I am interested in Alzheimer disease and related dementias (ADRD) because I feel encouraged to study these diseases from a variety of perspectives. In my two years of graduate school, I have had the opportunity to leverage my previous experience in imaging and histology to compare how tau pathology appears in positron emission tomography (PET) images versus immunostained tissue sections across autosomal dominant and late-onset Alzheimer disease. I have also had the opportunity to combine what I have learned from my professors in the engineering school and my colleagues on the medical campus to develop an algorithm for finding a threshold for positivity in tau PET images without hard *a priori* assumptions about how severe tau pathology should be in Alzheimer disease. More recently, I have been able to approach colleagues studying genetics, psychology, and Parkinson disease dementia to pursue lines of research into imaging-genetics, learn more about the psychology of aging, and explore the similarities and differences in etiology between Alzheimer and Parkinson disease dementia. Being involved in ADRD research has allowed me to indulge in my curiosity across multiple disciplines, under a common goal of investigating how a variety of implicated factors at the molecular level can converge to a family of related imaging and cognitive phenotypes recognizable as ADRD.

Specific goals I would pursue during training are:

1. Identify how to translate insights from different fields of study, say from neuropathology to imaging, or from imaging to genetics studies, by attending ADRC T32 trainee conferences, where I could have an opportunity to discuss these issues with students from other labs studying ADRD, and establish collaborations across relevant Knight ADRC cores. For example, when comparing tau pathology between immunostained tissue sections and PET images, it was difficult to interpret my findings in the context of tau pathological progression, as differences between the two datasets could reflect true differences in disease stage or reflect inherent differences in microscopy versus imaging data. Being able to discuss these issues extensively with experts in both fields could be useful. In the future, when drawing comparisons between imaging and genetics data, this could be even more crucial, given the amounts of data available and the differences between the two fields.
2. Learn how researchers from other institutions approach ADRD research by attending national and international conferences, and establishing collaborations to share data and understand whether observations at one research center hold universally across many centers, or whether additional harmonization is needed. For example, when replicating methods for establishing tau PET positivity thresholds from other centers, I found that they consistently underestimate the ideal threshold in data from the Knight Alzheimer Disease Research Center (ADRC). I would like to be able to evaluate my proposed threshold-finding method on data from other centers to determine whether my method is similarly biased, and determine how to reduce potential biases and harmonize datasets in general.
3. Learn how ADRD affect participants and patients with dementia by attending observations at the Knight ADRC Memory and Aging Project and Memory Diagnostic Center. For example, by attending cognitive testing assessments, I could personally gain a better understanding of what the Clinical Dementia Rating interview entails, as well as what additional psychometric testing involves. Understanding mild behavior and cognitive changes and impairments before the onset of dementia would allow me to develop more informed hypothesizes about which brain areas could be affected at the earliest disease stages.

SPECIFIC AIMS

By 2050, Alzheimer disease (AD) could afflict up to 14 million people in the United States and cost $1 trillion. Early diagnosis of 88% of those who will go on to develop Alzheimer disease could reduce that cost by $230 billion through better informed patient care. One promising approach for early AD diagnosis is tau positron emission tomography (PET) imaging. Tau protein, in the form of neurofibrillary tangles, is a diagnostic hallmark of AD alongside amyloid-beta plaques, and is implicated in its neurodegenerative pathology, correlating strongly with the severity of neurodegeneration and cognitive impairment. However, current methods for determining positivity in tau PET images are maximally sensitive to levels of tau radioligand binding across large portions of the temporal and parietal cortices. Although still contested, many theoretical models of tau pathology progression in Alzheimer disease suggest the presence of tau pathology across a large portion of cerebral cortex represents a relatively late stage in Alzheimer disease and propose structures such as the locus coeruleus or basal forebrain as possible regions where tau is localized in early stages of the disease. Here we propose to

develop a tau PET imaging procedure prioritizing the quantification of subcortical and brain stem structures for improved early diagnosis of AD. First, we will evaluate the concordance of tau and neurodegeneration of these small brain structures with diagnosis of AD dementia using postmortem assessment as a gold standard (Aim 1); then we will develop an imaging procedure to prioritize the quantification of subcortical and brain stem structures using second-generation tau PET radioligands and a new PET/CT imaging system (Aim 2); and finally develop a model from the tau imaging quantification of subcortical and brain stem structures to predict participant amyloid and cognitive status at follow-up (Aim 3). If successful, the development of such a model may help better predict who are at risk for developing AD dementia and allow physicians to stratify individuals for appropriate therapeutics of clinical trials, reducing the overall healthcare cost of AD.

