UK Dementia Platform: Methods

Roger Gunn
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UK DP Imaging Network

PET-MRI Scanners

4 x GE Signa PET/MR

3 x Siemens Biograph MMR
A UK-wide dementia imaging network equipped with state of the art tools for the support of experimental medicine and clinical trials

- Development of common operating procedures and analyses for outcome measures
- **Sharing expertise and resources** to enable more rapid uptake of technical advances (e.g., novel radioligands for PET or improved image analysis algorithms) and the coordinated development of related resources, such as 7T MRI and MEG, to enable advanced multi-modal studies
- Creating a world-leading environment for novel therapeutics development and a single point of access to a national imaging platform intended to foster both academic and industry dementia research.

**Network Coordination**
Paul Matthews (Chair), Franklin Aigbirho, Nick Fox (co-chairs)

**WG1: Procurement and set up**
Geoff Parker (Manchester)  
Edwin van Beek (Edinburgh)

**WG2: Radiotracer access and development**
Franklin Aigbirho (Cambridge)  
Jan Passchier (Imanova)

**WG3: Clinical governance for multicentre studies**
Karl Herholz (Manchester)  
John-Paul Taylor (Newcastle)

**WG4: Analysis pipelines and QC**
Roger Gunn (Imperial)  
David Thomas (UCL)

**WG5: IT & Data Management**
Sebastien Ourselin (UCL)  
Clare Mackay (Oxford)
MRC Deep and Frequent Phenotyping

- Full Study Funded
- £6.8M
- Screening Amyloid PET & Apoe4
- 250 subjects to be included
- PET
  - Amyloid (Baseline & 1 yr follow up in subset, n=100)
  - Tau (Baseline & 1 yr follow up in subset, n=100)
- MRI
  - 6 Time Points (1, 2-5, 30, 60, 1 yr, 2yr)
  - T1
  - DTI
  - fMRI
  - FLAIR
  - ASL
- Study start to be determined – but likely FSFV Jan 2017
Aβ and Tau in AD

- Two main pathological hallmarks of AD:
  - Amyloid plaques (Aβ)
  - Neurofibrillary tangles (Tau)

- Aβ FDA approved tracers:
  - Amyvid
  - Vizamyl
  - Neuraceq

- Tau tracers:
  - AV1451
  - GE5351

Kinetic characterization
In vivo selectivity
Evaluation of simplified acquisitions
Potential Ab and Tau PET Radiotracers

**Ab**
- $^{11}$C-PiB
- $^{18}$F-florbetaben
- $^{18}$F-florbetapir
- $^{18}$F-flutemetamol

**Tau**
- $^{18}$F[AV1451 (T807)

Note: There are a number of other tau tracers in development but they are either at too early a stage of development or have freedom to operate issues. E.g. Merck, Roche, Genentech.
From Preclinical to Clinical Alzheimer’s Disease

Ab

Tau

Abnormal

Aβ

Tau-mediated neuronal injury and dysfunction

Brain structure

Memory

Clinical function

Biomarker magnitude

Normal

Cognitively normal

MCI

Dementia

Clinical disease stage

Jack, Radiology (2012)
Deep and Frequent Phenotyping
(Pilot Study Results from PET)

All PET Pilot Data acquired at Imanova
Study overview

Aim:

• To design an appropriate acquisition protocol suitable for a large (non-interventional) longitudinal study.
  • Assess participants acceptability of extensive and repeated phenotyping
  • Determine the relationship between $BP_{ND}$ (Dynamic Imaging) and the simplified SUVR measure (Static Imaging) to give information on the validity of static acquisitions for the full study

Subjects:

• 15 subjects
  • Aged 55-85 (men and women)
  • MMSE score 20-29
Data acquisition

Scans:

- **Dynamic PET (with no blood sampling)**
  - Amyloid: \[^{18}\text{F}]\text{AV45} \ (0-60 \text{ min}; \ 150\pm24 \text{ MBq})
    - All subjects completed 60 min scan.
  - Tau: \[^{18}\text{F}]\text{AV1451} \ (0-120 \text{ min}; \ 163\pm10 \text{ MBq})
    - 12 subjects completed at least 110 min.

- **Structural MRI**
  - T1-weighted
Quantitative and Reproducible Analysis – MIAKAT™

Analysis+

• State-of-the-art algorithms
• Source Control
• Analysis Audit trails
• Reproducible
Image Analysis I: Pre-processing & TAC generation

• Motion correction of PET
• Brain extraction in MR
• Non-linear registration of CIC atlas into subject space
• Application of atlas to dynamic PET data and generation of TACs (n=123)

Quantitative analysis performed with MIAKAT™ analysis pipeline.
Data Analysis II: Kinetic Modelling and SUVr

In the absence of blood data we selected SRTM as the gold standard

- Dynamic Measurement
  \[ \text{SRTM} \rightarrow B_{\text{ND}} \]

- Static Measurement
  \[ SUV_r = \frac{SUV_{\text{target}}}{SUV_{\text{reference}}} \]

- Reference Region: Grey Matter Cerebellum
Results: Dynamic PET Scan Time Stability (SRTM)

Aβ ([18F]AV45 )

- Cortical
- Hippocampus
- Posterior-Cingulate-Gyrus
- Cerebellum-grey

SUV

Time [min]

0 10 20 30 40 50 60

0 1 2 3 4 5 6

Tau ([18F]AV1451 )

- Cortical
- Hippocampus
- Posterior-Cingulate-Gyrus
- Cerebellum-grey

SUV

Time [min]

0 20 40 60 80 100 120

0 0.5 1 1.5 2 2.5 3

Aβ ([18F]AV45 )

