Teaching Course 6

MDS-ES/EAN: Neuroimaging in movement disorders - Level 2

Imaging biomarkers for Parkinson’s disease

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Imaging biomarkers for Parkinson’s disease

David J Brooks

α-synuclein aggregation

Conflict of interest: David Brooks has worked as a Consultant for GE Healthcare who own the licence for DatSCAN
**BF227 binding to Lewy bodies and GCIs**

Kikuchi 2010

BF227 fluorescence α-Syn immunostaining

**Multiple System Atrophy**

Kikuchi 2010

$[^1]C$BF-227

Alzheimer’s disease

Aged normal AD

AARHUS UNIVERSITY

Imperial College London

Newcastle University
**Imaging nigrosome 1**

T2-weighted iron sensitive SWI

Blazejewska 2013

3 tesla MRI

**Imaging nigrosome 1**

Susceptibility weighted imaging

3 tesla MRI

Reiter 2015

<table>
<thead>
<tr>
<th>PD vs. HC</th>
<th>P &lt; 0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>88.3 (79.0 – 93.9)</td>
</tr>
<tr>
<td>Specificity</td>
<td>100 (93.6 – 100)</td>
</tr>
<tr>
<td>Positive PV</td>
<td>100 (93.6 – 100)</td>
</tr>
<tr>
<td>Negative PV</td>
<td>79.6 (65.2 – 89.1)</td>
</tr>
<tr>
<td>Correct classification</td>
<td>92.0 (85.2 – 96.9)</td>
</tr>
<tr>
<td>P &lt; 0.001</td>
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Diffusion tensor imaging
3 tesla MRI

Fractional anisotropy

Cerebral peduncle

Vaillancourt et al. Neurology 2009;72:1387–84

PPMI cohort

DTI changes in de novo PD

PPMI database

Substantia Nigra: 3% / year higher rates of FA reduction in PD vs HC
Midbrain and Thalamus: 2% / year higher rates of FA reduction in PD vs HC

Schuff et al. 2016
Free water is increased in Parkinson nigra

Free water changes in PD, MSA and PSP

Ofori 2015

Piancetta 2016
Free water pool progression in PD

Magnetisation transfer imaging of neuromelanin

Loss of substantia nigra signal in PD
Reduced melanin volumes in Parkinson’s disease

Imaging melanin with \(^{18}\)F-AV1451 PET

Hansen et al. 2016
Transcranial Sonography in clinically uncertain PD

- 60 cases had baseline TCS and were followed up for 12 months in a blinded prospective study
- Nigral hyperechogenicity had a sensitivity of 91%, a specificity of 82%, a positive predictive value of 93%, but a negative predictive value of 78% for detecting iPD.

Gaenslen 2008

Imaging dopamine terminal function

Normal PD
**Striatal DAT vs nigral melanin**

Hansen 2016

- No correlation between striatal DAT binding and nigral melanin
- No correlation between disease duration and melanin

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**DA imaging: diagnostic support**

<table>
<thead>
<tr>
<th>Nigrostriatal dopaminergic deficiency</th>
<th>No dopaminergic deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic PD</td>
<td>Drug-induced parkinsonism</td>
</tr>
<tr>
<td>Multiple system atrophy</td>
<td>Psychogenic parkinsonism</td>
</tr>
<tr>
<td>Progressive supranuclear palsy</td>
<td>Dopa responsive dystonia</td>
</tr>
<tr>
<td>Corticobasal degeneration</td>
<td>Essential tremor</td>
</tr>
<tr>
<td>Lewy body dementia</td>
<td>Dystonic tremor</td>
</tr>
<tr>
<td>Spinocerebellar ataxia SCA 2</td>
<td>Vascular parkinsonism</td>
</tr>
<tr>
<td>Vascular parkinsonism</td>
<td></td>
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</tbody>
</table>
Discriminating benign tremors from Parkinson's disease

158 PS and 27 ET cases: FP-CIT SPECT had a sensitivity 95% and specificity 93% for differentiating between clinically probable PD and ET patients. Benamer 2000

