Update on functional brain imaging in Movement Disorders

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New Frontiers in Parkinson’s Disease and Movement Disorders
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Objectives

• To provide an overview of functional imaging of Parkinson’s disease (PD) and related disorders
• To discuss the clinical utility of dopamine transporter (DAT) imaging in distinguishing essential tremor (and other conditions) from PD
• To discuss functional imaging in diagnosing both the presymptomatic and symptomatic stages of PD (both motor and cognitive presentations) and Dementia with Lewy bodies (DLB)
• Case example using most widely available imaging modalities
Alpha-synuclein brain pathology

Images: Juan Bilbao
Tau brain pathology

Progressive supranuclear palsy

Corticobasal degeneration


Images: Juan Bilbao
Functional imaging in Parkinson’s disease and related disorders

- Imaging biomarkers of:
  - Presymptomatic diagnosis
  - Symptomatic diagnostic confirmation
  - Differential diagnosis
  - Disease progression
  - Response to therapeutics
- Includes PET and SPECT with different tracers, as well as MRI
- Focus on dopamine transporter SPECT, perfusion SPECT and FDG-PET
Molecular Imaging to Track Parkinson’s Disease and Atypical Parkinsonisms: New Imaging Frontiers

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Antonio P. Strafella, MD PhD, Nicolaas I. Bohnen, MD, Joel S. Perlmutter, MD, David Eidelberg, MD, Nicola Pavese, MD, Thilo Van Eimeren, MD, Paola Piccini, MD, Marios Politis, MD, Stephane Thobois, MD, Roberto Ceravolo, MD, Makoto Higuchi, MD, Valtteri Kaasinen, MD, Mario Masellis, MD, PhD, M. Cecilia Peralta, MD, Ignacio Obeso, PhD, Jose Angel Pineda-Pardo, PhD, Roberto Cilia, MD, Benedicte Ballanger, PhD, Martin Niethammer MD, and Jon A. Stoessl, MD, on behalf of IPMDS-Nuroimaging Study Group
Ascending dopaminergic pathways

Strafella et al., 2017
Dopaminergic nerve terminal and various PET radiotracers

Strafella et al., 2017
$^{123}$I-FP-CIT SPECT in Normal (N), Alzheimer’s (AD) and Lewy body disorders

O’Brien et al, 2004
Imaging biomarkers in Parkinson’s disease and Parkinsonian syndromes: current and emerging concepts

Usman Saeed¹,², Jordana Compagnone¹,², Richard I. Aviv³, Antonio P. Strafella⁴,⁵,⁶, Sandra E. Black¹,²,⁶,⁷, Anthony E. Lang⁶,⁸,⁹ and Mario Masellis¹,²,⁶,¹⁰*
Dopamine transporter imaging in PD and “look-a-likes”

- Normal density of presynaptic DAT (¹²³I-FP-CIT SPECT) in healthy controls, patients with essential tremor and in drug-induced, vascular or psychogenic parkinsonism
- Reduced DAT uptake is indicative of nigrostriatal degeneration and is detected in PD, PDD, MSA-P and PSP patients versus controls
- Loss of DAT is typically > in hemisphere contralateral to the parkinsonian symptoms/signs and often is symmetric in patients with symmetric motor deficits
- More severe deficit in posterior > anterior putamen and caudate in PD
- DAT binding correlates with Hoehn & Yahr disease stage, UPDRS total motor score and bradykinesia subscale
- No associations with rigidity or tremor were observed

Reviewed in Saeed et al., 2017
Scans without evidence of dopaminergic deficit (acronym: SWEDD)

- 10-20% of PD patients, enrolled in clinical trials of PD undergoing DAT imaging, were found to have SWEDD
- Follow-up studies have established SWEDD as a heterogeneous group, with the following conclusions:
  - most cases represented a clinical misdiagnosis of PD (commonly dystonia)
  - some cases were false-negatives with true PD, as evidenced by abnormal follow-up scan and a + levodopa response
  - initial imaging reports may have been inaccurate in some due to methodological issues
  - accurate diagnoses in many cases remains unclear due to lack of neuropathological confirmation

Reviewed in Saeed et al., 2017
Diagnosis and management of dementia with Lewy bodies
Fourth consensus report of the DLB Consortium

McKeith et al., 2017
### Table 1 Revised criteria for the clinical diagnosis of probable and possible dementia with Lewy bodies (DLB)

**Essential** for a diagnosis of DLB is dementia, defined as a progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational functions, or with usual daily activities. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention, executive function, and visuo-perceptual ability may be especially prominent and occur early.

