DAT Imaging provides unique and clinically useful information

Danna Jennings, MD
Institute for Neurodegenerative Disorders
Applications of imaging markers

- Validate diagnosis
- Identify early diagnosis
- Monitor disease progression and develop neuroprotective agents
- Identify pre-clinical diagnosis and treat with potential neuropreventative agents
Parkinson Disease: Clinical Diagnosis

- Diagnosed by presence of cardinal clinical features
  - resting tremor
  - rigidity
  - bradykinesia

- In mid to late PD, may be difficult to differentiate from atypical parkinsonian syndromes (rare!)

- Early in the course (2 yrs from onset), may be difficult to differentiate from
  - Essential tremor
  - Vascular parkinsonism
  - Drug-induced parkinsonism
  - Primary dystonia
  - Psychogenic parkinsonism

Accuracy dependent on duration of follow-up
Natural History of Parkinson Disease

Neuronal density

Preclinical

Symptomatic

Time

Preclinical

Symptom Onset

Diagnosis

Clinical symptoms

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## Comparison of Dopamine Transporter ligands under development

<table>
<thead>
<tr>
<th>SPECT Tracer</th>
<th>$[^{123}\text{I}]\beta$-CIT</th>
<th>$[^{123}\text{I}]$FP-CIT</th>
<th>99mTc-TRODAT</th>
<th>$[^{123}\text{I}]$Altropane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to peak uptake</td>
<td>Protracted 8-18 h</td>
<td>Rapid 2-3 h</td>
<td>Rapid 2-3 h</td>
<td>Rapid 0.5-1 h</td>
</tr>
<tr>
<td>Washout phase</td>
<td>Prolonged</td>
<td>Prolonged</td>
<td>Intermediate</td>
<td>Rapid</td>
</tr>
<tr>
<td>DAT binding affinity</td>
<td>1.4 nM Ki</td>
<td>3.5 nM Ki</td>
<td>9.7 nm Ki</td>
<td>6.62 nM IC50</td>
</tr>
<tr>
<td>SPECT target:background tissue ratio</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>
Imaging in the brain: Molecular targets of radioligands.\(^7\)

Adapted from Science 2000; 289: 409-411.
The Query-PS Study:
to determine the sensitivity and specificity
of DAT imaging as a diagnostic tool
in clinically uncertain parkinsonian syndrome
Natural History of Parkinson Disease

Neuronal density

Clinical symptoms

Time

Preclinical

Symptom Onset

Diagnosis

Early Symptomatic
Query-PS study design

DAT deficit defined as <65% of age expected uptake

**I-MDE** = Independent Rater Movement Disorders Expert
**E-MDE** = Enrolling Movement Disorders Expert
**Mo** = month; **n** = number of subjects; **MNE** = nuclear medicine expert

Figure 1. Schematic of study design, visit schedule, and subject flow diagram.
Query AD:
DAT imaging diagnosis vs ‘gold standard’ clinical diagnosis (n=110)

false positives (n=7)
false negatives (n=8)
Comparing diagnostic accuracy and inter-rater reliability (12-mo clinical diagnosis -‘gold standard’ as the reference)

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<th>Comparison with 12-Month ‘Gold Standard’ (n=110)</th>
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<td>PS</td>
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Comparing diagnostic accuracy and inter-rater reliability
(12-mo clinical diagnosis - ‘gold standard’ as the reference)

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DAT imaging more accurate than clinicians at baseline!

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# Influence of DAT imaging data on referring neurologists’ management plan

<table>
<thead>
<tr>
<th>Referring Neurologist Management Plan</th>
<th>BL (%)</th>
<th>After review of imaging (%)</th>
<th>BL (%)</th>
<th>After review of imaging (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS (N=46)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjust non-PD meds</td>
<td>8.7</td>
<td>2.2</td>
<td>15.8</td>
<td>19.3</td>
</tr>
<tr>
<td>No meds/other testing</td>
<td>43.5</td>
<td>23.9</td>
<td>36.8</td>
<td>56.1</td>
</tr>
<tr>
<td>Trial of PD meds</td>
<td>47.8</td>
<td>73.9</td>
<td>47.4</td>
<td>24.6</td>
</tr>
<tr>
<td>Not PS (N=57)</td>
<td></td>
<td></td>
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</tbody>
</table>

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The CUPS (Clinically Uncertain Parkinsonian Syndromes) Study

• Subjects symptomatic with uncertain dx
• Clinical follow-up (unblinded to imaging) compared with baseline FP-CIT imaging
• Sens 85%, Spec 93%
• False positives in pts with vascular PD
• False negatives in pts with IPD

Neuropsychica 2007 Mar 22(2):86-92
SWEDD  
*Scans without evidence of dopaminergic deficit*

**Possible Explanations**

- Subjects do not have PD.
- Subjects with PD may not have nigral dopaminergic loss.
- Subjects with PD may have nigral dopaminergic loss, but the imaging is not sensitive to these changes.
## Summary of SWEDD in Parkinson Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>PD Stage</th>
<th>Duration of dx at baseline (mos)</th>
<th># of SWEDDs</th>
<th>% SWEDDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elldopa</td>
<td>Denovo</td>
<td>6</td>
<td>21/142</td>
<td>14%</td>
</tr>
<tr>
<td>InSPECT</td>
<td>Denovo</td>
<td>8</td>
<td>15/112</td>
<td>13%</td>
</tr>
<tr>
<td>PRECEPT</td>
<td>Denovo</td>
<td>8</td>
<td>85/799</td>
<td>11%</td>
</tr>
<tr>
<td>REAL-PET</td>
<td>Denovo</td>
<td>9</td>
<td>21/186</td>
<td>11%</td>
</tr>
<tr>
<td>CALM-CIT</td>
<td>start of DA rx</td>
<td>18</td>
<td>3/82</td>
<td>4%</td>
</tr>
<tr>
<td>GPI-1485</td>
<td>treated stable responder</td>
<td>23</td>
<td>3/212</td>
<td>1.40%</td>
</tr>
</tbody>
</table>
# Imaging Follow-up for SWEDDs in PD Trials

