# Movement Disorders
## CLINICAL PRACTICE

# Pragmatic Approach on Neuroimaging Techniques for the Differential Diagnosis of Parkinsonisms

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**ABSTRACT:** Background: Rapid advances in neuroimaging technologies in the exploration of the living human brain also apply to movement disorders. However, the accurate diagnosis of Parkinson's disease (PD) and atypical parkinsonian disorders (APDs) still remains a challenge in daily practice.
Methods: We review the literature and our own experience as the Movement Disorder Society–Neuroimaging Study Group in Movement Disorders with the aim of providing a practical approach to the use of imaging technologies in the clinical setting.
Results: The enormous amount of articles published so far and our increasing recognition of imaging technologies contrast with a lack of imaging protocols and updated algorithms for differential diagnosis. The distinctive pathological involvement in different brain structures and the correlation with imaging findings obtained with magnetic resonance, positron emission tomography, or single-photon emission computed tomography illustrate what qualitative and quantitative measures may be useful in the clinical setting.
Conclusion: We delineate a pragmatic approach to discuss imaging technologies, updated imaging algorithms, and their implications for differential diagnoses in PD and APDs.

Innovations in neuroimaging have enabled an accelerated understanding of movement disorders. They have been instrumental in reflecting the pathological changes that occur in Parkinson's disease (PD) and atypical parkinsonian disorders (APDs).[1]

These advancements have generated great expectations; however, a consensus approach on how to use them in everyday practice is lacking. The increasing recognition of imaging biomarkers contrast with PD diagnostic accuracy, which remains suboptimal, particularly among nonexperts compared with diagnosis performed by movement disorders experts (73.8%

vs. 83.9%)[2] and in early disease (26% during the first year of symptoms onset).[3]

The clinical application of advanced imaging technologies is still limited, and their standardization will take time given the multidimensionality of these diseases. However, newer imaging technologies are emerging, and with them emerges the need to determine which method, singly or in combination, can be used in daily clinical practice.

Needless to say, this translational value is urgently needed because at the moment the only approved approach is the use of

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a marker of the dopamine transporter with ^{123}I-fluoropropyl 2-carbomethoxy-3-(4-iodophenyl) tropane (CIT) with single-photon emission computed tomography (DAT-SPECT) in the differential diagnosis of degenerative from nondegenerative parkinsonism, although other markers for presynaptical dopaminergic function are used in clinical practice.

Here we intend to provide a clinical and pragmatic approach to the use of imaging techniques to improve the diagnosis of PD and APDs.

# Imaging Techniques Available in Clinical Practice in Parkinsonisms

## Parkinson's Disease

One of the key pathological structures affected by the neurodegenerative process in PD is the substantia nigra (SN). However, routine magnetic resonance imaging (MRI) shows a relative lack of structural pathology in T1 and T2 1.5 T MRI at the brainstem compared with other neurodegenerative diseases such as Alzheimer's disease (AD), where atrophy can be clearly evident at certain stages of disease.[4]

Currently, PD diagnosis is made clinically, and the new Movement Disorder Society (MDS) criteria, which maintain the centrality of the motor syndrome, are designed to be applicable without the need for ancillary diagnostic testing.[5] However, in the diagnostic work-up of PD, routine 1.5 T MRI is indicated with the main purpose of ruling out an underlying secondary cause for the disorder rather than making a specific diagnosis (Fig. 1).[6]

If there are no contraindications for undergoing a brain MRI, it is recommended to perform 1 at least in the course of the disease, and the protocol should include T1-weighted, T2 flair, diffusion-weighted imaging (DWI) and susceptibility weighted imaging (SWI), both in the sagittal and transversal planes.[7]

Although MRI is not approved as a biomarker for the differential diagnosis of parkinsonian syndromes,[6] in clinical practice and in certain contexts such as unclear cases or cases without good responses to dopaminergic treatment, MRI can be considered for this purpose combined with clinical diagnostic criteria.
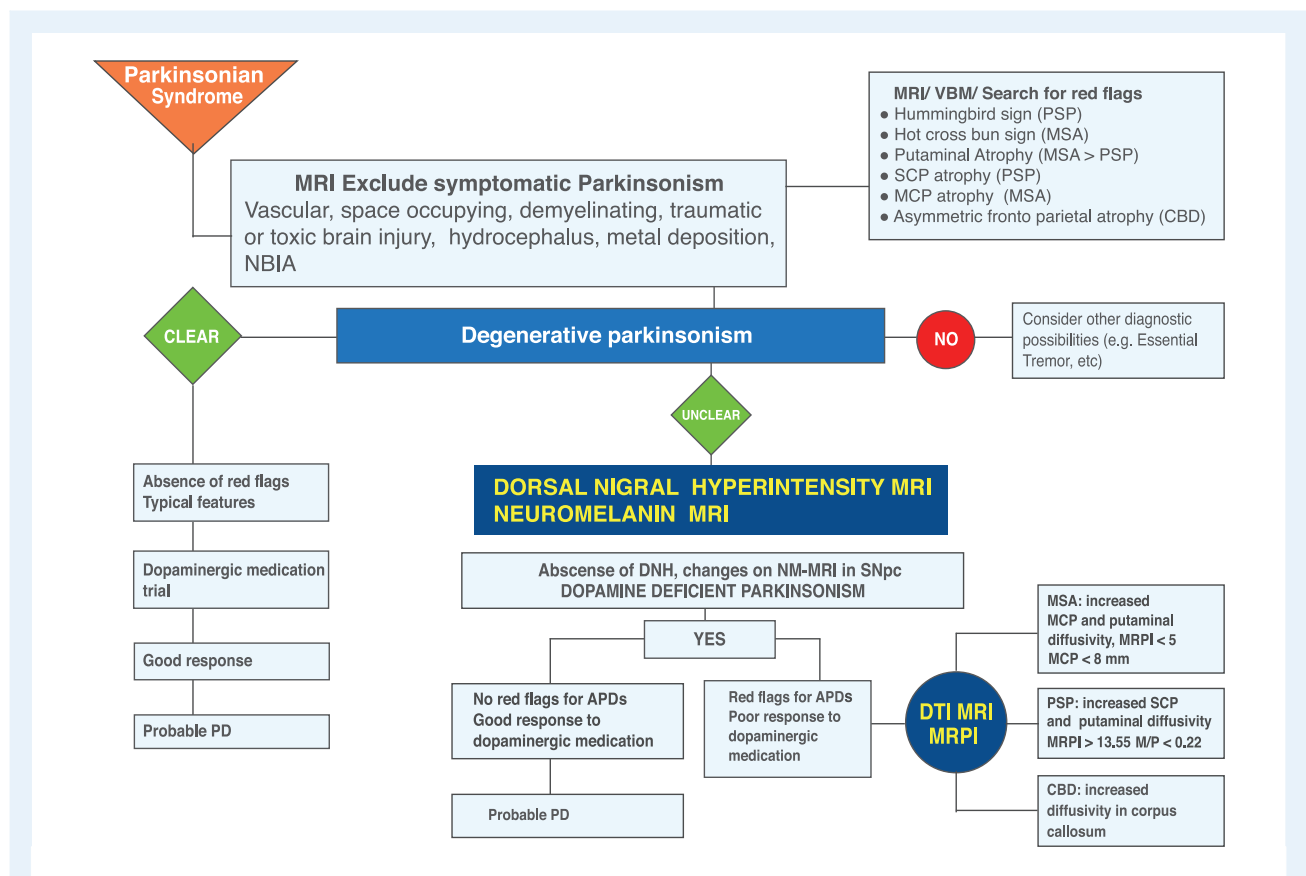


