Dementias Platform UK MR-PET Network Harmonisation Study

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Study aim:

To harmonise and quantify the repeatability and reproducibility of regional [^{18}F]florbetapir brain measurements using MR-PET scanners.

Specifically, the study will quantify measurement variability of imaging parameters in a within site test-retest paradigm (repeatability), and by comparing repeat measurements across different sites using the same scanner model and using a scanner of a different manufacturer (reproducibility). The selection of imaging parameters to be tested will be guided by the requirements of clinical trials in preclinical, prodromal or manifest Alzheimer's disease using MR-PET to provide multiple imaging biomarkers. The imaging protocol will aim to maximise the information gain and quantitative accuracy using the specific advantages offered by MR-PET, whilst aiming to control and alleviate the specific limitations of this technique.

The study is an essential preparatory study that will enable future multi-centre DPUK cohort studies, enable the optimisation of scanning approaches, and the evaluation of benefit of different approaches (including novel methods) for image reconstruction and analysis pipelines to reduce repeatability and reproducibility.

Formal classification:

Observational repeatability and reproducibility study in healthy human participants (no therapeutic intervention)

Sponsor: University of Manchester

Design summary:

To conduct 84 MR-PET scans in 42 elderly healthy participants (age range 65 to 90 years), each participant scanned twice (within 4 weeks), at seven sites, with each site recruiting six participant and conducting at least one scan at their site. For each site, two of these participants will be re-scanned at the same site using the same scanner, two will travel to a different site but equipped with a similar scanner, and two will travel to a site with a scanner of a different manufacturer (see table 1).

In addition to the imaging data, participants will complete: Geriatric Depression Scale 15 (GDR-15) questionnaire; undergo an Addenbrooke's Cognitive Examination (ACR-R); with a clinical history taken.

Table 1: Table summarising the study design and showing the location of scanning for each of the recruiting sites.

		Group 1 (repeatability)[1]	Group 2 (intra-scanner reproducibility)[2]		Group 3 (inter-scanner reproducibility)[2]	
Scanner model	Recruiting site	Number of participants	Site of second scan[3]	Number of participants	Site of second scan[3]	Number of participants
Siemens mMR	UCL	2	KCL or Edinburgh	2	Imperial, Cambridge, Manchester, or Newcastle	2
	KCL	2	UCL or Edinburgh	2	Imperial, Cambridge, Manchester, or Newcastle	2
	Edinburgh	2	UCL or KCL	2	Imperial, Cambridge, Manchester, or Newcastle	2
GE Signa MR-PET	Imperial	2	Cambridge, Manchester, or Newcastle	2	UCL, KCL or Edinburgh	2
	Cambridge	2	Imperial, Manchester, or Newcastle	2	UCL, KCL or Edinburgh	2
	Manchester	2	Imperial, Cambridge, or Newcastle	2	UCL, KCL or Edinburgh	2
	Newcastle	2	Imperial, Cambridge, or Manchester,	2	UCL, KCL or Edinburgh	2
Total		14		14		14

[1]Test-retest scans both at recruiting site

[2]Test-retest scans at recruiting site and specified site

[3]The sites will be chosen to minimise the travelling of participants and to try and keep the total number of scans performed at each site in the range 10-14

Inclusion Criteria

- Healthy volunteer
- 65 to 90 years old
- Understanding of English (for questionnaires)
- Mini Mental State Exam Score 28-30
- GDS-15 score of 0-9
- Participant is ambulant and able to tolerate lying still in the MR-PET scanner for 60 minutes
- Participant is able to tolerate the required travelling to other sites.

Exclusion Criteria

- Contraindications to MR scanning including participants who are claustrophobic

- Severe renal or hepatic impairment
- Severe head trauma, with evidence of structural brain damage
- Brain tumour
- Schizophrenia, bipolar disorders, or recurrent psychotic disorders
- Stroke resulting in physical impairment
- Neurodegenerative disorders (e.g. Huntington disease, Cortical basal degeneration, Multiple system atrophy, Creutzfeldt-Jacob disease, primary progressive aphasia, Parkinson's disease)
- Epilepsy, currently using antiepileptic drugs (AEDs)
- Brain infection (e.g. herpes simplex encephalitis)
- Cancer with terminal life expectancy
- Any disorder or condition that would impair attendance of scanning sessions
- Pregnancy, breastfeeding or planning to become pregnant within 1 month of participating in the study
- Women of childbearing potential that do not use any form of contraception
- Any participant previously or currently involve in other research studies that would result in a unacceptable cumulative burden; an excessive cumulative radiation dose; or which would interfere with an active intervention trial.

Recruitment and participant consent will occur in the knowledge that the participant will undergo one of 3 scanning options, two of which would require the participant travelling to another site for the repeat scan. Following consent the participant will be randomly allocated to one of these options with stratification to ensure 2 participants at each site from each of the three groups.