<table>
<thead>
<tr>
<th></th>
<th># of SWEDDs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CALM-PD CIT</strong></td>
<td>Baseline - 3</td>
</tr>
<tr>
<td></td>
<td>22 months - 3/3</td>
</tr>
<tr>
<td><strong>ELLDOPA CIT</strong></td>
<td>Baseline – 21</td>
</tr>
<tr>
<td></td>
<td>9 months – 19/19</td>
</tr>
<tr>
<td></td>
<td>18 months – 17/17</td>
</tr>
<tr>
<td></td>
<td>36 months - 12/12</td>
</tr>
<tr>
<td></td>
<td>48 months - 9/9</td>
</tr>
<tr>
<td><strong>Real-PET</strong></td>
<td>Baseline - 21</td>
</tr>
<tr>
<td></td>
<td>24 months - 19/19</td>
</tr>
<tr>
<td><strong>InSPECT</strong></td>
<td>Baseline 15</td>
</tr>
<tr>
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<td>3 months - 12/12</td>
</tr>
</tbody>
</table>
Conclusions - DAT Imaging in Early PS

• Early dx of PS can be difficult based on clinical data
• Clinical dx offers high sensitivity
• DAT imaging offers high sensitivity and specificity
• Addition of DAT imaging difficult to dx cases improves overall accuracy of diagnosis
• Management of care influenced by DAT imaging data
• Percent of SWEDD subjects increases when enrolled early after diagnosis.
• DAT imaging at screening has potential to enhance confidence of accurate diagnosis in clinical trials participants
Prediction and prevention: The future of neuroimaging in Parkinson’s disease

Earlier detection $\Rightarrow$ Earlier treatment $\Rightarrow$ Decreased functional decline
Natural History of Neurodegenerative Disorders
When Does PD begin?

Total age adjusted neuron count vs symptom duration – Presymptomatic phase – 4.7 years.
Fearnley and Lees, Brain 1991

%Loss DAT density vs diagnosis duration – Pre-motor phase – 13 years. (Elldopa/Precept)
The Parkinson Complex: Parkinsonism is Just the tip of the Iceberg
Langston, Ann Neurol, 2006
Progression of PD Neurodegeneration

- Begins in the Dorsal Medulla and olfactory tract
- Progresses upward through the brainstem
- Cortical involvement begins in the anteromedial temporal cortex, through the limbic cortices into the sensory association and prefrontal cortices and finally to primary sensory and motor cortices

Braak et al.
Idiopathic Hyposmia as a Preclinical Sign of Parkinson’s disease.


361 first degree Asymptomatic family members

40 Hyposmic ß-CIT imaging

5 Abn ß-CIT at 2 years
4 Incident PD at 2 years (10%)
Parkinson’s Disease Associated Risk Syndrome

- Subtle motor features
- Non-motor features
- Neuroimaging changes
- Genetic predisposition
Model for Screening

Primary Screen-Sensitivity
(Genetics, “Omic”, Non-motor)

Secondary Screen-Specificity
(Imaging)

‘Gold Standard’
Clinical F/U
**PARS Study Design**

**Phase I:** Recruitment and Olfactory Testing  
**Phase II:** Longitudinal Clinical and Imaging Study

- **PD probands**  
  - N=3,000

- **Eligible 1st degree Relatives**  
  - N=3,000

- **Advertise, etc.**

- **Hyposmic relatives for the longitudinal Cohort**  
  - n=225

- **Normosmic relatives for longitudinal Cohort**  
  - n=75

- **Subset of normosmic relatives for mail follow-up**  
  - N=

- **Timeline:**  
  - BL  
  - yr1  
  - yr2  
  - yr3  
  - yr4

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3,000 PD patients provide letters to first-degree relatives \((n=6,000)\)

- (40% willing and eligible)

Eligible relatives sent UPSIT’s \((n=2,400)\)

- (72% return rate)

Valid UPSIT’s \((n=1,728)\)

- (≤12th percentile)

Olfactory loss \((n=210)\)
3,000 PD patients (897) provide letters to first-degree relatives (n=6,000)

(40% willing and eligible)

Eligible relatives sent UPSIT’s (n=2,400) (1,685)

(72% return rate)
(57% return)

Valid UPSIT’s (n=1,728) (971)

(≤12th percentile)

Olfactory loss (n=210) (93)
Conclusions:

DAT imaging is a clinically valuable diagnostic tool in patients with early parkinsonian syndrome.

DAT imaging provides the unique potential of identifying pre-clinical parkinsonian syndrome.
2nd International Symposium on Neuroimaging in PD and Related Disorders
Chatham, Massachusetts, USA
October 21-22, 2008

Supported by The Movement Disorder Society
For more information please contact: info@NeuroimagingSymposium.com

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