional connectivity changes associated with dopamine release and tau burden.

Aim 3: Define the best predictors of who will show memory benefits following dopamine enhancement.

Rationale: A robust literature suggests that not all individuals benefit equally from an increase in dopamine availability (e.g. inverted-U trends)[41–43]. Partial least squares correlation (PLSC) is a multivariate statistical approach that has been employed to identify patterns of interindividual brain measures that optimally explain interindividual differences in cognitive measures[44–46]. The *objective* of this aim is to determine which factors best predict memory enhancement in our sample of older adults. Using PLSC, we will test the *working hypothesis* that lower baseline dopamine D2/3 receptor availability and lower tau pathology best predict pharmaceutically-induced improvements in memory performance.



Preliminary Data: Dr. Berry's (Co-Mentor) lab has employed PLSC models to examine the multivariate relationships between one latent variable extracted from locus coeruleus brain measures and a second latent variable extracted from neuropsychological scores (**Fig. 6A**)[44,47]. To examine which specific brain measures best explained interindividual differences in neuropsychological scores, a bootstrap method was employed (**Fig. 6B**). Red bars indicate brain measures that were most predictive in this model, in this case MRI and PET measures from the rostral locus coeruleus.

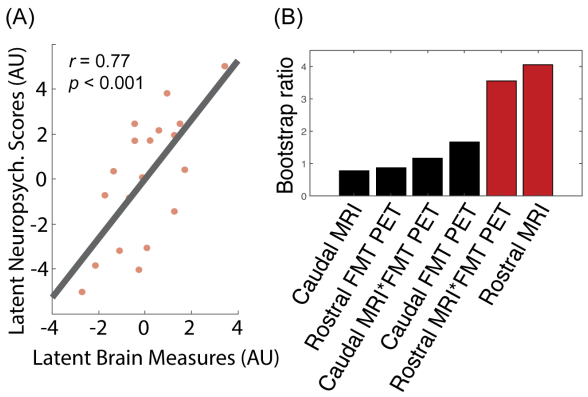


Fig. 6: Example PLSC Analysis (A) Scatter plot depicting the association between latent brain measures and latent neuropsychological scores. **(B)** Contribution of individual brain measures to the latent PLSC variable (bootstrap ratios > 1.96 in red are considered reliable). (Adapted from [47].)

Research Design & Hypothesis Testing: We will employ a PLSC analysis to capture the multivariate association between improved memory performance following methylphenidate administration and neurocognitive measures. The PLSC analysis will estimate the brain measures that are maximally related to interindividual differences in memory performance. Brain measures in the model will include baseline D2/3 receptor density ([^{11}C]raclopride binding potential during placebo scan), endogenous dopamine release (the percent change in [^{11}C]raclopride binding potential during placebo scan vs. the methylphenidate scan), entorhinal and hippocampal tau burden ([^{18}F]MK-6240 SUVR), and hippocampal-striatal functional connectivity on and off methylphenidate. To evaluate the statistical strength of the latent variables that are extracted by the PLSC method, a bootstrapping procedure (n = 10,000) will be employed. Vector weights with bootstrap ratios <-1.96 or >1.96 will be considered reliable. **Follow-up analyses will also consider age, sex, and years of education, and plasma measures of tau and amyloid-β**.

Alternative Approaches: Our older adult sample of n=45 should reliably show interindividual differences in brain imaging and neuropsychological measures. However, extrapolating interindividual differences to the general population may be difficult with a sample of this size. Follow-up analyses can also be conducted in large open datasets such as ADNI and the Human Connectome Lifespan dataset to validate the predictors we identify in our sample. Successful completion of this research will improve our understanding of who might benefit from future therapies that target the dopamine system in cognitive aging. Additionally, this research may improve our understanding of how the dopamine system is associated with cognitive resilience in healthy older adults.

Statistical Power 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). Aim 3 will employ a partial least squares correlation analysis (PLSC) to determine the biomarkers (dopamine, tau, and FC) that best predict pharmaceutically-induced change in memory scores. Follow-up/exploratory PLSC analyses will also examine the cognitive, neuropsychiatric, and lifestyle factors that best predict pharmaceutically-induced change in memory scores. ***Power*:** We estimate medium effect sizes ($f^2 > 0.18$) from our preliminary data (see Fig. 1). Assuming 80% power and 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.

Feasibility: This proposal will leverage data being collected for ongoing projects: R01AG074330 and R00AG058748 (PI: Berry, Co-PI: Hooker). Currently 45 subjects have completed the [^{11}C]raclopride portion of the study, and ten 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[21]. Dr. Hooker and has experience using [^{18}F]MK6240 to measure tau burden[48,49]. I have extensive training in functional MRI and memory research[37,38,50]. My role in the project will be to lead the team of graduate students and full-time research staff in experimental design, subject recruitment, data collection, analysis, and publication of results.

