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Using simultaneous PET/MRI to compare the accuracy of diagnosing frontotemporal dementia by arterial spin labelling MRI and FDG-PET

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ABSTRACT

Purpose: The clinical utility of FDG-PET in diagnosing frontotemporal dementia (FTD) has been well demonstrated over the past decades. On the contrary, the diagnostic value of arterial spin labelling (ASL) MRI – a relatively new technique – in clinical diagnosis of FTD has yet to be confirmed. Using simultaneous PET/MRI, we evaluated the diagnostic performance of ASL in identifying pathological abnormalities in FTD (FTD) to determine whether ASL can provide similar diagnostic value as FDG-PET.

Methods: ASL and FDG-PET images were compared in 10 patients with FTD and 10 healthy older adults. Qualitative and quantitative measures of diagnostic equivalency were used to determine the diagnostic utility of ASL compared to FDG-PET. Sensitivity, specificity, and inter-rater reliability were calculated for each modality from scores of subjective visual ratings and from analysis of regional mean values in thirteen a priori regions of interest (ROI). To determine the extent of concordance between modalities in each patient, individual statistical maps generated from comparison of each patient to controls were compared between modalities using the Jaccard similarity index (JI).

Results: Visual assessments revealed lower sensitivity, specificity and inter-rater reliability for ASL (66.67%/62.12%/0.2) compared to FDG-PET (88.43%/90.91%/0.61). Across all regions, ASL performed lower than FDG-PET in discriminating patients from controls (areas under the receiver operating curve: ASL = 0.75 and FDG-PET = 0.87). In all patients, ASL identified patterns of reduced perfusion consistent with FTD, but areas of hypometabolism exceeded hypoperfused areas (group-mean JI = 0.30 ± 0.22).

Conclusion: This pilot study demonstrated that ASL can detect similar spatial patterns of abnormalities in individual FTD patients compared to FDG-PET, but its sensitivity and specificity for discriminant diagnosis of a patient from healthy individuals remained unmatched to FDG-PET. Further studies at the individual level are required to confirm the clinical role of ASL in FTD management.

1. Introduction

Frontotemporal dementia (FTD) is a progressive neurodegenerative disorder associated with atrophy of the frontal and temporal lobes and is characterized by impairments in behaviour and language (Weder et al., 2007). In adults 65 years or younger, FTD is the second most common form of early-onset neurodegenerative dementia (Onyike and Diehl-Schmid, 2013). Diagnosis of FTD is often challenging, as symptoms and features can overlap with those of Alzheimer's disease (AD) and psychiatric conditions such as late-onset schizophrenia and bipolar disorders (Weder et al., 2007). This diagnostic challenge, coupled with rapid functional decline and relatively short survival rate (3–14 years

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from symptom onset (Onyike and Diehl-Schmid, 2013)), highlights the need for identification of sensitive biomarkers to improve early diagnosis of FTD, which can also be used for monitoring disease progression and treatment outcomes.

Cerebral glucose metabolism (CMRglc) measured using ^{18}F-fluorodeoxyglucose (FDG) and positron emission tomography (PET) is an established biomarker for accurate ante-mortem diagnosis of FTD (Diehl-Schmid et al., 2007; Dukart et al., 2011; Foster et al., 2007; Ishii et al., 1998; Tosun et al., 2016) and for distinguishing FTD from other dementias (Foster et al., 2007; Tosun et al., 2016). A 2005 consensus report prepared by the Neuroimaging Work Group of the Alzheimer's Association concluded that FDG-PET is helpful for differentiating FTD from AD (Albert et al., 2005). In the US, costs for FDG-PET scans for differential diagnosis of FTD have been covered nationwide via Medicare benefits for the past 7 years (Centers for Medicare & Medicaid Services, 2009). Recently, a number of studies have shown that the MRI-based perfusion technique arterial spin labelling (ASL) can potentially provide comparable diagnostic information to FDG-PET in both FTD (Fällmar et al., 2017; Moodley et al., 2015; Tosun et al., 2016; Verfaillie et al., 2015) and AD (Musiek et al., 2012; Verclytte et al., 2015) patients due to the coupling of perfusion to glucose metabolism (Anazodo et al., 2015; Cha et al., 2013). Since ASL is completely non-invasive – using endogenous blood-water as a flow contrast – it offers an appealing opportunity for cost-effective monitoring of FTD progression and treatment outcomes, free from the radiation burden of PET. Additionally, it *frees* PET for use in studies involving targeted tracers of pathophysiology, such as tau protein or neuroinflammation markers.

However, the reported sensitivity and specificity of ASL-CBF compared to FDG-PET in FTD studies vary widely, with some studies showing agreement with FDG-PET (Tosun et al., 2016; Verfaillie et al., 2015), better specificity than FDG-PET (Fällmar et al., 2017), and no added benefit of ASL (Binnewijzend et al., 2013; Bron et al., 2014). These conflicting findings are possibly due to heterogeneity of relatively small sample populations, variations in ASL techniques, and inherent limitations with sequential PET and MRI acquisitions. Errors in spatial registration and differences in brain states between separate PET and MRI scans are minimized by simultaneous imaging leading to stronger association between ASL-CBF and FDG-PET (Anazodo et al., 2015). Given the nature of FTD disease progression, accurate sequential evaluation of perfusion to glucose metabolism in FTD patients using ASL and FDG-PET can be limited if PET and MRI data are acquired a few months apart (Teipel et al., 2015). To circumvent this issue, this study utilized simultaneous PET/MR imaging to evaluate regional coupling of ASL-CBF to FDG-PET in patients with FTD. This analysis was conducted at group and single-subject level to determine if ASL-CBF performed equally well to FDG-PET for clinical diagnosis of FTD. Because FDG-PET is now clinically used to evaluate FTD on a single-subject basis, emphasis was placed on comparing diagnostic performance of ASL-CBF and FDG-PET at the individual level. Specificity and sensitivity of ASL-CBF were compared to FDG-PET using receiver operating characteristic (ROC) curve analysis, visual rating reports from trained readers, and statistical *t*-score maps.

