BRAIN HEALTH ALLIANCE

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The EPSMS Study: A Multiple Sclerosis Clinical Trial in Progress*

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Background

The EPSMS Study investigates use of state-of-the-art entire-body PET scans (EPS) with molecular imaging of the nervous system to evaluate both peripheral and central demyelination and remyelination in multiple sclerosis (MS). This study hypothesizes that the improved sensitivity and resolution of advanced PET scanners can detect demyelination not only in the brain and spinal cord but also in peripheral nerves, an approach that has not been fully explored in past conventional imaging for MS with MRI. The study employs FDA-approved PET amyloid imaging radiopharmaceuticals (F18-florbetapir, F18-florbetaben, and F18-flutemetamol) which also bind to myelin, enabling the assessment of demyelination and remyelination dynamics. Related radiotracers have shown promise (see Table 1 for differential grey-white matter binding, Figure 1 for normal subject, and Figure 2 for MS patients) in prior studies demonstrating quantifiable changes in myelin content and remyelination potential (Stankoff et al. 2006; Stankoff et al. 2011; Glodzik et al. 2014; Veronese et al. 2015; Matias-Guiu et al. 2015; Bodini et al. 2016; Pietroboni et al. 2018; Bodini et al. 2021).

The EPSMS Study NCT04390009 was initially registered at ClinicalTrials.gov in 2020 with the protocol published in 2020 and amended in 2023 (Taswell 2020; Taswell 2023) but was then delayed with a hold on the start due to the COVID19 pandemic. The trial protocol emphasizes standardization of PET molecular imaging at multiple imaging sites to ensure consistent data acquisition across different scanners. If successful, the findings could support better patient care decisions, improve clinical trial outcome measures, and advance therapeutic evaluations for MS. This study represents a pioneering effort to apply entire-body PET molecular imaging for comprehensive monitoring of MS pathology for the entire nervous sytem.

Entire-body PET scans not only enable molecular imaging with neuroPET of both central and peripheral nervous system to include brain, spinal cord and peripheral nerve roots, but also enable molecular imaging with immunoPET (see Figure 3) of the immune system in bone marrow, spleen, thymus, and lymph nodes (Wei et al. 2020; Gao et al. 2022; Wu et al. 2022; Lucas et al. 2023; Mohr et al. 2024). Dual-tracer PET scans will enable molecular imaging of both immune and nervous systems with immunoneuroPET for MS.

Methods

The experimental paradigm involves an approach similar to that demonstrated for amyloid imaging tracers used for Alzheimer's disease and related disorders with safety of imaging results disclosure monitored with pre- and post-scan psychometrics (Taswell, Villemagne, et al. 2015; Taswell, Donohue, et al. 2018). The current phase of the EPSMS Study uses advanced PET-CT imaging to analyze the activity of myelin-binding radiopharmaceuticals in the nervous systems of patients with MS. This *study aims (1) to assess the differences in uptake of the radiotracer F18-florbetapir in demyelinated and remyelinated white matter between MS patients and healthy controls, and (2) to explore the psychological effects on participants when informed about their imaging results.* Participants will undergo PET-CT scans with the most recent state-of-the-art high-resolution PET scanners (eg, Zhang et al. 2024) at international imaging sites.

A total of 20 participants (15 MS patients and 5 healthy controls) will participate in the exploratory phase of this study. *Specific assessments include MS-related disability, psychological health (pre- and post-scan), and myelin-related changes in the brain, spinal cord, and peripheral nerve roots as visualized in the PET scans.* Eligibility includes adults age 25–55 as control subjects with normal health or as MS patients diagnosed by credentialed neurologists with MS experience, and excludes individuals with complicating illnesses, recent medical procedures, or contraindications to medical imaging. PET scan images are analyzed to measure relative tracer activity levels in key regions, correlating these results with clinical symptoms, psychometrics, and with MS-related lesions observed in other imaging modalities (eg, MRI) when available from patients' medical records.

Findings expected include (1) differences in radiotracer activity between MS patients and healthy controls, (2) identification of topographic variations in activity across regions of the central and peripheral nervous systems, and (3) an initial data repository with web-enabled workflow infrastructure to support future studies on the role of PET imaging for MS diagnostics, monitoring of disease modifying therapies, and future theranostics. *All participants must consent to the study and can opt in/out of imaging results disclosure for neither, either, or both of gray and white matter results.* Radiation exposure levels are minimal and within safety standards for the FDA-approved radiopharmaceuticals used. Potential risks include adverse reactions to the tracer, discomfort during imaging, and the possibility of unrelated incidental findings. *The website EPSMS.brainhealthalliance.net serves as the online management service for the EPSMS Study.* Current imaging sites for the EPSMS Study include Northern California PET Imaging Center (NCPIC) in Sacramento CA and Center for Molecular Imaging and Therapy Louisiana (CMITLA) in Shreveport LA.