**FIG 1.** MR imaging diagnosis algorithm. APDs, atypical parkinsonian disorders; CBD, corticobasal degeneration; DNH, dorsal nigral hyperintensity; MCP, middle cerebellar peduncle; MR, magnetic resonance; MRI, magnetic resonance imaging; MRPI, Magnetic Resonance Parkinsonism Index; MSA, multiple system atrophy; NM, neuromelanin; PD, Parkinson's disease; PSP, progressive supranuclear palsy; SCP, superior cerebellar peduncle; NBIA, Neurodegeneration with Brain Iron Accumulation.
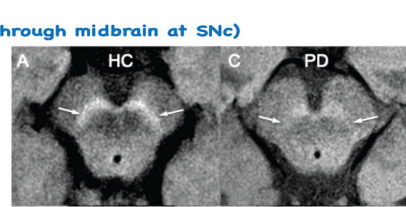
# PARKINSON'S DISEASE – VISUAL ANALYSIS

## The Dorsolateral Nigral Hyperintensity DNH

## Neuromelanin Imaging

**(Axial imaging passing through midbrain at SNc)**
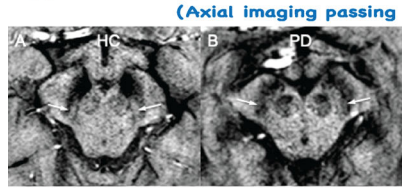


The DNH is visible in the dorsolateral part of the SN in HC as an area of high signal intensity surrounded by two bands of low signal intensity

The SNc is seen as an area of high signal in the HC. In PD, the decrease in signal intensity predominates in the posterior and lateral part of the SN

**PARKINSON'S DISEASE**
- Substantia nigra: Reduced NM and loss of DNH
- M/P ratio: normal (typical >0.21)
- MRPI: Normal (typical <12.9)
- Superior cerebellar peduncle (typical 3 mm)
- Putamen and cerebellum normal

## SUPRANUCLEAR GAZE PALSY – Visual Analysis



**Hummingbird sign**          **Morning Glory sign**          **Frontal Lobe atrophy**
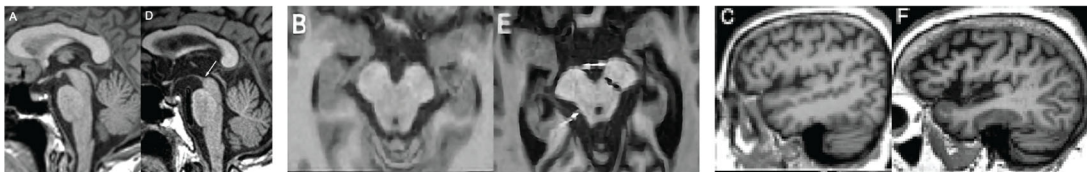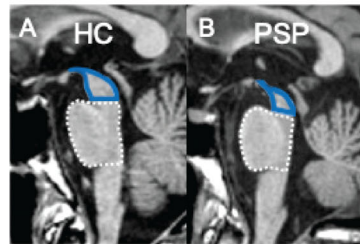
A) Normal midbrain, (D) Concavity of superior midbrain ("hummingbird" sign) (B ,E) Enlargement of interpeduncular cistern (white arrow), narrowing of the cerebral peduncle (black), concavity of the lateral margin of the midbrain tegmentum ("morning glory" sign).
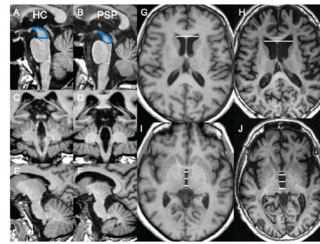(C , F) Frontal sulci enlargement

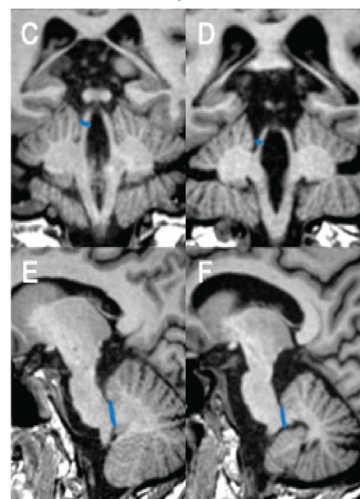## Quantitative analysis – Brainstem Planimetry



Midbrain area (M)

Pontine area (P)

**M- P ratio : M/P area, cut off < 0.21**

- V3 = average width (from three measurements) of third ventricle on an axial image at the level of anterior and posterior commissures
FH = maximal left to right frontal horn width on axial image in AC-PC plane
MRPI X $\frac{V3}{FH}$

**MRPI 2.0, cut off > 2.18**

Superior cerebellar peduncle
On coronal image in the first image on which the SCP and the inferior colliculus are separated

Middle cerebellar peduncle
On the parasagittal image that best shows the MCP between the pons and the cerebellum
MRPI $\frac{P}{M}$ x $\frac{MCP}{SCP}$

**MRPI index: cut off > 13.55**

**Progressive Supranuclear Palsy**
- Substantia nigra: Reduced NM and loss of DNH
- Hummingbird and morning glory signs
- M/P ratio: decreased <0.215 vs. PD and MSA-P
- MRPI: increased >13.6 vs. PD and HC, >12.9 vs. MSA-P
- Superior cerebellar peduncle: atrophy (typical 2 mm)
- Frontal cortex: enlarged sulci
- Third ventricle: enlarged
- Putamen: normal (may present moderate signal reduction in T2* and SWI)

The limit between the midbrain and pons is defined by a line passing through the inferior border of the inferior colliculus and the pontomesencephalic sulcus. The inferior border of the pons is parallel to the previous one.

**FIG 2.** MR imaging in PD and PSP. DNH, dorsal nigral hyperintensity; HC, healthy control; MCP, middle cerebellar peduncle; MR, magnetic resonance; MRI, magnetic resonance imaging; MRPI, Magnetic Resonance Parkinsonism Index; NM, neuromelanin; PD, Parkinson's disease; PSP, progressive supranuclear palsy; SN, substantia nigra; SNc, substantia nigra pars compacta; SCP, superior cerebellar peduncle; SWI, susceptibility weighted imaging; AC-PC, anterior commissure - posterior commissure; MSA-P, Multiple system atrophy-parkinsonian type; M/P, midbrain-to-pons ratio.