2. Materials and methods

2.1. Participants

This study was approved by the Western University Health Sciences Research Ethics Board and conducted in accordance with the Declaration of Helsinki ethical standards. All participants provided written informed consent. The study cohort included 10 neurologically healthy controls and 11 patients with FTD recruited from the Cognitive Neurology and Aging Brain clinics at Parkwood Hospital (London, ON) between January 2014 and October 2014. Of the 11 patients, 7 were diagnosed with bvFTD (including 2 with right temporal variant bvFTD), 1 patient met criteria for bvFTD and non-fluent primary progressive aphasia (nfPPA), 1 patient was diagnosed with semantic variant PPA ((svPPA) with behavioural features and significant left and right temporal atrophy), and 2 patients were diagnosed with possible bvFTD (based on presence of clinical symptoms and cognitive testing profile but normal structural MRI imaging). All participants were free from confounding neurological diseases or psychiatric disorders (i.e. stroke, multiple sclerosis, brain tumor, bipolar disorder, schizophrenia, current major depression). All patients met the International consensus criteria for bvFTD or semantic variant PPA (Gorno-Tempini et al., 2011; Rascovsky et al., 2011) based on their clinical evaluation, neurocognitive testing performance (Table 1), clinical MRI brain imaging and genetic testing. Participants completed standard clinical neuropsychological assessments including Mini-Mental State Examination (MMSE) (Folstein et al., 1975), Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005), tests for memory (prose recall), language/verbal fluency (semantic and phonemic, and naming from the Western Aphasia Battery), visuospatial skills (clock drawing tests), and attention (Trail Making Tests A and B), as outlined in an earlier study (Coleman et al., 2017). The clinical MRI scans, neurology history examination and neurocognitive testing used in diagnosis of FTD were completed within 2–4 weeks of PET/MRI scanning. Since, PET/MRI is not approved clinically in Canada for diagnosis of dementias, no FDG-PET scans were available at the time of clinical diagnosis.

Table 1
Summary of participant demographics (mean ± standard deviation).

	bvFTD	Controls
Demographics		
Age (years)	66.3 ± 6.62	67 ± 6.62
Gender (males)	5	4
Years of illness	5.30 ± 2.50	–
Education (years)	13.10 ± 2.56	12.60 ± 2.50
Cognitive testing		
MOCA	17.57 ± 7.52	28.20 ± 1.75[§]
MMSE	21.25 ± 8.35	29.40 ± 0.97[§]
Prose delay	5.22 ± 3.95	8.89 ± 2.61[§]
Prose immediate	4.13 ± 2.33	9.40 ± 2.94[§]
Trail Making Test A	7.60 ± 4.40	8.88 ± 2.75[§]
Trail Making Test B	8.20 ± 4.56	7.25 ± 0.35
Naming aphasia	5.50 ± 3.90	9.25 ± 2.54
Semantic fluency	5.83 ± 3.88	9.57 ± 2.56[§]
Phonemic fluency	6.40 ± 4.07	9.25 ± 2.64[§]
Clock command	7.15 ± 4.55	8.50 ± 2.12[§]
Clock copy	7.50 ± 4.37	8.88 ± 2.25
Neuroimaging		
Global GM-CBF (ml/100 g/min)	31.21 ± 8.50	42.30 ± 15.65
Global GM-FDG (SUV)	0.43 ± 0.11	0.40 ± 0.08

[§] Statistical significance set at $p < 0.05$.

2.2. PET/MRI acquisition

Serial MRI sequences were acquired during 60 min of dynamic PET acquisition on an integrated PET/(3 T) MRI scanner (Biograph mMR, Siemens Healthineers, Erlangen, Germany) using a 12-channel PET-compatible head coil. To minimize head motion, an immobilizing foam head mold was used (Smithers Medical Products, Alpha Cradle). List-mode PET data were acquired immediately after bolus intravenous injection of FDG (203 ± 30 MBq; fasting blood glucose = 5.1 ± 0.8 mmol/L). PET data from 30 to 45 min were reconstructed to one image volume (344 × 344 × 127 matrix) using Siemens e7 tools and an iterative algorithm (ordered subset expectation maximization with point-spread function model; 3 iterations, 21 subsets, 3D Gaussian filter with a full-width-half-maximum (FWHM) of 2 mm and zoom factor of 2.5). Scatter, decay and dead-time corrections were applied while attenuation correction was performed using the vendor-provided ultra-short echo time (UTE) sequence. Attenuation maps were generated using the RESOLUTE (Ladefoged et al., 2015) approach. The spatial