Essential tremor

Parkinson's disease

Essential tremor

Putamen ¹⁸F-dopa Ki

Ki min⁻¹

Nor familial sporadic

PD

18F-dopa

123I-FP-CIT

99mTc-TRODAT
**Vascular Parkinsonism**

Nigral infarct  
Internal capsule infarct

Courtesy of Per Borghammer

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**Glucose metabolism in parkinsonian disorders**

PD  
MSA  
PD mild  
PD mod  
MSA  
PSP  
CBD

Eckert 2007
Baseline DAT binding in PPMI series of 400 untreated PD

Mean Striatal DAT binding in PD over 4 Years
FP-CIT SPECT
Clinical progression of the PPMI cohort

- Anti-Parkinson’s therapy had been initiated in 36 (24%)
- Therapy withdrawn in 27 - no evidence of deterioration in 25
- Final proportion taking anti-Parkinson’s therapy 7.3%

Two-year follow-up in 150 consecutive cases with normal dopamine transporter imaging
Vicky L. Marshall, Jim Patterson, Donald M. Hadley, Katherine A. Grosset and Donald G. Grosset
**SWEDD follow-up**
PPMI cohort

43 of 64 completed 24 mo DAT imaging
5 of 43 now have a visual DAT deficit at follow-up

Abnormal SWEDD

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**DTI findings in SWEDDs**
PPMI cohort

SWEDD has lower FA than HC

SWEDD has lower FA than PD

Schuff - unpublished
18F-dopa decreases in PD
Statistical Parametric Mapping
p<0.001

Cingulate
Striatum
Early hemi-PD       Advanced PD

Cortical thinning in PD over 18 months
Cortical thickness correlates with MOCA scores in PD
Cortical thinning progresses faster in PD-MCI than PD
Mak 2015
Resting network connectivity changes in PD-MCI

Decreased dorsal attention network connectivity with frontal and insula regions

Increased default mode network connectivity with parieto-occipital regions

Baggio 2015

Resting fMRI

Basal Ganglia network

Reduced BG connectivity in PD
Szewczyk-Krolkowski 2014
Abstract | Dementia is increasingly being recognized in cases of Parkinson’s disease (PD); such cases are termed PD dementia (PDD). The spread of fibrillar α-synuclein (α-syn) pathology from the brainstem to limbic and neocortical structures seems to be the strongest neuropathological correlate of emerging dementia in PD. In addition, up to 50% of patients with PDD also develop sufficient numbers of amyloid-β plaques and tau-containing neurofibrillary tangles for a secondary diagnosis of Alzheimer’s disease, and these pathologies may act synergistically with α-syn pathology to confer a worse prognosis. An understanding of the relationships between these three distinct pathologies and their resultant clinical phenotypes is crucial for the development of effective disease-modifying treatments for PD and PDD.
Amyloid is linked to cognitive decline in patients with Parkinson disease without dementia
Stephen N. Gomperts, Joseph J. Locascio, Dorene Rentz, et al. Neurology 2013;80;85; Published online before print December 12, 2012;

Microglial activation in Parkinson's disease

healthy volunteer

Early Parkinson's

AARHUS UNIVERSITY
Inflammation in Parkinson’s disease correlates with disability

$^{11}$C-PK11195 PET

Striatal $^{11}$C-PK11195 uptake correlates with disability (UPDRS III scores - p<.001)

Insular $^{11}$C-PK11195 uptake correlates with impaired semantic fluency (p<.01)

Inflammation in Parkinson’s disease correlates with disability

Inflammation in PD + dementia

$^{11}$C-PK11195 PET

PD

PDD

PDD>PD
 Decreased putamen dopamine and increased nigral inflammation in REM Behaviour Disorder

Conclusions

• Nigral changes can now be detected with MRI/DTI, TCS, and PET in Parkinson's disease

• Imaging DA terminal function detects dopamine deficient parkinsonism. Normal DA imaging in uncertain PD has a good prognosis

• PD is associated with cortical thinning and reduced basal ganglia cortical connectivity

• The presence of amyloid in PD is associated with rapid cognitive impairment

• Both DTI and FDG PET sensitively discriminate atypical from typical PD.