

Overview

Neuroinflammation has been suggested to be a major component of the pathological mechanism underlying Alzheimer's disease (AD). Specifically, excessive activation of resident glial cells in the central nervous system, such as microglia and astrocytes, is thought to contribute to the development or progression of AD. However, the interaction between reactive astrocytes and microglia and their pathophysiological mechanisms are largely *unknown*, which will have a great benefit from a positron emission tomography (PET) image study using radiotracers that specifically target each cell type. We have launched two novel PET radiotracers at the Stony Brook University PET Core for human research: [¹¹C]PS13 for microglia and [¹⁸F]SMBT-1 for astrocytes.

The *overall objective* of this research is to explore the association between the reactive astrocyte densities measured by the [¹⁸F]SMBT-1 PET and the microglial densities measured by the [¹¹C]PS13 PET in the brains of older adults in the clinical spectrum between cognitive unimpaired (CU) healthy aging and Alzheimer's disease (AD). Over the last years, we have collected brain [¹¹C]PS13 PET imaging data in more than 25 older adults who are in the clinical spectrum of the AD continuum. Furthermore, we have recently established the synthesis of in-house [¹⁸F]SMBT-1 at the Stony Brook University PET Core for human research in collaboration with the inventor of the radioligand at Tohoku University of Japan. We will enroll a total of 12 individuals who have already completed a [¹¹C]PS13 PET scan: 4 cognitively unimpaired, 4 MCI, and 4 AD dementia. We will match the demographic profiles across the groups so that the findings are minimally confounded by other factors. Each participant will undergo a brain [¹⁸F]SMBT-1 PET scan. Since there is no known brain tissue with minimal astrocyte density, we will use the gold-standard method of PET acquisition with concurrent arterial blood sampling and radiometabolite analyses for absolute quantification of [¹⁸F]SMBT-1 binding. However, once an alternative method with a reference tissue is established in the initial data, we may proceed with the rest of the study without arterial blood sampling. Participants' blood will also be collected and stored to be able to measure plasma biomarker levels for A β 42/40 ratio, plasma phosphorylated Tau-217, and inflammatory markers later.

To attain the overall objective, the following two Specific Aims are proposed:

Aim #1: Compare the density of reactive astrocytes and microglia in the brains of AD, MCI, and cognitively unimpaired older adults.

Hypothesis #1: The astrocyte density measured by the [¹⁸F]SMBT-1 binding and the microglial density measured by the [¹¹C]PS13 binding in the brain will show significant spatial overlap in each individual.

Hypothesis #2: AD and/or MCI patients will show a higher density of both astrocytes and microglia compared to cognitively unimpaired individuals.

Aim #2: Develop and validate non-invasive [¹⁸F]SMBT-1 brain PET imaging methods to be more applicable in larger populations for future studies.

Hypothesis: A static [¹⁸F]SMBT-1 scan without arterial blood samplings can substitute the gold-standard full-length dynamic scan with continuous arterial blood sampling. This will improve the feasibility of [¹⁸F]SMBT-1 PET in larger populations with preserved accuracy.

This research is *significant* because neuroinflammation is a major component of AD pathology, but the association between the major components (i.e., reactive astrocytes and microglia) is largely unknown. This proposal is *innovative* because two novel radiotracers that are specific to reactive astrocytes and microglia with excellent pharmacokinetic and pharmacodynamic characteristics are used to investigate their interactive roles in the neuroinflammatory mechanisms of AD pathogenesis. On completion, we expect to have obtained the initial evidence on the association between reactive astrocytes and microglia in the brain at different stages of the AD continuum, which will let us prepare for an NIA R01 grant application.