If distinctive signs are present, 1.5 T MRI can provide clues to the differential diagnosis of PD and APDs, showing atrophy and signal changes of the putamen and T2-hyperintensity of the pons (the "hot cross bun" sign) and middle cerebellar peduncles (MCP) in multiple system atrophy (MSA), midbrain atrophy relative to the pons (the "hummingbird" sign) in progressive supranuclear palsy (PSP), or asymmetric dorsal frontal or parietal atrophy in corticobasal degeneration (CBD). The limitation here is sensitivity because approximately half of the patients with APDs will not present these signs, especially early in the disease.[8]

Brain morphometry does not have a practical impact in the daily diagnostic work-up of PD and is probably used more in research or in clinical trials. Morphometric studies allow the visualization of brain volume, shape, and surface as well as the segmentation of the basal ganglia (BG). In PD, cortical thinning was observed in the orbitofrontal, ventrolateral prefrontal, and occipitoparietal regions as well as a small decrease in striatal volume in some studies.[9]

As knowledge advances, more sophisticated imaging will become available, as is the case in high-field and ultra–high field MRI, and in the future, methods will become available that integrate a single hybrid scanner MRI and positron emission tomography (PET) or automated imaging analysis.[1]

# High-Field MRI
## Dorsal Nigral Hyperintensity

Currently, the advent of higher field MRI reflects SN neurodegenerative changes. The SN pars compacta (SNpc) is located dorsally and contains dopaminergic neurons distributed in calbindin-rich zones or a matrix and also in 5 calbindin-poor zones, known as nigrosomes.[10] Using high-resolution SWI, nigrosome-1 can be seen as a hyperintense ovoid area, called the dorsal nigral hyperintensity (DNH) sign, which has the appearance of a "swallow tail" (Fig. 2).[11]

Several studies using 3 T MRI with an optimized sequence have shown the absence of the DNH signal in most patients with PD but not in healthy controls (HCs), revealing 100% sensitivity and 95% specificity in distinguishing PD from HCs,[12] although it is unable to differentiate PD from APDs because the DNH signal loss is also seen in patients with APDs. A recent meta-analysis suggested that the visual assessment of DNH could provide excellent differential diagnostic accuracy for PD compared with HCs.[13]

Although there is no definitive consensus as to the use of DNH imaging in clinical practice, and it is not approved for the diagnosis or differential diagnosis of PD, the wide availability of 3 T scanners and the use of 3 T MRI in the clinic has led to an increased use of this technique. In this regard, DNH imaging may be considered in the differential diagnosis of degenerative from nondegenerative parkinsonisms or from essential tremor (ET), and in this context its use may be comparable to DAT-SPECT (Figs. 2 and 5).

However, more studies are required to demonstrate if this technique can be equivalent to DAT-SPECT.[14] The lack of standardization of imaging protocols including spatial resolution and imaging planes may limit its use[15] as well as the relative low sensitivity of MRI compared with nuclear imaging techniques such as PET or SPECT, although 3 T MRI avoids the risks associated with ionizing radiation.[16]

The correlation between DNH abnormality and nigrostriatal dopaminergic dysfunction was analyzed in a few studies, as in a study of PD carriers of the G2019S, Leucine-rich repeat kinase 2 (LRRK2) mutation, in whom the loss of DNH predicted the ipsilateral striatal DAT signal abnormality with a sensitivity of 87.5% and a specificity of 83.6%.[17]

The ultra–high field MRI (7 T and higher) in brain imaging provides improvement in contrast and spatial resolution, and it will probably find its way to be integrated into clinical practice. However, at this moment, it still remains a research tool because of the technical and safety aspects that need further development.[16]

# Iron Imaging

The iron content in the SN increases in PD by about 30% in histological studies compared with HCs.[18] Although patients with APDs have also increased iron content in the SN, they present more prominent subcortical iron deposition in the striatum than in PD or HCs.[19]

Iron-sensitive MRI has been applied to identify iron-related signal changes for the diagnosis and differential diagnosis of PD in research studies.

In clinical practice, the use of iron imaging is limited to the use of SWI, which is purely a qualitative method, for visual inspection and detection of paramagnetic iron as exemplified by a decreased signal in the putamen in patients with APDs (Fig. 3 ).[12]

Results on subcortical topographical iron deposition between patients with MSA and PSP vary among studies; however, they are more prevalent and severe in PSP compared with MSA-P, except in the putamen that contains more iron in MSA-P, presenting as hypointense signal changes with atrophy and flattening of lateral border of the posterior putamen, which together are quite specific for Multiple system atrophy- parkinsonian type (MSA-P).[20] In PD, the increased iron content in nigrosome-1 produces the loss of the DNH signal that can be observed in 3 T MRI.
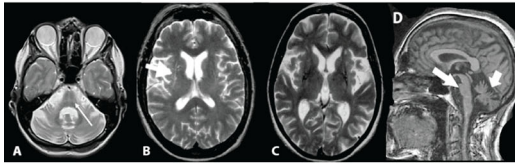
# Atypical Parkinsonisms
## Progressive Supranuclear Palsy
### Midbrain and Superior Cerebellar Peduncle Atrophy

PSP is an APDs challenging to distinguish from PD.[21] Traditionally the clinical diagnostic criteria of PSP rely on the

## MULTIPLE SYSTEM ATROPHY – Visual Analysis

A The hot cross bun sign. B Putaminal atrophy with the putaminal hyperintense rim (arrow). C Putaminal atrophy with putaminal hypointensity. D Atrophy of the pons and the cerebellum

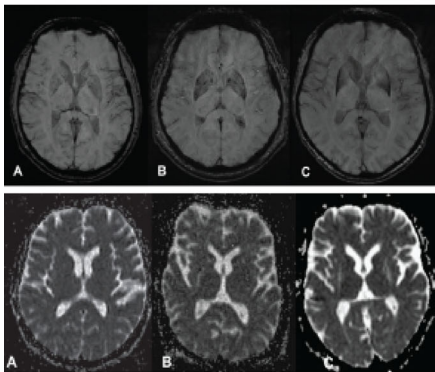### Quantitative Analysis
### MCP and Putaminal Atrophy
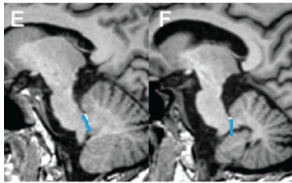
A MCP diameter <8.0 mm has high diagnostic accuracy in separating MSA from PD

### Multimodal DTI MR
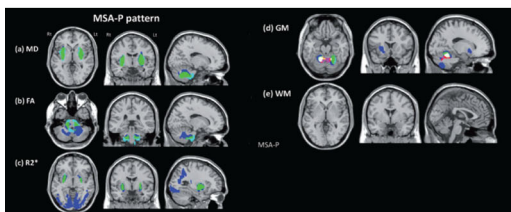
↑ MD putamen, pons, MCP.↓FA values pons, MCP and cerebellar WM.
R2↑putamen, occipital WM. GM↓ cerebellar cortex, putamen, caudate. (54)