PET scanning

The PET component of the scanning protocol will use the amyloid tracer [^{18}F]florbetapir at the recommended standard dose of 370 MBq. The choice of the tracer is motivated by the fact that amyloid scanning now is the most common PET biomarker included in AD trials and, as far as known, does not depend on the functional state of the brain. Therefore, the variation observed with amyloid imaging will not be confounded by functional changes (which would, for instance, need to be considered when using FDG). Additionally we also would not expect significant changes of amyloid load in participants' brains during the short time interval between scans (4 weeks max). Kinetics of florbetapir will allow completion of a full dynamic scan within 60 minutes, comprising both the initial tracer distribution immediately after injection which is mostly governed by cerebral blood flow, and the later amyloid binding distribution at 40 to 60 minutes after injection. Scans will be performed during simultaneous MR acquisition (see section on MR scanning).

Whenever possible, participants should receive a low dose CT for attenuation correction either at baseline or follow-up. This may be done separately on a different day or following the MR-PET on a standard PET-CT scanner with the option of conducting a brief emission scan.

Justification

Measurement variability limits the ability of clinical trials to demonstrate changes in measurements such as that due to therapeutic inventions. Consequently, knowledge of this is critical in the design of clinical trials and establishing the number of participants that will need to be studied in order to demonstrate anticipated changes. Additionally, measurement variability can be reduced through the standardisation of data acquisition, and the subsequent processing of the data. However, there are practical limits on what can be standardised and it is important to know as to which factors are important and which factors are less important. For instance, a clinical trial could be conducted using

a single site, multiple sites with similar scanning equipment, or multiple sites with different scanning equipment. The use of more sites will enable more timely completion of a trial, but could come at the expense of more variability with a greater number of participants needing to be recruited. MR-PET is a new modality and to our knowledge similar research has not previously been conducted with initiatives such as Alzheimer's Disease Neuroimaging Initiative (ADNI) yet to address MR-PET scanners.

While it has already been demonstrated that visual classification of amyloid scans as positive or negative is feasible without bias using MR-PET (compared to PET/CT) [1], quantitative analysis of amyloid scans has not yet been standardised and results depend heavily on factors such as choice of the reference region, scanner resolution, time of scanning, partial volume correction, etc. [2, 3]. Initial advances towards standardisation have been published [4], and further projects are underway (e.g., QIBA, https://www.rsna.org/QIBA-Process/). The obvious main challenges relate to the transition from normal to increased amyloid deposition in cortex, at a time when cortical binding is still below non-specific uptake in white matter but spill-over due to insufficient spatial resolution especially in atrophic cortex may be a substantial confounder. MR-PET with MR-based grey-white matter segmentation has specific potential for accurate partial volume correction and/or resolution recovery. Elderly normal controls are an ideal population to cover that issue because some of them are expected to be in that transition period, whereas young controls or most MCI and AD patients would not be in transition.

Within the proposed age range, about 25% of normal elderly (70+) control participants are expected to show positive amyloid scans, which will be about 10 positive participants in this cohort.

Image reconstruction, data storage and analysis

This harmonisation study will be the first multicentre study to make use of the computing infrastructure developed within the DPUK Imaging Informatics programme encompassing all the DPUK imaging centres. The infrastructure employs the open source XNAT informatics platform, which will facilitate storage, common analysis, sharing and management of imaging data and any other associated data.

All acquired imaging data will be anonymised and uploaded to a local XNAT server, which then will be sent to the central XNAT hub for analysis and harmonisation. Additionally, PET list mode data will be uploaded once logistics are resolved to the central XNAT hub for image reconstruction. After the main analysis and harmonisation, the data will be available to any local XNAT node allowing to the partner sites, and others to test and implement new image reconstruction and analysis methods. MR data will be reconstructed using standard scanner software.

The main analysis will consist of image reconstruction as implemented by the manufacturers including recommended methods for attenuation correction and using conventional analysis approaches. Subsequent alternative image reconstruction and analysis methods will be explored, with emphasis on accurate attenuation correction for quantitative PET, led through UCL but with significant contribution from each of the partners and include:

1) Alternative attenuation correction methods adapted to the offline image reconstruction platforms provided by the manufacturers (Siemens' E7 tools and GE's PET toolbox). This will include:
    a. The multi-atlas CT synthesis method that provides a significant improvement in PET quantitative accuracy when compared to the ultra-short echo time (UTE)-based AC; developed at UCL by Burgos, et al. [5]

b. An atlas based AC method independently developed at KCL/Lyon by Mérida, et al. [6].
c. Only methods that are equally applicable to all manufacturers will be used with synthetic AC maps or measured by a CT scan.
d. However, other techniques available with GE Signa scanners such as the time-of-flight (TOF) based attenuation techniques [7] and the zero TE MR method for imaging bone [8] will also be explored (zero TE and TOF is not available on the Siemens Biograph mMR scanners).

