Agenda

• Lessons learned from PPMI- camera standardization, measurand, VOI strategy
• Writing the Profile
Definition of Measurands

- Striatial binding ratio
- Ratio of putamen to caudate
- Asymmetry of caudate and putamen
- % injected dose/gram tissue
System Variance Sources Model – Ioflupane SPECT

Each source contributes variance to final measure and ideally should be measured/controlled

**Equipment QC**
- Time synchronization
- Dose calibrator
- SPECT calibrations & QC
  - Uniformity
  - Alignment
  - Sensitivity
- CT calibrations* & QC
  - HU accuracy
  - Uniformity

**Acquisition Protocol**
- CT acquisition*
- Injected dose
- Uptake time
- Head position
- Data statistics
- Detector/Collimator response
- Data sampling
  - Framing
  - Time sampling
  - Angular sampling

**Patient**
- Size
- Motion
- Tracer kinetics
- Brain condition
  - Age
  - Atrophy
  - Pathology

**Image Reconstruction**
- Attenuation correction
- Scatter correction
- Gantry response correction
- Reconstruction algorithm and settings
- Detector/collimator response corrections

**Image Analysis**
- Partial volume correction
- Spatial normalization to template
- Target VOIs
- Reference region
- Age correction

*If SPECT/CT or CT image used for attenuation correction
## Parkinson’s Progression Marker Initiative (PPMI)

### Study synopsis

| Study population                      | 400 *de novo* PD subjects (newly diagnosed and unmedicated)  
|                                      | 200 age- and gender-matched healthy controls  
| Subjects will be followed for a minimum of 3 years and a maximum of 5 years |

| Assessments/ Clinical data collection | • Motor assessments  
|                                      | • Neuropsychiatric/cognitive testing  
|                                      | • Olfaction  
|                                      | • DaTSCAN imaging  
|                                      | • DTI, resting state MRI  
|                                      | • AV-133 |

| Biologic collection/ Verification studies | • DNA collected at baseline  
|                                          | • Blood collected at each visit; CSF collected at 6mo and then annually  
|                                          | • Samples aliquoted and stored in central biorepository  
|                                          | • Lead biologic candidates potential to be tested: alpha-synuclein, DJ-1, urate |

| PD treatment | • De novo for 6 months  
|             | • Can participate in clinical trials after 12 months |
PPMI Study Sites

Northwestern Univ
IND- New Haven
Johns Hopkins
Federico II - Naples
Parkinson’s Institute- Sunnyvale
Univ Pennsylvania
Univ Rochester
APDC- Sun City, Az
Baylor
London
Univ Cincinnati

Univ Alabama-Birmingham
Boston University
Portland
Innsbruck
Marburg
Tübingen
Univ Washington
Tampa
Emory Univ
San Diego
Cleveland Clinic
Boca Raton
Sydney
Technical Challenges in Multicenter Imaging Trials

- Different cameras have different physical characteristics
- Image reconstruction and filtration
- Post hoc processing: attenuation correction, spatial normalization,
- VOI strategies
- Normal controls: what’s normal, how heterogeneous
- Camera drifts, especially over long studies
- Other sources of increased variance:
  - updates in reconstruction
  - software
  - ambient changes in background radiation levels
Factors Which Influence the Specific Binding Ratio

• Biological factors
  • Dopamine transporter density
  • Age
  • Pharmacokinetic factors - rate of uptake, metabolism and elimination of tracer
  • Genetic: allelic variants of DAT
  • Drugs competing with DATScan for DAT binding
  • Patient ability to remain motionless in the camera

• Technical factors
  • Equipment: Resolution and sensitivity of selected camera, collimator
  • Performance drifts over time
  • Photon flux - counts in image
  • Reconstruction/filtration
  • Size and placement of regions of interest
Anthropomorphic Striatal Phantom for Set-up Calibration
Dual Energy Window Acquisition Protocol for both 57Co phantom and PD patient
57-Co Striatal Phantom

mid-brain

2 striata

occipital
Striatal sampling strategy

• Different region of interest sampling strategies are needed for within subject longitudinal sampling vs. cross-sectional separation of populations to assess the presence or absence of DAT deficit.

• Changes in putamenal DAT density in PD: reductions extend from posterior to anterior
Volume of Interest Strategies

A

B

Caudate
Ant putamen
Post putamen
DAT Analyses

• On spatial normalized SPECT image volumes the transaxial slice with the highest striatal uptake is identified and the 8 hottest striatal slices around it were averaged in to generate a single slice image.

• Regions of interest (ROI) were then placed on the left and right caudate, the left and right putamen, and the occipital cortex (reference tissue).

• Count densities for each region were extracted and used to calculate specific binding ratios (SBRs) for each of the striatal regions. SBR is calculated as (target region/reference region)-1.
Summed sagittal slices view of brain volume showing selection of transverse slices (between red lines); total slices added for analysis is $2 \cdot \text{iwid} + 1$.

Figure 3: Summed transverse slice showing ROI placement and region statistics for calculating the Striatal Binding Ratios (referred to as 'V3'' in the image).
Baseline DAT SBR, Age-corrected

Mean Striatal SBR

Contralateral Putamen SBR

PD n= 423
HC n= 196
SWEDD = 64
## Baseline DAT Data

<table>
<thead>
<tr>
<th>Striatal Binding Ratio</th>
<th>PD Subjects (n=423)</th>
<th>Healthy Volunteers (n=196)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowest caudate</td>
<td>1.83</td>
<td>2.87</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lowest putamen</td>
<td>0.67</td>
<td>2.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean caudate</td>
<td>1.99</td>
<td>2.98</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean putamen</td>
<td>0.87</td>
<td>2.15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean striatum</td>
<td>1.41</td>
<td>2.57</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>