### SWI and ADC Maps in PD and APDs

**MULTIPLE SYSTEM ATROPHY**
- Substantia nigra: Reduced NM and loss of DNH
- Midbrain: usually normal

**Parkinsonian form**
- Putamen: atrophy, hypointense in 3D gradient echo, T2-weighted or SWI, flat lateral border, hyperintense T2 rim
- Reduced posterior putaminal signal intensity in T2* and SWI ,increased putaminal ADC or MD
- M/P ratio: variable or increased
- MRPI: variable or decreased
- Hot cross bun sign, MCP and cerebellar atrophy may also be present
- Reduced MCP diameter < 8 mm

**Cerebellar form**
- M/P ratio: increased
- MRPI: decreased (typical <5)
- Hot cross bun sign
- Cerebellum: atrophy
- Cerebellar peduncles: atrophy, T2 hypersignal in MCP
- Putaminal atrophy may also be present
- Reduced MCP diameter < 8 mm

**SWI: PD (A): normal putamen,**
**PSP (B): diffuse bilateral putaminal hypointensity.**
**MSA (C): bilateral hypointensity pronounced in the posterior half of the putamen**

**ADC: PD (A): normal putamen, PSP**
**(B): diffuse bilateral putaminal hyperintesity**
**↑ MD. MSA (C): hyperintensity pronounced in the posterior half of the putamen**

**FIG 3.** MR imaging in MSA and APDs. ADC, apparent diffusion coefficient; APDs, atypical parkinsonian disorders; DNH, dorsal nigral hyperintensity; FA, fractional anisotropy; HC, healthy control; MCP, middle cerebellar peduncle; MD, mean diffusivity; MR, magnetic resonance; MRI, magnetic resonance imaging; MRPI, Magnetic Resonance Parkinsonism Index; MSA, multiple system atrophy; NM, neuromelanin; PD, Parkinson's disease; PSP, progressive supranuclear palsy; SWI, susceptibility weighted imaging; VM, white matter; GM, gray matter; M/P, midbrain-to-pons ratio.

demonstration of a vertical supranuclear gaze palsy plus postural instability and falls within the first year of symptom onset. However, 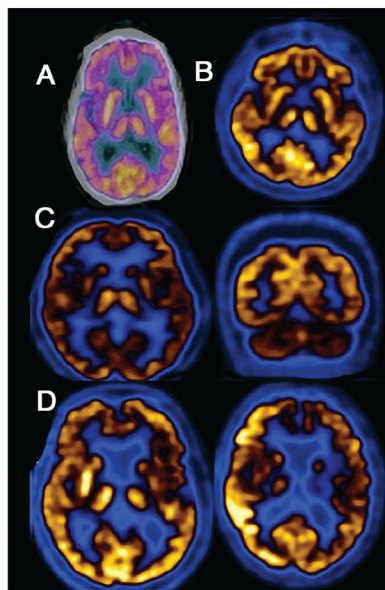considering the phenotypic heterogeneity of PSP, the new MDS diagnostic criteria identify 4 functional domains (ocular motor dysfunction, postural instability, akinesia, and cognitive dysfunction) as clinical predictors of PSP. Within each of them,

## A) PRESYNAPTIC DA TERMINAL
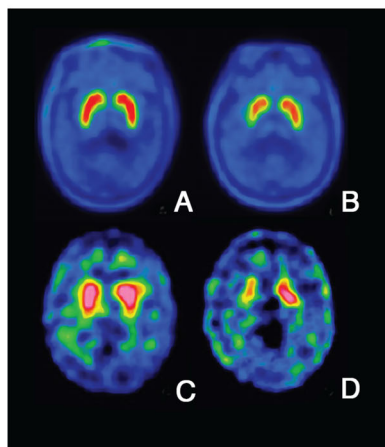
A: Normal FDOPA    B: Abnormal FDOPA
C: Normal TRODAT   D: Abnormal TRODAT

## B) GLUCOSE, FDG- PET

**A**. Normal

**B**. PD:↑activity in BG, TH, pons;↓activity premotor and parietal cortex

**C**. MSA:↓activity in BG, putamen, pons and cerebellum

**D**. PSP:↓ activity in BG, TH, fronto temporal cortex (asymmetric)

### PARKINSON'S DISEASE

- **DAT SPECT**: asymmetric striatal loss of DAT, more marked at the dorsal putamen, normal caudate

- **FDG PET**: increased metabolic activity at basal ganglia, thalamus, decreased activity in premotor and parietal cortex

### SUPRANUCLEAR GAZE PALSY

- **DAT SPECT**: decreased putaminal uptake, putamen to caudate nucleus ratio increased, less pronounced asymmetry (not useful for differential diagnosis with PD)

- **FDG PET**: asymmetric decrease in metabolic activity in basal ganglia, thalamus, and fronto temporal cortex

### MULTIPLE SYSTEM ATROPHY

- **DAT SPECT**: striatal uptake reduction, no significant asymmetry index (not useful for differential diagnosis with PD)

- **FDG PET**: decreased metabolic activity in basal ganglia, putamen, pons and cerebellum

## C) TAU PET
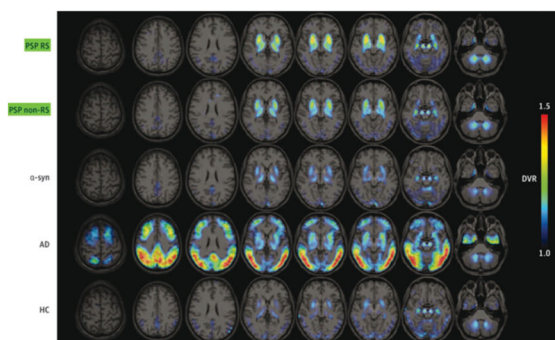
Average in-vivo [18F]-PI-2620 uptake (distribution volume ratio, DVR) in PSP, PD or MSA (α-syn), AD and HC. Figure from Brendel, Barthel, van Eimeren et al. JAMA Neurol 2020.

