Research Protocol for Exploratory Study of Entire-body PET Scans for Multiple Sclerosis (EPSMS)

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Outline

- Multiple sclerosis (MS)
- Imaging demyelination and remyelination in MS
- Advances in PET-CT and PET-MR imaging
- Entire-body PET Scans for MS (EPSMS) Clinical Trial

Multiple sclerosis (MS)

- First described by French neurologist Jean-Martin Charcot in 1868 (Kumar 2010, Zalc 2018)
- An auto-immune mediated demyelinating disease which damages the insulating myelin sheaths of nerve cells in the brain and spinal cord
- Destruction of oligodendrocytes, the myelin-producing cells, results in disruption of communication between neurons
- Demyelination in both peripheral and central nervous systems plays a key role in the neuronal and axonal degeneration that occurs in the pathophysiology of MS (Lucchinetti 2000, Zephir 2008, Friese 2014)
- Classification of MS (Lublin 2014) considers several types:
  - Clinically isolated syndrome (CIS)
  - Relapsing-remitting MS (RRMS)
  - Primary progressive MS (PPMS)
  - Secondary progressive MS (SPMS)

Imaging demyelination and remyelination in MS

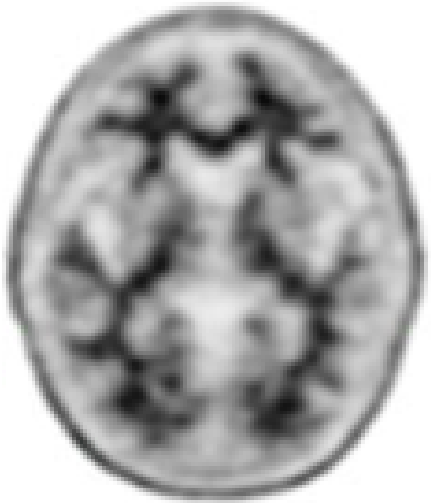
- Magnetic resonance imaging (MRI) has been well established as the imaging modality most used in routine clinical practice (Losseff 1996, Thorpe 1996, Barkhof 1999, Lycklama 2003, Bakshi 2008)
- Molecular imaging with PET scanners has been considered as an alternative imaging modality for MS (Niccolini 2015, Moccia 2017)
- PET imaging has been demonstrated to be safe for monitoring neurodegenerative disorders other than MS, and the amyloid imaging radiotracers are known to bind to myelin in addition to amyloid
- FDA-approved amyloid imaging agents (Amyvid F18-florbetapir, Neuraceq F18-florbetaben, Vizamyl F18-flutemetamol) have not yet been validated as myelin imaging probes for the routine clinical evaluation of MS patients

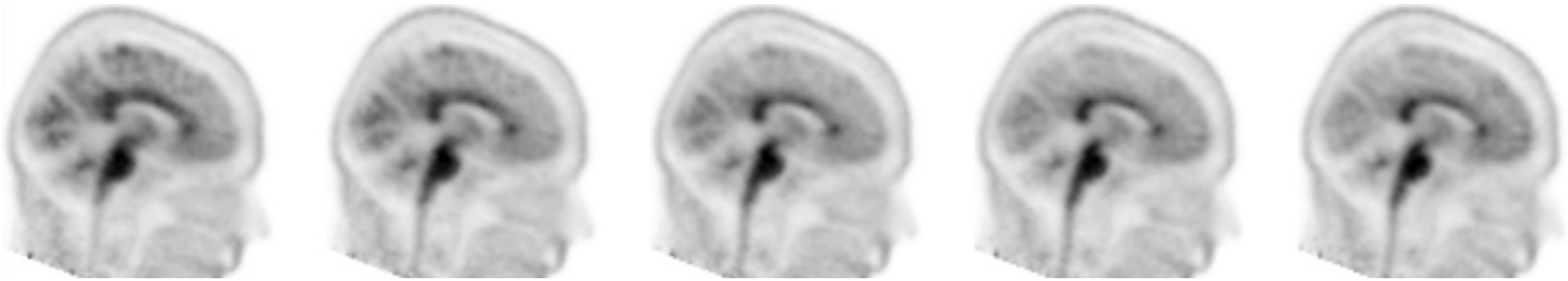
Signal versus Noise for Amyloid Imaging Agents

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

- What is indication for PET scan? AD or MS?
- What is considered answer to diagnostic question present in target signal rather than an incidental finding present in off-target noise?
- With results that may or may not be reported to patient per personal preferences of the patient in routine clinical setting?
- Questions relevant to appropriate use criteria and informed consent for both clinical practice and research trials.