Aim 1: Evaluate the concordance of tau and neurodegeneration of subcortical and brain stem structures with AD dementia diagnosis using postmortem assessment. Here we propose to evaluate, via postmortem assessment, the severity of neurodegeneration of subcortical and brain stem structures using available semi-quantitative scoring of measures such as neurofibrillary tangle count and neuron loss provided by the Knight ADRC Neuropathology Core, and determine their concordance with a diagnosis of AD dementia through categorical clustering algorithms or logistic regression. *We hypothesize that subcortical and brain stem structures may be consistently elevated in tau pathology and neurodegeneration compared to other brain regions when contrasting healthy controls against AD dementia.* If semi-quantitative scoring is not sufficiently precise to draw meaningful conclusions, we will perform traditional stereological quantification of a more limited tissue sample or use pre-trained machine learning methods developed for quantifying digitized histology sections. Additionally, in a subset of the postmortem cohort, we can collaborate with the Knight ADRC Genetics Core to acquire a proteomic assay of parietal lobe tissue to determine the levels of microtubule-associated tau protein and proteins related to neurodegeneration as another source of quantitative postmortem assessment.

Aim 2: Develop an imaging procedure to prioritize the quantification of subcortical and brain stem structures. Here we propose to develop an imaging procedure to more accurately quantify tau radioligand binding levels in subcortical and brain stem structures using the second-generation tau radioligand PI-2620, which has been shown to demonstrate reduced levels of off-target binding in subcortical structures, which have been a large source of noise for quantifying subcortical brain regions. Additionally, we will use the new Siemens Biograph Vision PET/CT imaging system, which has been shown to image at an axial spatial resolution of ~3.5 mm, likely sufficient for imaging the basal forebrain, which has an estimated bilateral volume of ~99 mm^3 in a case study of a healthy young adult. *We hypothesize that the combination of a second-generation tau radioligand with an advancing PET/CT imaging system will allow for detection of tau radioligand binding more precisely localized to small subcortical and brain stem structures.* If certain structures cannot be precisely imaged (for example, while the length of the locus coeruleus is ~14.5 mm, its height and width can be ~2.0 mm and ~2.5 mm in adults), priority will be given to model data from sufficiently resolved brain structures in Aim 3. Additionally, we can establish collaborations with other centers using PI-2620 as a tau radioligand to determine, though data sharing or a federated approach, which brain structures are most consistently resolved across different participant cohorts, and should be prioritized in Aim 3.

Aim 3: Develop a model from tau imaging quantification of subcortical and brain stem structures to predict participant clinical stage at follow-up. Here we propose to model when participants transition to AD dementia using longitudinal data. *We hypothesize that the new imaging phenotypes identified in Aim 2 will be more sensitive predictors of longitudinal follow-up than currently existing methods focused on tau presence in cortical regions.* If the new imaging phenotypes predict AD dementia conversion less consistently than existing methods, for example, in a hypothetical case when subcortical tau measures elevate and saturate well before the onset of dementia, we can explore the predictive power of these new imaging phenotypes for more specific psychometric measures, for example, attentional control and episodic memory composite scores, which have been previously shown to correlate with high baseline CSF tau in longitudinal study. Additionally, we can, through collaboration with the Knight ADRC Clinical Core, determine the most appropriate psychometric composites specific for early preclinical study, which may involve modifying the Multivariate Cognitive Endpoint originally developed for assessing autosomal dominant AD cohorts, or developing an instrument for assessing Mild Behavioral Impairment, a recently proposed construct describing neuropsychiatric symptoms preceding cognitive impairment.