**FIG 4.** PET imaging of DA, Glucose and Tau protein aggregation. AD, Alzheimer's disease; APDs, atypical parkinsonian disorders; BG, basal ganglia; DAT-SPECT, dopamine transporter single-photon emission computed tomography; FDOPA, [18F]fluoro-L-dopa uptake; HC, healthy control; MR, magnetic resonance; MSA, multiple system atrophy; PD, Parkinson's disease; PET, positron emission tomography; PSP, progressive supranuclear palsy; TH, thalamus; FDG:18 Fluorodeoxyglucose; DA, dopaminergic; RS, Richardson´s Syndrome; TRODAT, technetium-labeled dopamine transporter ligand. Fig 4C is reprinted from Brendel et al.[71]

3 clinical features are proposed defining the diagnostic criteria, stratified by 3 degrees of diagnostic certainty.[22]

Brain imaging is relevant to demonstrate predominant midbrain atrophy and to rule out alternative diagnosis. In patients with PSP with vertical supranuclear gaze palsy, midbrain atrophy is observed as the "hummingbird" sign and the "morning glory" sign (Fig. 2). Using voxel-based morphometry, patients with PSP also show atrophy in the thalamus (TH) and insula.[8]

Recently, 2 sets of measures have been found to be useful to differentiate PSP from PD and MSA: the midbrain-to-pons ratio

with a cut-off value <0.21 and the MR Parkinsonism Index (MRPI) calculated by pons area/midbrain area × MCP diameter/superior cerebellar peduncle (SCP) diameter, with a cut-off value ≥12.9 versus MSA-P, and 13.6 versus PD and HCs, which is significantly higher in PSP compared with HC.

A recent version, the MRPI 2.0 includes the measurement of the third ventricle width and has a cut-off value ≥2.91. The MRPI differentiates Progressive Supranuclear Palsy—Parkinsonism Predominant (PSP-P) from PD with a sensitivity and a specificity of 73.5% and 98.1%, respectively, whereas the MRPI 2.0 shows a higher sensitivity (100%) and similar specificity (94.3%) in differentiating these 2 groups.[23]

This index may well become extremely useful in clinical practice, as a recent report from the MDS-PSP Study Group indicated that the MRPI and the midbrain-to-pons ratio were the most reliable biomarkers for the diagnosis of PSP-RS, supporting a clinical diagnosis at the individual level in both the early and late stages of the disease.[22]

In clinical practice, this pattern of brain atrophy in PSP is also supported by a recently published meta-analysis, which found that the presence of reduced midbrain and SCP diameters were useful to separate PSP from PD.[24]

# Multiple System Atrophy

## Putaminal and MCP Atrophy

MSA is an adult-onset, sporadic, progressive neurodegenerative disease characterized by variable severity of parkinsonian features, cerebellar ataxia, autonomic failure, urogenital dysfunction, and corticospinal signs.[25]

The underlying neuropathological changes that occur in MSA can be visualized using regional volume changes that reflect significant brain atrophy in the putamen, MCP, cerebellum, pons, and medulla oblongata.[24,26] In daily practice and integrated with clinical criteria, structural imaging can assist in the diagnosis and differential diagnosis of MSA, as exemplified by the demonstration of putaminal, pontine, and MCP atrophy in MRI in both Multiple system atrophy - cerebellar subtype (MSA-C) and MSA-P. The signal increases on T2-weighted sequences, which include the "hot cross bun" sign, the "MCP" sign (hyperintensity in the MCP), and the "putaminal rim" sign (hyperintense signal in the dorsolateral margin of the putamen), have high positive predictive values for the diagnosis of MSA. However, it has to be taken into account that the signal abnormalities are more intense at 3 T than at 1.5 T, which could increase false positives for MSA, and the "hot cross bun sign" can occasionally be found in nondegenerative parkinsonism and in spinocerebellar ataxias (Fig 3).[27]

Conventional MRI demonstrated high specificity for distinguishing MSA from PD and HCs; however, its sensitivity can be suboptimal in the early stages of the disease, where patients with MSA-P may not present putaminal or infratentorial changes at 1.5 T,[8] although in up to 30% of patients with MSA, putaminal MRI abnormalities may precede clinical diagnostic criteria for about 1 year and more.[28]

Other quantitative measures available in clinical practice include brainstem area and cerebellar peduncle widths that can be manually obtained. An MCP diameter <8.0 mm has good diagnostic accuracy in separating MSA from PD[29] but seems to also discriminate MSA from PSP with fairly acceptable diagnostic accuracy (Figs.3).[24]

# Diffusion Magnetic Resonance Imaging (dMRI)

Although DWI estimates water diffusion through the application of magnetic field gradient pulses, diffusion tensor imaging (DTI) requires the application of strong diffusion gradients to quantify the degree of fractional anisotropy (FA) and the global movement of the water molecules (apparent diffusion coefficient [ADC] and mean diffusivity [MD]), which are useful for assessing white matter integrity and tractography.[30]

In clinical practice, DWI can be used to increase the sensitivity of MRI as a diagnostic tool to detect changes in brain tissue integrity, which produce a decrease in the number of barriers that restrict the movement of water, causing the ADC to increase in brain areas where neurodegeneration occurs.[31] Nonetheless, it has some limitations because it is a quantitative method that requires experience and a normative database for its interpretation.

In parkinsonisms, DWI is useful for the discrimination of MSA from PD and HCs even in the early stages because the increase in putaminal diffusivity is directly visible in the ADC or MD maps,[32] although PD with longer disease duration and concomitant white matter changes, as well as PSP, may also present increased putaminal diffusivity (Fig. 3), hence additional measures such as volume changes or increased diffusivity within the posterior fossa need to be introduced to reliably separate MSA from PSP.[33] In addition, abnormal diffusion metrics in the MCP can be found in MSA and in the SCP in PSP.[34]

# Molecular Imaging Studies—PET and SPECT Studies

## Presynaptic Dopaminergic Imaging

Molecular imaging gives us the opportunity to assess neurotransmitter function or metabolic activity in vivo, or neuropathology as in the case of abnormal protein deposition. Presynaptic dopaminergic imaging allows a better understanding of disease pathophysiology and can sometimes aid in the process of differential diagnosis.