Myelin binding of F18-flutemetamol





Images courtesy of Chris Rowe, Univ Melbourne, Australia

Advances in PET-CT and PET-MR imaging

- Improved detector sensitivity and spatial resolution of recent state-of-the-art PET-CT and PET-MR scanners
  - GE Healthcare Discovery MI PET-CT
  - Siemens Biograph Vision PET-CT
  - United Imaging uEXPLORER PET-CT
  - GE Healthcare SIGNA PET-MR
  - Siemens Biograph mMR PET-MR
- For tech specs and performance characteristics of these scanners, see Karlberg 2016, Cherry 2018, Badawi 2019, Sluis 2019, Caribe 2019
- Entire-body (also called whole-body and total-body) PET scanners will enable molecular imaging of both central and peripheral nervous system, to include brain, spinal cord, and peripheral nerve roots

Entire-body PET scans for MS (EPSMS) Clinical Trial

- Basic question: Can an entire-body PET scanner be exploited to improve evaluation, monitoring and measurement of both peripheral and central demyelination in multiple sclerosis (MS) patients?
- Initial approach: Adopt a cost-effective and reduced-risk approach initially for an exploratory study by using commercially available and already FDA-approved PET amyloid imaging radiopharmaceuticals that also bind to myelin to follow radiotracer uptake in white matter, thereby tracking demyelination versus remyelination for MS patients in comparison with normal healthy subjects.
- Future approach: Investigate other possible radiotracers (including those not yet FDA approved) that may be useful for monitoring demyelination, neuroinflammation and/or microglial activation in both the PNS and CNS of MS patients. In addition, PET myelin imaging by PET-CT scanners will be compared with analogous imaging by PET-MR scanners.

EPSMS clinical trial: objectives and design

- Pilot study conducted on 20 participants as clinical research trial of PET amyloid and myelin imaging with
  - *primary objective* of identifying differences in F18-florbetapir radiotracer activity for MS patients compared to normal healthy subjects,
  - *secondary objective* of monitoring psychological health of those participants who complete a panel of psychometric scales before and after imaging results disclosure
- Trial design established as a non-randomized prospective longitudinal cohort study following a protocol similar to that described by Taswell 2018 with an approximate ratio of 3:1 for MS patients to normal healthy subjects and the
  - protocol for *both study groups*, MS patients and normal healthy subjects, will be the same
  - protocol for *different study arms* will be distinguished only by the make and model of the PET-CT or PET-MR scanner

EPSMS participants: inclusion criteria

- Adult men and women between the ages of 25 and 55 inclusive will be selected for both MS patients and normal healthy subjects
- MS patients diagnosed by credentialed neurologist according to the revised McDonald criteria (Thompson et al. 2018)
- Participants must be able to designate a study partner (family member, relative or friend) to assist and accompany them
- Willing and able to lie motionless in a supine position on the PET-CT scanner bed for at least 10 and up to 20 minutes
- Willing and able to give informed consent, personal contact information (phone number, email and postal address), their health care insurance information, and the contact information for their primary care or specialty care physician

EPSMS participants: exclusion criteria (partial list)

- MS patients with any additional complicating medical illness other than MS such as major gastro-intestinal, pulmonary or cardiovascular disease, and any other neuropsychiatric illness unrelated to MS diagnosed prior to the onset of initial symptoms of MS.
- No direct care provider and/or no health insurance.
- Body weight more than 200 kilograms (440 pounds). Claustrophobia. Inability to lie in PET-CT scanner.
- Creatinine levels $>$ 1.5 mg/dL or estimated glomerular filtration rate (eGFR) $<$ 60 ml/minute. Recent ($<$ 90 days) CT scan with contrast.
- Any known concomitant acute infection including upper respiratory infections, genitourinary infections, etc.
- History of metastatic or newly (last 5 years) diagnosed locally invasive cancer. Chemotherapy in the last 5 years. Radiation therapy in the last 3 years. Major surgery within the last 6 months.
- Pregnancy or breast-feeding.

EPSMS clinical trial: status and timeline

- EPSMS Study registered 14 May 2020 at ClinicalTrials.gov with Identifer NCT04390009
- Complete details for the EPSMS Study with citations to references available in the BHA-2020-11 research protocol and amended protocol with accompanying BHA informed consent and UCSD informed consent for trial participants
- Funding from Brain Health Alliance for operational and management support; Avid Radiopharmaceuticals for material support providing use of the Amyvid radiopharmaceutical; collaborating medical imaging centers for material support providing use of PET-CT scanners.
- EPSMS now recruiting trial participants who may register online at EPSMS.brainhealthalliance.net; Amyvid PET-CT scans anticipated beginning summer 2024

EPSMS clinical trial: 2024 proposed revisions to protocol

- Extend study to include 20 Vizamyl scans and 20 Neuraceq scans in addition to the 20 Amyvid scans
- Modify image scanning protocol to reduce scan time to that now possible with current state-of-the-art scanners, enabling 5 minute PET-CT scan followed by 15 minute PET-MR scan for same dose of the imaging agent (Amyvid, Vizamyl, or Neuraceq) at imaging sites where both PET-CT and PET-MR scanners are available
- Anticipated partner imaging centers include UC San Diego Health, UC Davis Health, Washington Univ St Louis, University Hospitals in Cleveland OH, BAMF Health in Grand Rapids MI
- 2024 proposed revisions for EPSMS amended protocol pending IRB approval anticipated summer 2024

Significance of the EPSMS Clinical Trial

Molecular imaging with new entire-body PET scanners that provide improved detection sensitivity and spatial resolution for quantitative measurement of demyelination and remyelination will support better decision-making for patient care with more robust outcome measures when monitoring therapeutic drugs evaluated in clinical trials for the treatment of multiple sclerosis.

MS support organizations

- MS America
- MS Australia
- MS Canada
- Multiple Sclerosis Foundation
- Multiple Sclerosis World
- National Multiple Sclerosis Society
- Can Do Multiple Sclerosis
- My MS Team
- Multiple Sclerosis International Federation lists many more MS organizations around the world

Contacts for the EPSMS clinical trial

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