**Core clinical features** *(The first 3 typically occur early and may persist throughout the course.)*

- Fluctuating cognition with pronounced variations in attention and alertness.
- Recurrent visual hallucinations that are typically well formed and detailed.
- REM sleep behavior disorder, which may precede cognitive decline.
- One or more spontaneous cardinal features of parkinsonism: these are bradykinesia (defined as slowness of movement and deceleration in amplitude or speed), rest tremor, or rigidity.

**Supportive clinical features**

- Severe sensitivity to antipsychotic agents; postural instability; repeated falls; syncope or other transient episodes of unresponsiveness; severe autonomic dysfunction, e.g., constipation, orthostatic hypotension, urinary incontinence; hyposmia; hallucinations in other modalities; systematized delusions; apathy, anxiety, and depression.

**Indicative biomarkers**

- Reduced dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET.
- Abnormal (low uptake) $^{123}$iodine-MIBG myocardial scintigraphy.
- Polysomnographic confirmation of REM sleep without atonia.

**Supportive biomarkers**

- Relative preservation of medial temporal lobe structures on CT/MRI scan.
- Generalized low uptake on SPECT/PET perfusion/metabolism scan with reduced occipital activity ± the cingulate island sign on FDG-PET imaging.
- Prominent posterior slow-wave activity on EEG with periodic fluctuations in the pre-alpha/theta range.

McKeith et al., 2017
\[ ^{123}\text{I}-\text{FP-CIT SPECT in distinguishing Lewy body disorders from AD} \]

- Multi-centre study: \(^{123}\text{I}-\text{FP-CIT SPECT} - \text{sensitivity of 78\% for detecting Dementia with Lewy bodies (DLB) and specificity of 90\% for excluding AD (McKeith et al., 2007; Sinha et al., 2012)}\)
- Reduced striatal DAT uptake in patients with possible DLB strongly suggestive of a diagnosis of DLB: 44 patients with possible DLB, 19 converted to probable DLB and 12 had reduced DAT uptake (sensitivity = 63\%); 7 had F/U diagnosis of AD and all had normal DAT uptake (specificity = 100\%) (O’Brien et al., 2009; Sinha et al., 2012)
- Caveat: other atypical Parkinsonian disorders also have reduced striatal DAT uptake
Striatal Region of Interest $^{123}$I-FP-CIT Uptake

Striatal $^{123}$I-FP-CIT Binding Ratio = (Striatal ROI uptake – Occipital ROI uptake) / Occipital ROI uptake
Presymptomatic Diagnosis of Parkinson’s – Idiopathic REMBD (IRBD) and DAT uptake

- 20 IRBD patients vs. 20 controls
- Follow-up at 1.5 and 3 years with $^{123}$I-FP-CIT scans (DAT)
- 10/20 IRBD patients had reduced striatal DAT uptake (<2SD) vs no controls at baseline
- 13/20 IRBD patients had reduced DAT uptake at 3 years
- 3 patients developed PD (Iranzo et al., 2011)
Perfusion SPECT and FDG-PET in distinguishing LBD from AD

- Occipital lobe hypoperfusion (SPECT)/ hypometabolism (PET) has shown some utility in distinguishing between DLB and AD
- Compared to $^{123}$I-FP-CIT SPECT, the diagnostic accuracy is lower; however, one large SPECT study of 36 DLB and 96 AD cases yielded a reasonable sensitivity (85%) and specificity (85%) (Shimuzu et al., 2005; Sinha et al., 2012)
- A large FDG-PET study of 27 DLB, 199 AD, and 110 controls demonstrated that hypometabolism in the parietotemporal and posterior cingulate cortices in AD, and occipital cortex in DLB distinguished DLB from AD (sens.=71% and spec.=91%) (Mosconi et al., 2008; Sinha et al., 2012)
- ‘Cingulate island sign’ and occipital hypometabolism also had good diagnostic accuracy (Lim et al., 2009; Sinha et al., 2012)
$^{123}\text{I-MIBG SPECT: LBD vs. AD}$

