Study Design for Medical Imaging Trials NEtwork of Canada (MITNEC) - Project C6 - Amyloid and glucose PET Imaging in Alzheimer and Vascular Cognitive Impairment patients with significant White Matter Disease

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BACKGROUND

- Alzheimer's Disease (AD) and stroke are major causes of dementia, and their prevalence doubles each decade over 65
- The annual cost of dementia in Canada ($15B) is expected to increase to $150B annually, as dementia cases double to more than 1 million within a generation[1]
- In population studies of persons over 65, "covert" cerebral small vessel disease (SVD) appears on MRI as covert lacunar infarcts in 25%[2], as microbleeds in 10%, and as focal or diffuse 'incidental' white matter disease (WMD) in 95%[3]
- SVD is more common in dementia and stroke
- SVD can manifest as periventricular white matter hyperintensities (pvWMH), can be extensive in 20% of the elderly[4] and resembles vasogenic edema
- SVD independently contributes to cognitive decline and progression to dementia in the elderly[5;6;7]
- Most PET studies of amyloid have focused on subjects without significant WMH
- Longitudinal amyloid PET imaging opens a new avenue to understand the additive/interactive effects of SVD and AD

STUDY PURPOSE

- To explore the relationships between brain metabolism, amyloid burden and measures of moderate/severe small vessel disease in dementia and stroke

METHODS

- The study design includes recruitment of two cohorts from 12 sites across Canada (figure 1)
  - Alberta: University of Alberta, Edmonton, University of Calgary
  - British Columbia: University of British Columbia
  - Nova Scotia: Dalhousie University
  - Ontario: McMaster University, University of Ottawa, University of Toronto – Sunnybrook HSC, Toronto Western Hospital, Western University
  - Quebec: Laval University, McGill University, Université de Sherbrooke

METHODS

Figure 1 – Map of Canada showing recruitment sites

- Overall MITNEC Trial supervised by the Montreal Heart Institute Coordinating Centre (MHICC)
- Subject Cohort:
  - 75 Mild Cognitive Impairment (MCI) and/or early AD subjects from memory clinics and
  - 75 subjects with strokes/TIA from stroke prevention clinics
  - ❑ Recruited subjects will be compared to publicly available ADNI subject data
- Inclusion criteria:
  - ✓ ≥ 60 years of age
  - ✓ Mini-Mental State Exam (MMSE) scores ≥ 20
  - ✓ presence of moderate/extensive WMD, specifically Fazekas score of >2 (with confluent pvWMH), as determined by previous MR or CT

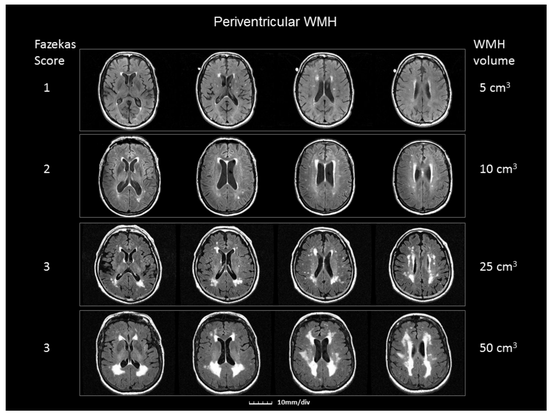

Figure 2 – Fazekas rating scale examples with associated WMH volumes

- MR Imaging: Subjects will undergo 3T MRI, including 3D T1, PD/T2, FLAIR, GRE (or SWI when available), DTI, ASL, and resting state fMRI