From a clinical perspective, presynaptic dopaminergic PET and SPECT tracers are mainly used to differentiate degenerative
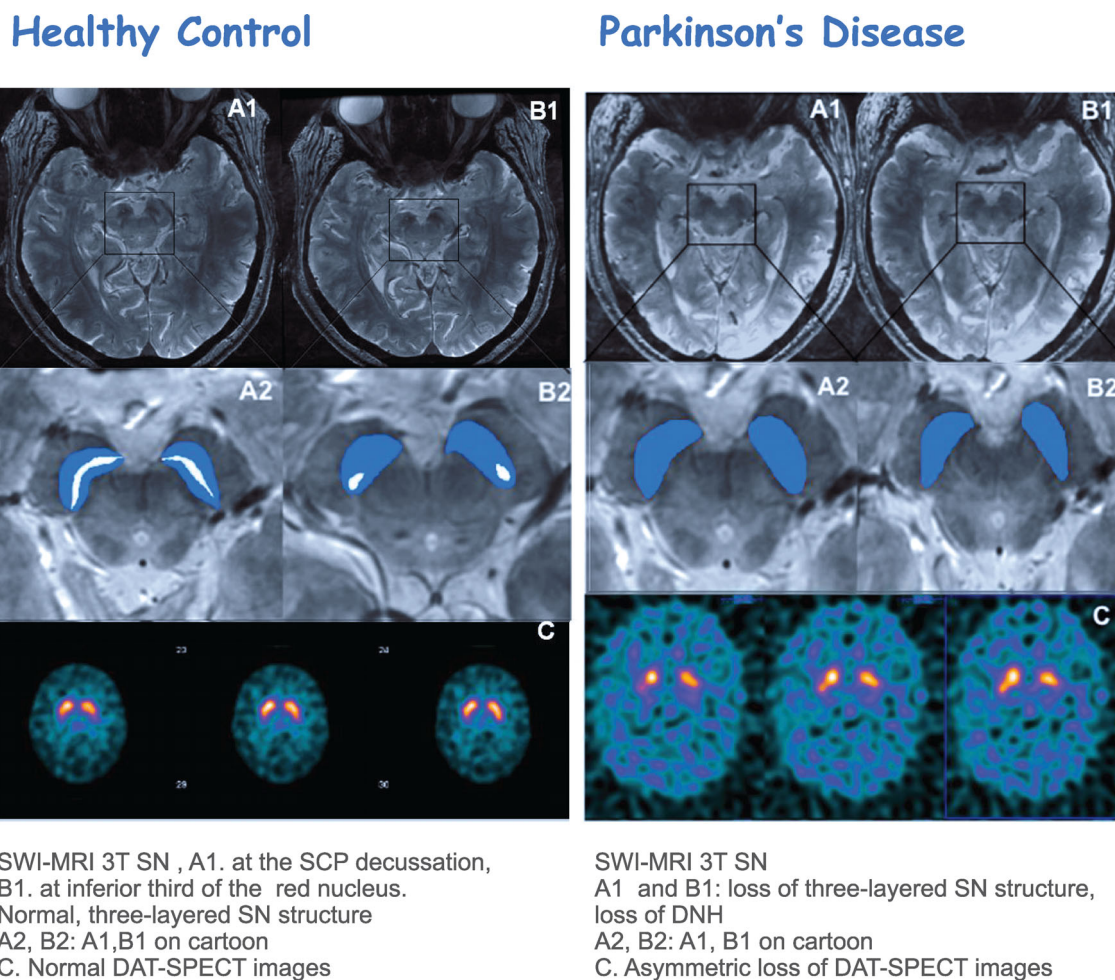
**FIG 5.** Multimodal imaging SWI MRI 3T- DAT SPECT. DAT-SPECT, dopamine transporter single-photon emission computed tomography; DNH, dorsal nigral hyperintensity; PET, positron emission tomography; SCP, superior cerebellar peduncle; SN, substantia nigra; SWI, susceptibility weighted imaging.

parkinsonism from nondegenerative conditions at the diagnostic phase. For the differentiation of PD from other forms of parkinsonism, the combination of a presynaptic dopamine, dopaminergic (DA) tracer with Fluorodeoxyglucose (FDG)-PET (studying glucose metabolism) can shed light into differential diagnoses (Figs 4, 5 and 6)[35,36]

## Use of PET and SPECT Tracers

Using PET, DA synthesis can be measured through [18F]fluoro-L-dopa uptake and decarboxylation into fluorodopamine by L-aromatic amino acid decarboxylase.[37] DA storage into synaptic vesicles can be assessed with [11C] or [18F]dihydrotetrabenazine, having the advantage of being less prone to compensatory changes.[38,39]

Several tracers have been used to study DAT availability with PET, such as [11C]CFT: 2-beta-carbomethoxy-3-beta-(4- fluorophenyl)tropane [11C]CFT, [11C]RTI-32: 11C carboxymethoxy-3B-aryltropan [11C]RTI-32, [11C]methylphenidate, or [18F]FP-CIT.

With SPECT (Fig. 4 and 5), presynaptic DAT function has been mainly investigated with the ^{123}I-linked tropane derivatives FP-CIT (ioflupane) and beta-CIT or Technetium-99m –labeled dopamine transporter ligand ([99mTc]TRODAT-1).

The mechanism of the decreased striatal DAT binding remains unclear as the binding deficit does not seem to associate well with axonal or somal loss of nigrostriatal neurons in PD.[40,41]

DAT-SPECT imaging has been approved by both the US Food and Drug Administration (FDA) and the European Medicines Agency for the differentiation of parkinsonism from ET, and the normal functional neuroimaging of the presynaptic dopaminergic imaging has been included as an absolute exclusion criterion in the last version of the MDS Clinical Diagnostic Criteria for PD.[5]
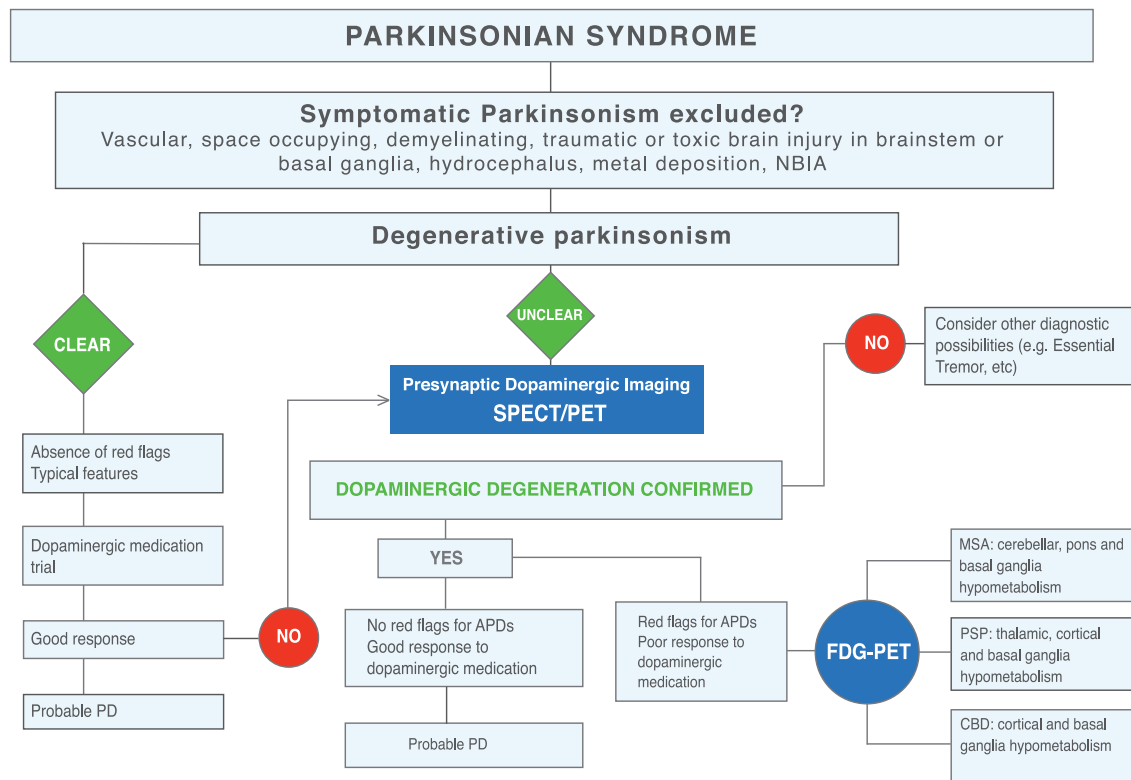
**FIG 6.** PET imaging diagnosis algorithm. APDs, atypical parkinsonian disorders; CBD, corticobasal degeneration; MSA, multiple system atrophy; PD, Parkinson's disease; PET, positron emission tomography; PSP, progressive supranuclear palsy; SPECT, single-photon emission computed tomography; NBIA: Neurodegeneration with Brain Iron Accumulation.