- Cardiac sympathetic denervation is common in LBD due to peripheral autonomic involvement by alpha-synuclein inclusions.
- Heart-to-mediastinal ratios of MIBG uptake are useful in distinguishing LBD from AD and other neurodegenerative diseases (Sinha et al., 2012).
FDG-PET and PD-related motor pattern
FDG-PET and PD-related cognitive pattern

A. PD-related cognitive pattern (PDCP)

B. Δ Verbal Learning (ON-OFF)

C. PDCP Expression

D. Subject 1

- Post Parietal
- Precuneus
- Pre-SMA

Subject 2

- Post Parietal
- Precuneus
- Pre-SMA

Martin Niethammer, MD, PhD, and David Eidelberg, MD

ANN NEUROL 2012;72:635–647
Biomarkers: PIB Amyloid PET

http://www.hih-tuebingen.de/en/clinical-neurodegeneration/
Clinical viewpoint

In patients with parkinsonism presenting with atypical features (see list immediately below), we recommend as a minimum that structural imaging with high resolution brain MRI be pursued, including volumetric T1, T2/FLAIR, gradient-echo echo and/or SWI sequences. This will allow for visualization of regional atrophy patterns and neuroimaging signatures seen in some atypical parkinsonian disorders, and exclude structural lesions such as tumours and vascular pathology (e.g., strokes, white matter hyperintensities, microbleeds). In complex cases, perfusion SPECT or FDG-PET, as well as DAT-SPECT may be considered to help sort out the differential diagnosis.

Atypical features
- Poor response to at least 900 mg total daily dose of levodopa
- Rapidly progressive course of parkinsonism
- Early falls
- Early dysphagia
- Other neurological signs (e.g., upper motoneuron findings, cerebellar features, supranuclear gaze palsy)
- Early dysautonomia
- Early prominent cognitive impairment or dementia
- Early prominent behavioural changes
- Early prominent language changes
- Apraxia
- Early psychotic features
Summary and Conclusions

- Imaging biomarkers may be applied in order to stratify patients into more homogeneous subgroups.
- Several unique SPECT, PET and MRI based biomarkers can be used to increase the accuracy of a clinical diagnosis of LBD.
- Combinations of individual imaging biomarkers will yield improved diagnostic accuracy over the individual markers on their own.
- Predictive modeling of the biomarker combinations will require large, multi-centre datasets.
- Imaging biomarkers may also be used to predict responses to symptomatic therapies and, in the future, potential disease-modifying therapies.
Cholinergic and serotonergic PET radiotracers

Strafella et al., 2017
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Available Imaging Biomarkers

• SPECT
  – Striatal dopamine transporter (DAT) activity – $^{123}$I-FP-CIT
  – Cerebral perfusion - $^{99m}$Tc-HMPAO, $^{99m}$Tc-ECD, $^{123}$I-IMP
  – Myocardial sympathetic nerve integrity - $^{123}$I-MIBG

• PET
  – Cerebral metabolism – $^{18}$F-FDG
  – Amyloid – $^{11}$C-PIB, $^{18}$F-Florbetapir (AV-45), $^{18}$F-Florbetapen, $^{18}$F-Flutametamol (will be covered in amyloid lecture)
Mesiotemporal structures on MRI in distinguishing LBD from AD

• Preservation of mesiotemporal lobe structures in DLB and Parkinson’s disease dementia (PDD) vs. mesiotemporal atrophy in AD is a robust diagnostic biomarker (Barber et al., 2001; Burton et al., 2002; Tam et al., 2005; Whitwell et al., 2007; Sinha et al., 2012)

• With respect to cholinesterase inhibitor treatment response, DLB patients with preserved hippocampal volumes were more likely to have a positive benefit to treatment than those with hippocampal atrophy (Graff-Radford et al., 2012)
• PET imaging of the cholinergic system
  – Acetylcholinesterase PET activity shows more severe reductions in medial occipital cortex in DLB and PDD than that of temporal regions in AD (Bohnen et al., 2003; Shimada et al., 2009)

• Amyloid PET – to be discussed in later talk
A Genetic and Perfusion Study of Response to Cognitive Enhancers in Lewy Body Disease (NCT01944436)