Timeline: Data collection and analysis will be completed by the end of Year 1. Submission of a K99 award application and manuscript preparation/submission will occur during Year 2 (see *Training & Mentoring Plan*).

Future Directions: Expanding upon the proposed project, I will write and submit a career development award (e.g. K99). Possible topics include investigating the longitudinal implications of endogenous dopamine release on the relationship between tau burden and memory, or examining the dynamic brain network changes that are modulated by dopamine in older adults and AD. With the BABS longitudinal cohort, we have the unique capability of "deep sampling" within the same participants – acquiring a range of measurements to assess the influence of both neurochemistry and protein pathology on cognition over time and throughout healthy/pathological aging.

References:

1. Braak, H., et al. Stages of the pathologic process in Alzheimer disease... *J. Neuropathol. Exp. Neurol.* (2011).
2. Braak, H. & Del Tredici, K. The pathological process underlying Alzheimer's.... *Acta Neuropathol. (Berl.)* (2011).
3. Bäckman, L., et al. The correlative triad among aging, dopamine, and cognition: Current status and future prospects. *Neurosci. Biobehav. Rev.* (2006).
4. Bäckman, L., et al. Linking cognitive aging to alterations in dopamine neurotransmitter functioning: Recent data and future avenues. *Neurosci. Biobehav. Rev.* (2010).
5. Maass, A. *et al.* Entorhinal Tau Pathology, Episodic Memory Decline, and Neurodegeneration… *J. Neurosci.* (2018).
6. Ciampa, C. J. *et al.* Associations among locus coeruleus catecholamines, tau... *Neuropsychopharmacol.* (2022)
7. Ciampa, C. J. *et al.* Elevated Dopamine Synthesis as a Mechanism of Cognitive Resilience... *Cereb. Cortex* (2022).
8. Ehrenberg, A. J. *et al.* Priorities for research on neuromodulatory subcortical systems in Alzheimer's disease: Position paper from the NSS PIA of ISTAART. *Alzheimers Dement. J. Alzheimers Assoc.* (2023).
9. Mitchell, T. W. *et al.* Parahippocampal tau pathology in healthy aging, mild cognitive impairment, and early Alzheimer's disease. *Ann. Neurol.* 2002).
10. Hanseeuw, B. J. *et al.* Association of Amyloid and Tau With Cognition in Preclinical Alzheimer Disease: A Longitudinal Study. *JAMA Neurol.* (2019).
11. Scherman, D. *et al.* Striatal dopamine deficiency in parkinson's disease: Role of aging. *Ann. Neurol.* (1989).
12. Nyberg, L. *et al.* Dopamine D2 receptor availability is linked to hippocampal–caudate functional connectivity and episodic memory. *Proc. Natl. Acad. Sci.* (2016).
13. Chowdhury, R., et al. Dopamine Modulates Episodic Memory Persistence in Old Age. *J. Neurosci.* (2012).
14. Gibbs, S. E. B. & D'Esposito, M. Individual capacity differences predict working memory performance and prefrontal activity following dopamine receptor stimulation. *Cogn. Affect. Behav. Neurosci.* (2005).
15. Berry, A. S., et al. The Influence of Dopamine on Cognitive Flexibility Is Mediated by Functional Connectivity in Young but Not Older Adults. *J. Cogn. Neurosci.* (2018).
16. Lisman, J., et al. A neoHebbian framework for episodic memory; role of dopamine... *Trends Neurosci.* (2011).
17. Shohamy, D. & Adcock, R. A. Dopamine and adaptive memory. *Trends Cogn. Sci.* (2010).
18. Garrett, D. D. *et al.* Amphetamine modulates brain signal variability and working memory in younger and older adults. *Proc. Natl. Acad. Sci.* (2015).