# Glucose Metabolism

The cerebral glucose metabolism is associated with the integrity and synaptic activity of neurons (Fig. 4). This condition makes [18F]FDG-PET studies especially relevant in neurodegenerative diseases because they can identify "patterns of brain hypometabolism."[42] They offer the clinicians the advantage of being at hand in the majority of clinical centers and a strong "imaging–clinical" correlation where the reciprocity with the clinical symptoms is more significant than with the underlying pathology, as demonstrated by Granert et al, who built a topo-logical map to localize a single subject's disease status according to "PD-typical" or "AD-typical," observing a strong correlation between the cognitive and motor patterns.[43]

According to studies with group comparisons, PD is associated with a pattern of increased activity in the BG, TH, and pons (and often cerebellum) combined with reduced activity in the premotor and parietal cortex. However, on an individual basis and at first glance/visual analysis, [18F]FDG-PET may also not show major abnormalities in PD.[44,45] On the other hand, APDs present a more consistent pattern, even on an individual basis. MSA is associated with impaired glucose metabolism in the BG, putamen, pons, and cerebellum and PSP in the BG and thalamic

and cortical areas (Figs. 4 ,and 6),[46] therefore the clinical utility of [18F]FDG-PET as a means of discriminating PD from APDs has been supported by the latest criteria for PSP and MSA.[22,25]

As opposed to the advantage of [18F]FDG PET studies that reliably differentiate PD from APDs, presynaptic dopaminergic terminal imag-ing is not sufficient alone for differential diagnosis because the pattern of reduced tracer binding is similar in these disorders. Likewise, post-synaptic dopaminergic terminal imaging has lower diagnostic accuracy when compared with [18F]FDG-PET studies in the prediction of a clinical diagnosis of PD or APDs at 2 years of follow-up.[47,48]

# Imaging Techniques Available in Research in Parkinsonisms

## Neuromelanin Imaging

Neuromelanin (NM) is a dark granular intracellular pigment found in catecholaminergic neurons of the SNc and locus coeruleus (LC), which provides protection for endogenous

dopamine, which is highly susceptible to oxidative stress.[49] NM-containing regions present high signal intensity on T1-weighted fast spin-echo images at 3 T.

In the past decade, several studies have used NM-sensitive MRI to evaluate patients with PD, showing high accuracy in the differential diagnosis from HCs.[11]

In a study of patients with early PD, the lateral part of the SN showed the most significant signal attenuation. Remarkably, the change in LC signal was similar to that of the SN, and the signal attenuation in LC presented higher sensitivity and specificity than that of the SN in differentiating PD from HCs (82% sensitivity and 90% specificity for LC and 73% sensitivity and 87% specificity for SN), suggesting early neuronal depletion in this structure as well.[50]

The role of NM imaging in distinguishing PD from APDs is less clear. Some studies suggested lower reductions in NM signal in the SN in PSP versus MSA and PD,[51] whereas others have found that the NM-sensitive substantia nigra pars compacta (SNpc) area and midbrain volume were significantly smaller in patients with PSP compared with patients with PD and HCs.[52]

The investigations of the relationship of NM-MRI and DAT-SPECT have found a positive correlation between the loss of NM signal and the corresponding striatal ^{123}I-FP-CIT binding of striatal dopamine presynaptic terminals.[53]

This is a promising technique to improve PD diagnosis, and although there are some studies that show that the visual analysis of NM imaging offers high diagnostic values and comparable results with quantitative analyses,[50] there are some steps that still need to be taken in terms of imaging protocols and analysis before this technique can be used in clinical practice.

## Iron Imaging

Quantitative measurements of iron deposition are mostly used in research protocols using iron-sensitive techniques such as relaxation rate R2$\star$ and quantitative susceptibility mapping (QSM). Compared with relaxation rates, SWI and QSM generated through magnitude and phase images from gradient-echo MRI sequences reflect susceptibility of local tissues being less influenced by changes in water content, local water diffusion rates and macroscopic magnetic field inhomogeneities. Therefore, these techniques are potentially superior methods of measuring iron in vivo, and QSM is a promising biomarker of disease-related iron accumulation in PD, more reproducible than R2$\star$ and more suited to multicenter studies.[54]

In addition, QSM allows to quantify the magnetic susceptibility value of brain tissue from gradient-echo MRI and provide excellent contrast between gray matter nuclei and surrounding tissues and is more precise than SWI.[20]

According to a recent meta-analysis of iron imaging studies, iron overload in the SN was detected in patients with PD compared with HCs, even in the early stages of the disease, confirming that R2$\star$ and QSM provide reliable markers of iron content in PD, although QSM seemed to be a more robust biomarker than R2$\star$. Nonetheless, imaging processing guidelines for QSM are not yet fully standardized.[55]

## Diffusion Tensor Imaging

The DWI and DTI techniques allow quantitative analysis of microstructural changes in parkinsonisms, and therefore several studies have analyzed DTI of the SN as a diagnostic marker for PD.

Some studies found highly significant FA reduction in SN,[56] whereas others concluded that there was no sufficient evidence for nigral DTI parameters to serve as a biomarker for PD.[57]

A further study applying a multitarget DTI approach using different DTI metrics (FA, radial diffusivity, longitudinal diffusivity, and MD) focused on the BG and cerebellum in 15 patients with PD and 12 patients with ET found that DTI measurements from the caudate and SN separated PD from ET with a sensitivity of 92% and a specificity of 87%.[58]

Recently, advanced postprocessing methods including freewater (FW) imaging and neurite orientation dispersion and density imaging have been introduced.