2) All PET list-mode data files will be processed for quality control (QC), which is already deployed for the Insight 1946 cohort study at UCL using the XNAT platform [9]. The QC involves checks for all recorded counts per second, motion detection and dynamic projection view videos for quick visual inspection.
3) An open-source software platform developed at UCL specifically for PET/MR scanners [9] will be used for estimation of any image statistic using both static and dynamic imaging [SUVr and binding potential, BP_{ND}] accompanied by voxel- and ROI-level uncertainty estimation using fast and efficient generation of multiple bootstrap realisations of list-mode datasets. The datasets are then processed independently within complex reconstruction and analysis chains involving motion correction as well as kinetic analysis.
4) Motion will be detected and corrected using (i) the rapid processing of list-mode data and generation of the centre of radioactivity mass in short time frames [4-6 seconds]; (ii) the MR data acquired simultaneously during PET acquisition; (iii) joint motion correction and kinetic analysis. Improvements in image quality obtained by motion correction will be tested and compared with uncorrected standard image reconstructions.
5) All MR-PET co-registration will be performed using a robust and symmetric affine scheme based on a block-matching approach [10] whereas other approaches based on mutual information will also be investigated. The T1w MR images will be parcellated into multiple regions of interest using multi-atlas segmentation propagation strategy [11,12]. The previously obtained global transformations will then be used to propagate the regions of interest from the T1w MRI space to the PET space.

The above QC, image reconstruction and analysis will be used to estimate the following biological parameters:

1) Participant static images using 40-60 min static scan reconstruction followed by intensity normalisation using a number of reference regions to generate SUVr. The impact of different reference regions (including the cerebellum, eroded white matter, brain stem and combinations or data driven approaches [13]) on the reproducibility of the SUVr per participant will be investigated.
2) Binding potential (BP) calculated by a dynamic image reconstruction and a suitable implementation of kinetic model such as the SRTM and using a variety of reference regions.
3) Binding potential (BP) calculated through kinetic analysis with the blood flow estimated by the simultaneously acquired ASL to reduce PET acquisition time. The usefulness and robustness of this method will be investigated, including (i) the relationship between blood flow measured by ASL and the transfer rate constant from blood plasma to tissue as measured by early PET time frames as well as (ii) the estimation of reference input function required by the SRTM kinetic model method adapted in this approach. Compared to the standard SUVr method, this approach shows smaller bias in areas of high amyloid burden [14]

For all parameters, regional (grey/white matter segmented VOIs as defined in [12] and implemented in [11]) and voxel-based analyses will be conducted on the repeatability and reproducibility data pairs using repeated measures longitudinal data analysis framework to compare bias and ICC between the two groups of the same and different scanner manufacturer as well as between different reconstruction and analysis techniques (e.g., static, dynamic and ASL/PET analyses).

MR scanning

Concurrent MR protocols also will be harmonised, informed by ongoing dementia studies currently running on the Siemens Biograph mMR scanner at UCL. The protocol will consist of:

- UTE and Dixon sequences (for attenuation correction)
- EPAD core protocol set
    - 3D T1-weighted structural imaging for brain tissue segmentation
    - 3D FLAIR research/diagnostic scan for white matter lesion detection and filling
    - Axial T2* for microbleed detection
    - Axial T2 with fat sat diagnostic scan
- Advanced sequences
    - Resting state fMRI to assess functional networks and connectivity
    - Multi-shell diffusion (b=0,700,2000), for DTI and analysis using more advanced models e.g. NODDI to assess structural connectivity and tissue microstructure
    - 3D multi-echo gradient echo for SWI and quantitative susceptibility mapping
    - 3D pCASL, with either single or multiple post-labelling delays, to measure cerebral blood flow and associated haemodynamic parameters
    - Field map for EPI distortion correction

Cross-platform harmonisation will be achieved by transfer of the above protocols to the GE scanners, with any incompatibilities resolved to enable matched acquisitions to be performed on both scanner types.

MR data analysis

Data analysis will proceed similar to PET data analysis for all MR-based parameters. We will also explore the accuracy of amyloid BP calculated from late static scans in combination with ASL, which could potentially provide an important advantage of MR-PET over PET/CT for routine scanning.

Phantom studies

Once the most useful and commonly available phantom has been identified by the respective working subgroup (led by Julian Matthews), a schedule of phantom scanning will be proposed and conducted to ensure that basic scanner performance is comparable prior to the beginning of the human study and assess the stability of the scanner during the period of data acquisition. Phantoms will specifically be used to assess scanner sensitivity and spatial resolution. Phantom measurement protocols will be informed by previous and current experience of NIHR oncology network activities, led by Paul Marsden.

Ethical considerations

Participants will be requested to undergo two MR-PET scans within a period of 4 weeks, with some travel needed for some of the participants. Each scanning session will last approximately 1 hour and involve injection of radio-active tracer on each occasion. When using the recommended dose (370 MBq), each tracer administration will involve a radiation exposure of 7 milli-Sievert (mSv); a low

does CT scan of the brain for attenuation correction involves 0.5 mSv of radiation or less. Thus the total dose is 14.5 mSv. Justification of doses > 10 mSv according to ARSAC and ICRP (addendum 1 to publication 53: category III) requires a substantial level of societal benefit, directly related to the prevention or mitigation of serious disease.

As the clinical significance of amyloid deposition in normal controls is still unknown, we would not communicate scan results to participants. Communication of any other incidental findings (in particular on the MR scans) would be handled in line with standard practice at partner institutions (and according to EPAD procedures – www.ep-ad.org).

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