- Cortical
- Hippocampus
- Posterior-Cingulate-Gyrus

BP ND

Scan duration [min]

0 10 20 30 40 50 60

0 0.5 1 1.5 2 2.5 3

Tau ([18F]AV1451 )

- Cortical
- Hippocampus
- Posterior-Cingulate-Gyrus

BP ND

Scan duration [min]

0 20 40 60 80 100 120

0 0.5 1 1.5 2
Results: Analysis of Static Time Windows

\[ A\beta (^{18}F)AV45 \]

\[ \text{SUV} \]

\[ \text{Time [min]} \]

\[ \text{Cortical} \]
\[ \text{Hippocampus} \]
\[ \text{Posterior-Cingulate-Gyrus} \]
\[ \text{Cerebellum-grey} \]

\[ \text{SUVR} \]

\[ \text{Scan window [min]} \]

\[ \text{Cortical} \]
\[ \text{Hippocampus} \]
\[ \text{Posterior-Cingulate-Gyrus} \]

\[ \text{SUVR} \]

\[ \text{Scan window [min]} \]
Results: Static versus Dynamic PET Scans

12 subjects x 123 regions

Late

SUVR 30-50

Aβ ([18F]AV45)

晚期

Aβ ([18F]AV45)

SUVR 80-100

R² = 0.74

R² = 0.88

Early

SUVR 10-30

Aβ ([18F]AV45)

早期

Aβ ([18F]AV45)

SUVR 30-50

R² = 0.65

R² = 0.69

BPND

BPND

BPND

BPND
Results: $\text{BP}_{\text{ND}}$ Parametric images (SRTM)
Results: Tau and Amyloid Correlation

The diagram shows the correlation between Tau and Amyloid (Aβ) in various brain regions, indicated by $R^2$ (signed). The color scale ranges from -1 to 1, where red represents a positive correlation and blue represents a negative correlation.
Results: Tau and Amyloid Correlation

![Graph showing correlation between Tau and Amyloid](image)

- $R^2$ value for Tau and Amyloid correlation: 0.7
- $P$ value: 0.0006

![Graph showing correlation between Tau and Hippocampus](image)

- $R^2$ value: 0.68
- $P$ value: 0.001

![Graph showing correlation between Tau and Thalamus](image)

- $R^2$ value: 0.6
- $P$ value: 0.003
Conclusion

Within the cohort studied SUVR values from short static PET scans at appropriate time windows are in good agreement with SRTM $\text{BP}_{\text{ND}}$ values for subjects stratification in AD with $[^{18}\text{F}]\text{AV45}$ and $[^{18}\text{F}]\text{AV1451}$. 

### Dynamic

- **30 min**
  - $A_0 / [^{18}\text{F}]\text{AV45}$
  - $\text{BP}_{\text{ND}}$

- **80 min**
  - $\text{BP}_{\text{ND}}$
  - $\text{Tau} / [^{18}\text{F}]\text{AV1451}$

### Static

- **30-50 min**
  - $A_0 / [^{18}\text{F}]\text{AV45}$
  - SUVR

- **80-100 min**
  - SUVR
Deep and Frequent Phenotyping
(Plans for Full Study)
D&FP Study Design

Cohort A
N=150
Ab

Cohort B
N=150
Ab

Cohort C
N=100
Ab

Cognition battery, MRI, MEG, EEG, CSF, Blood, Urine, Gait and Peripherals, Ophthalmology (multiple measures over 12 mths)

Cognition battery, MRI, MEG, EEG, CSF, Blood, Urine, Gait and Peripherals, Ophthalmology (multiple measures over 12 mths)

Screening  Baseline  1 Year
Full DF&P PET: Scanners

<table>
<thead>
<tr>
<th>Site</th>
<th>Scanner</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edinburgh</td>
<td>Siemens Biograph MMR</td>
</tr>
<tr>
<td>Newcastle</td>
<td>GE Signa PET/MR</td>
</tr>
<tr>
<td>Manchester</td>
<td>GE Signa PET/MR</td>
</tr>
<tr>
<td>Cambridge</td>
<td>GE Signa PET/MR</td>
</tr>
<tr>
<td>Oxford</td>
<td>PET/CT &amp; MR</td>
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<tr>
<td>ICL (Imanova)</td>
<td>GE Signa PET/MR</td>
</tr>
<tr>
<td>KCL</td>
<td>Siemens Biograph MMR</td>
</tr>
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## Full DF&P PET: Multisite imaging with Ab and tau

<table>
<thead>
<tr>
<th>Site</th>
<th>Ab</th>
<th>Tau</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buy in*</td>
<td>Onsite GMP</td>
<td></td>
</tr>
<tr>
<td>Edinburgh</td>
<td>✓</td>
<td>[¹⁸F]GE216</td>
</tr>
<tr>
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<tr>
<td>Manchester</td>
<td>✓</td>
<td>✗</td>
</tr>
<tr>
<td>Cambridge</td>
<td>✓</td>
<td>[¹⁸F]AV1451</td>
</tr>
<tr>
<td>Oxford</td>
<td>✓</td>
<td>✗</td>
</tr>
<tr>
<td>ICL (Imanova)</td>
<td>✓</td>
<td>[¹⁸F]AV1451, [¹⁸F]GE216</td>
</tr>
<tr>
<td>KCL</td>
<td>✓</td>
<td>✗</td>
</tr>
</tbody>
</table>
Key Activities over the coming months

- Establish PET/MR scanners for Q1 2017 start
- Establish confidence in PET attenuation correction
- Establish IT Data Management Infrastructure
- Confirm choice of PET Ab and tau tracers
Acknowledgment