METHODS

- PET Imaging:
  - 18F-FDG PET
  - 18F-florbetapir (AV-45) amyloid PET

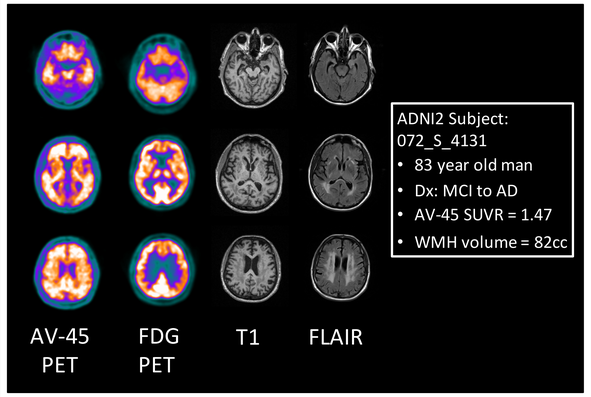

Figure 3 – FDG and AV-45 PET and MRI examples from an ADNI subejct

- Cognitive testing:
  - Mini Mental State Exam (MMSE)
  - Montreal Cognitive Assessment (MoCA)
  - Phonemic and Semantic Fluency
  - Trails A & B
  - Centre for Epidemiologic Studies Depression scale (CES-D)
  - Symbol Digit Modalities Test
  - ANART (American National Adult Reading Test)
  - BNT (Boston Naming Test)
  - TUG (Timed up and Go)
  - FAQ (Functional Assessment Questionnaire)
- Other Study Features:
  - Blood sampling for ApoE e4 analysis
  - Repeat MR and PET imaging and cognitive testing will be conducted at 24 months
  - Imaging protocols closely parallel the Alzheimer's Disease Neuroimaging Initiative (ADNI), permitting access to age and education matched comparisons to elders, MCI and AD subjects with minimal WMH
  - Recruitment is underway with several sites coming on-board in September-October 2015
  - Baseline recruitment is expected to be completed by April 2016

HYPOTHESES AND DISCUSSION

- Primary objectives are to compare subjects with significant pvWMH at baseline and 2-year follow-up on uptake 18F-florbetapir, 18F-FDG, regional volumetric measures from MRI, and standardized cognitive testing
- Specific hypotheses are that patients with high pvWMH volumes will show greater increase in amyloid deposition over two years, after accounting for appropriate covariates (eg. baseline scores, age, education, ApoE-e4 status), as well as decreased executive function, speed of processing, and instrumental ADL's
- Greater cortical thinning and glucose hypometabolism in the signature areas of AD are also expected
- 60-85% of AD/MCI subjects are predicted to have "positive" amyloid scan (Am+), while only 20-40% of stroke/TIA subjects will be Am+
- Further subgroup analysis will aim to compare and contrast Am+ and Am- subjects from each cohort as well as the ADNI subjects
- This data will provide new insight into the role of pvWMH in amyloid accumulation

REFERENCES AND ACKNOWLEDGMENTS

1. Alzheimer Society of Canada. Rising Tide: The Impact of Dementia on Canadian Society. 2010. Alzheimer Society of Canada. Ref Type: Report
2. W. T. Longstreth et al., "Lacunar Infarcts Defined by Magnetic Resonance Imaging of 3660 Elderly People: the Cardiovascular Health Study," *Archives of Neurology* 55, no. 9 (1998): 1217-1225.
3. W. T. Longstreth, Jr. et al., "Clinical Correlates of White Matter Findings on Cranial Magnetic Resonance Imaging of 3301 Elderly People. The Cardiovascular Health Study," *Stroke.* 27, no. 8 (1996): 1274-1282.
4. C. DeCarli et al., "The Effect of White Matter Hyperintensity Volume on Brain Structure, Cognitive Performance, and Cerebral Metabolism of Glucose in 51 Healthy Adults," *Neurology* 45, no. 11 (1995): 2077-2084.
5. O. Carmichael et al., "Longitudinal Changes in White Matter Disease and Cognition in the First Year of the Alzheimer Disease Neuroimaging Initiative," *Archives of Neurology* 67, no. 11 (2010): 1370-1378.
6. E. E. Smith et al., "Magnetic Resonance Imaging White Matter Hyperintensities and Brain Volume in the Prediction of Mild Cognitive Impairment and Dementia," *Arch Neurol.* 65, no. 1 (2008): 94-100.
7. S. E. Black et al., "Understanding white matter disease: imaging-pathological correlations in vascular cognitive impairment. Stroke 40, no. 3 (2009): S48-52.

We gratefully acknowledge the support of AVID Radiopharmaceuticals for their contribution of the AV-45 radioligand

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