FW imaging is an advanced dMRI method that allows for the separation of the fluid (ie, FW) and tissue (FW-corrected FA) components. Recent work suggests that FW imaging might be helpful for the diagnosis of PD based on regional changes across the BG and cerebellum and their tracts.[59] Moreover, it was observed that FW values increase in the posterior SN of patients with PD compared with HCs, correlate with motor symptom severity, and increase longitudinally for 1 year, suggesting that it may be a suitable marker of disease progression.[60]

A recent multicenter study provided an objective, validated, and generalizable dMRI approach to distinguish different forms of parkinsonian syndromes using disease-specific machine-learning comparisons of FW and FW-corrected FA with 60 template regions and tracts of interest.[61]

## Postsynaptic Dopaminergic Imaging

Dopamine receptors are found on postsynaptic dopaminergic neurons. The output responses to dopaminergic stimulation can be imaged measuring D2/D3 receptor activity using different radioligands such as [11C]Raclopride, carbon-labelled ((+)-4-propyl-3,4,4a,5,6,10b-hexahydro-2H-naphtho[1,2-b][1,4]oxazin-9-ol hydrochloride) [11C]PHNO, [18F]Fallypride, or carbon-labelled ((S)-N-((1-ethyl-2-pyrrolidinyl)methyl)-5-bromo-2,3-dimethoxybenzamide) [11C]FLB-457.[62]

PET studies in patients with PD show that the striatal binding to the postsynaptic dopaminergic receptors is either normal or increased. The reduction of striatal dopamine may lead to D2 receptor upregulation as a compensatory reaction, which presents an increased activity contralateral to the clinically most affected side. In contrast, patients with APDs present reduced uptake attributed to the loss of postsynaptic receptors.[63]

In the clinical setting, the role of postsynaptic D2 receptors for differential diagnosis is poor because of the low negative

predictive value.[64] Therefore, this technique is mostly used in research centers for investigational purposes.

## Tau Pet

Molecular imaging of pathologically misfolded and hyperphosphorylated tau proteins is of immense interest in PSP and CBD; however, its use is within the scope of research studies.

The variance in the appearance of tau pathology (3R vs. 4R, paired helical vs. straight filaments and different aggregation states) complicates the development of tau-imaging tracers, none of the current tracers have surpassed exploratory stages, and their specificity is still questionable, especially the off-target binding of the first generation of tracer molecules to the monoamino oxidase (MAO) enzyme family.[65,66]

In PSP, studies with first-generation tracers mostly using [18F]-AV1451 found elevated retention in the pallidum, midbrain, dentate nucleus of the cerebellum, TH, caudate nucleus, and frontal cortical regions, whereas Coakeley et al did not report such elevated binding.[67] However, evidence of unspecificity regarding an elevated signal in the posterior putamen in patients with MSA put this utility into question.[68]

Second-generation tracers ([18F]-PI2620, [18F]-MK-6240, [18F]-RO-948, and [18F]-PM-PBB3) hold the promise of greater specificity. [18F]-PI-2620 currently is the most validated tracer with relatively high in vitro binding affinity for aggregated 4-repeat isoforms and no substantial off-target binding to β-amyloid or MAO A or B.[69] This tracer was used in a recently published German multicenter study that compared patients with PSP with α-synucleinopathies, AD, and HCs and found that patients with PSP-RS and non-RS showed significant elevation of tracer binding in PSP target regions (Fig. 4) When using classification by at least 1 positive target region, the sensitivity and specificity for detection of PSP-RS versus any control group were 85% and 77%, respectively.

Tau-PET may evolve as an in vivo modality supportive of the pathological PSP diagnosis at the individual patient level. However, the currently available evidence regarding its sensitivity and specificity, as assessed against the neuropathological gold standard, is too limited to draw diagnostic conclusions.[22]

## Practical Perspectives of Imaging in Parkinsonisms

### Can Imaging Differentiate PD from Nondegenerative Conditions?

Although PD diagnosis still remains a clinical diagnosis, the new MDS clinical diagnostic criteria include imaging as "supportive criteria" (cardiac sympathetic denervation using (123)I-meta-iodobenzylguanidine -MIBG- scintigraphy) and "absolute exclusion criteria" (normal presynaptic dopaminergic terminal scan).

In this regard, the use of DAT-SPECT was approved by the FDA for routine clinical use in the differential diagnosis of PD and ET. Moreover, it may also help to differentiate other causes of parkinsonisms such as those attributed to neuroleptic treatment or vascular or functional parkinsonism. Other PET and SPECT markers of presynaptic dopaminergic terminal function are used in clinical practice, which contribute to the differential diagnosis.

However, they are unable to differentiate PD from other neurodegenerative parkinsonisms such as MSA and PSP and should not be used isolated for this purpose.

Approximately 10% of patients with a diagnosis of PD may present normal functional imaging (Scans without Evidence of Dopamine Deficit, SWEDDs).[70] This situation reinforces the importance of integrating imaging with clinical diagnostic criteria and a careful neurological examination.

Newer imaging techniques such as DNH and NM-MR are emerging and may probably enter the clinical practice to help distinguish PD from nondegenerative conditions.

### Can Imaging Differentiate PD from APDs?

Recent advances in imaging using different markers of neurodegeneration such as MRI and iron imaging or DWI showed that the diagnostic accuracy in the differential diagnosis of PD and APDs increased by combining these methodologies, analyzing patterns of atrophy in the MCP, SCP, putamen, midbrain, the MRPI index, the distribution of iron deposition and DWI maps.(Figs. 2 and 3).

Similarly, glucose metabolism imaging with [18F]FDG-PET can reliably help in the differential diagnosis of PD from APDs, and they have been demonstrated to be superior to D2/D3 SPECT (Figs. 4 and 6).[48]

## Imaging Work-Up of Parkinsonisms in Clinical Practice

The role of imaging biomarkers has progressed from merely excluding secondary causes of parkinsonisms to aiding in the differential diagnosis of PD from APDs based on changes in brainstem structures and the BG.

Here we propose 2 imaging-based algorithms, 1 for MRI (Fig. 1) and other for PET/SPECT imaging (Fig. 6), to guide the clinician in the use of imaging methods for differential diagnosis between PD and APDs.

Briefly, both imaging algorithms reflect the basic steps that may not be missed in clinical practice when assessing a parkinsonian disorder: the first step is to rule out a secondary cause of the disorder, the second step is to evaluate if the etiology of the

disorder is clearly degenerative (typical features, absence of red flags, good response to dopaminergic trial), and the third step refers to unclear degenerative parkinsonism cases or atypical parkinsonism (atypical features, presence of red flags, poor response to dopaminergic medication, no evidence of dopaminergic degeneration in imaging). In this situation, other imaging methods can be integrated with clinical diagnostic criteria and a detailed clinical and neurological evaluation to aid in the differential diagnostic process.

## Conclusion

We delineated a pragmatic imaging-based diagnostic approach based on current experience and published literature to guide the use of imaging methods in movement disorders clinics for the differential diagnosis of parkinsonisms. However, there are still great challenges to face regarding priorities in the use of imaging technologies in PD and APDs, depending on whether it is in clinical practice and/or in research protocols. The challenges may include decision making on various aspects such as standardization of the imaging interpretation and normal/pathological thresholds, the quality performance in detecting early disease and disease progression, and the application of multimodal imaging.

## Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

C.P.: 1A, 1B, 1C, 2A
A.P.S.: 1A, 1B, 1C, 2A, 2B
T.v.E.: 1A, 1B, 1C, 2A, 2B
R.C.: 1A, 1B, 1C, 2B
K.S.: 1A, 1B, 1C, 2A, 2B
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## Disclosures

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