Future phases of the EPSMS Study will involve novel radiotracers to evaluate neuroinflammation and biomarkers of immune system activity. *This study represents a pioneering effort to apply entire-body PET molecular imaging from top-of-head to bottom-of-pelvis for comprehensive monitoring of MS pathology in the nervous system and immune system with immunoneuroPET.*

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Table 1: Signal versus Noise for Amyloid Imaging Agents

	Target Signal	Off-target Noise
Alzheimer's Disease	grey matter	white matter
Multiple Sclerosis	white matter	grey matter

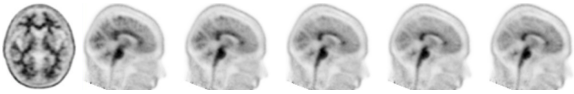

Figure 1: High binding of F18-flutemetamol in white matter with low binding in gray matter; images courtesy of Chris Rowe, Univ Melbourne, Australia.

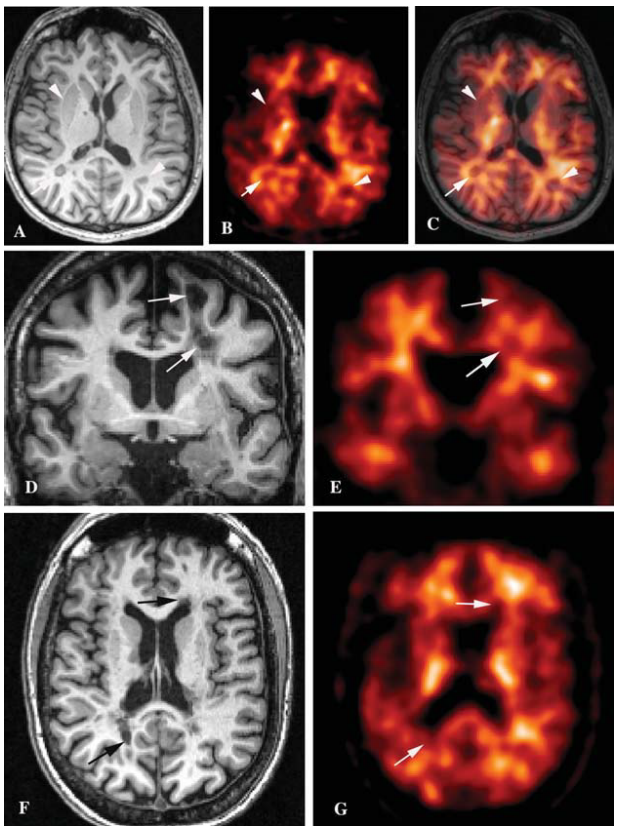

Figure 2: MP-RAGE 3T MRI and C11-PiB PET images for MS patient 1 (A-C) and MS patient 2 (D-G); reprinted from Stankoff et al. 2011.

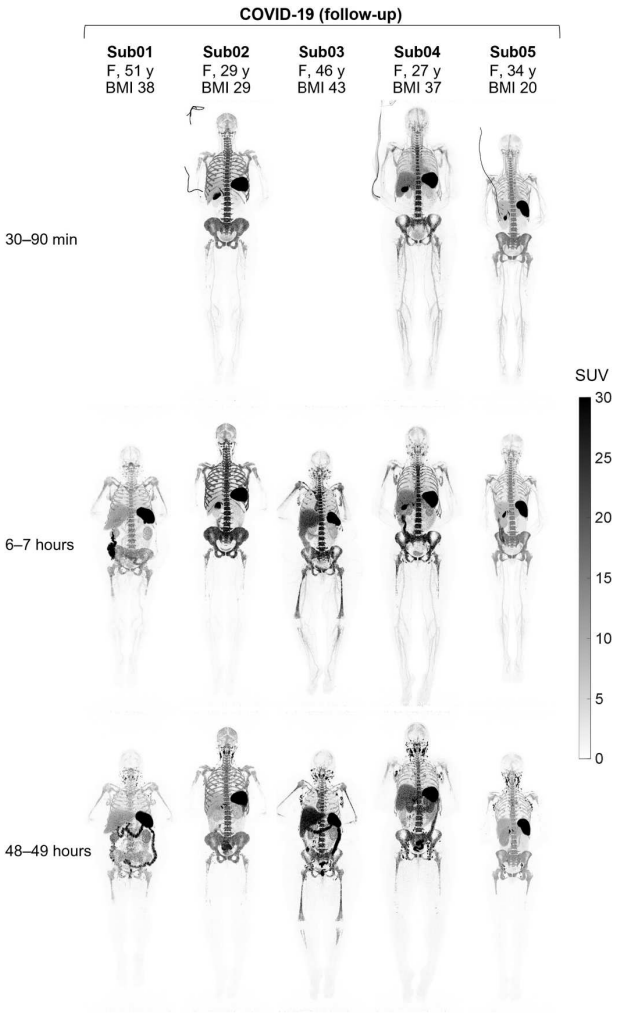

Figure 3: Dynamic immunoPET imaging of COVID19 convalescent patients with CD8-targeted minibody; reprinted from Omidvari et al. 2023.

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