19. Grady, C. L. & Garrett, D. D. Understanding Variability in the BOLD Signal and Why it... *Brain Imaging Behav.* (2014).
20. Garrett, D. D. *et al. Dynamic regulation of neural variability during working memory reflects dopamine, functional integration, and decision-making*. (2022).
21. Berry, A. S. *et al.* Dopamine Synthesis Capacity is Associated with D2/3 Receptor Binding but Not Dopamine Release. *Neuropsychopharmacology* (2018).
22. Gunn, R. N., et al. Parametric imaging of ligand-receptor binding in PET using a simplified... *NeuroImage* (1997).
23. Berry, A. S. *et al.* Aging Affects Dopaminergic Neural Mechanisms of Cognitive Flexibility. *J. Neurosci.* (2016).
24. Dang, L. C., et al. Dopamine Supports Coupling of Attention-Related Networks. *J. Neurosci.* (2012).
25. Betthauser, T. J. *et al.* In Vivo Characterization and Quantification of Neurofibrillary Tau PET Radioligand 18F-MK-6240 in Humans from Alzheimer Disease Dementia to Young... *J. Nucl. Med. Off. Publ. Soc. Nucl. Med.* (2019).
26. Gogola, A. *et al.* Direct Comparison of the Tau PET Tracers 18F-Flortaucipir and 18F-MK-6240... *J. Nucl. Med.* (2022).
27. Harrison, T. M. *et al.* Optimizing quantification of MK6240 tau PET in unimpaired older adults. *NeuroImage* (2022).
28. Rousset, O. G., Ma, Y. & Evans, A. C. Correction for partial volume effects in PET: principle and validation. *J. Nucl. Med. Off. Publ. Soc. Nucl. Med.* (1998).
29. Cullen, N. C. *et al.* Plasma biomarkers of Alzheimer's disease improve prediction of cognitive decline in cognitively unimpaired elderly populations. *Nat. Commun.* (2021).
30. Lin, S.-Y. *et al.* Plasma amyloid assay as a pre-screening tool for amyloid positron emission tomography imaging in early stage Alzheimer's disease. *Alzheimers Res. Ther.* (2019).
31. Murray, M. E. *et al.* Global neuropathologic severity of Alzheimer's disease and locus coeruleus vulnerability influences plasma phosphorylated tau levels. *Mol. Neurodegener.* (2022).
32. Lois, C., et al. PET imaging of tau protein targets: a methodology perspective. *Brain Imaging Behav.* (2019).
33. Sanchez, J. S. *et al.* The cortical origin and initial spread of medial temporal tauopathy in Alzheimer's disease assessed with positron emission tomography. *Sci. Transl. Med.* (2021).
34. Buysse, D. J., et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric... *Psychiatry Res.* (1989).
35. Stewart, A. L. *et al.* CHAMPS physical activity questionnaire for older adults… *Med. Sci. Sports Exerc.* (2001).
36. Valenzuela, M. J. & Sachdev, P. Assessment of complex mental activity across the lifespan: development of the Lifetime of Experiences Questionnaire (LEQ). *Psychol. Med.* (2007).
37. Morin, T. M., et al. Dynamic Network Analysis Demonstrates the Formation of Stable Functional Networks During Rule Learning. *Cereb. Cortex* (2021).
38. Morin, T. M., et al. Functional reconfiguration of task-active frontoparietal control network facilitates abstract reasoning. *Cereb. Cortex* (2022).
39. Schlösser, R. g. m. *et al.* Dopaminergic modulation of brain systems subserving decision making under uncertainty: A study with fMRI and methylphenidate challenge. *Synapse* (2009).
40. Farr, O. M. *et al.* The effects of methylphenidate on cerebral activations to salient stimuli in healthy adults. *Exp. Clin. Psychopharmacol.* (2014).
41. Cools, R. Dopaminergic control of the striatum for high-level cognition. *Curr. Opin. Neurobiol.* (2011).
42. Cools, R. & D'Esposito, M. Inverted-U-shaped dopamine actions on human working... *Biol. Psychiatry* (2011).
43. Vijayraghavan, S., et al. Inverted-U dopamine D1 receptor actions on prefrontal neurons engaged in working memory. *Nat. Neurosci.* (2007).
44. Dahl, M. J. *et al.* Locus coeruleus integrity is related to tau burden and memory loss in autosomal-dominant Alzheimer's disease. *Neurobiol. Aging* (2022).
45. Krishnan, A., et al. Partial Least Squares (PLS) methods for neuroimaging: a tutorial and review. *NeuroImage* (2011).
46. McIntosh, A. R. & Lobaugh, N. J. Partial least squares analysis of neuroimaging data... *NeuroImage* (2004).
47. Chen, H.-Y. *et al.* Interactive effects of locus coeruleus structure and catecholamine synthesis capacity on cognitive function. *Front. Aging Neurosci.* (2023).
48. Fu, J. F. *et al.* Kinetic evaluation and assessment of longitudinal changes in reference region and extracerebral [18F]MK-6240 PET uptake. *J. Cereb. Blood Flow Metab.* (2023).
49. Edlow, B. L. *et al.* Long-Term Effects of Repeated Blast Exposure in United States Special Operations Forces Personnel: A Pilot Study Protocol. *J. Neurotrauma* (2022).
50. Isenburg, K., et al. Functional network reconfiguration supporting memory-guided attention. *Cereb. Cortex* (2023).