The Use of Imaging Modalities in Diagnosing Parkinson's Disease

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Abstract :

Parkinsonism is one of the most common Neurologic disorders affecting approximately 1% population above the age of 60 years. This review article provides an effective summary of Brain functional imaging in the evaluation of Parkinson's Disease.(PD) These imaging modalities include functional MRI, FDG Brain PET scans, and DAT (Dopamine Transporter scans). These help in evaluations of neurotransmitter changes noted in the disease. Each modality provides a specific and unique aspect in being able to identify Parkinson's disease. Parkinson Disease Cognitive Patterns (PDCP) and Parkinson's disease related Patterns(PDRP) are further analyzed to evaluate intraparenchymal structures. The Imaging review also helps to better understand the neurotransmitter activity, and the resting symptoms of Parkinson's as well as motor dyskinesias assosciated with levodopa.

Key words: fMRI, Imaging, Parkinson Disease, PET, SPECT

Background:

Functional Magnetic Resonance Imaging (fMRI)

Over the years, fMRI has developed a significant role in being able to describe the functions of brain structures; especially in the context of PD. Hemoglobin carrying oxygen has a different magnetic resonance when compared to deoxygenated hemoglobin in a magnetic field.[1] Via a hemodynamic response, the blood releases oxygen to the active neurons at a greater rate as compared to the inactive neurons. This results in a difference in magnetic susceptibility between oxygenated hemoglobin and deoxygenated hemoglobin, resulting in a magnetic signal variation which can be detected by an MRI. This difference in magnetic susceptibility based on oxygen level is referred to as BOLD (Blood Oxygenation Level-Dependent) contrast. Areas in the brain with increased metabolic demands are thought to reflect areas with higher neuronal activity, thereby requiring a greater blood flow which results in a decrease in deoxyhemoglobin and an increase in BOLD signal.[2] fMRI is practical for neuroimaging because it has a high spatial and temporal resolution; thereby making it ideal for establishing changes and patterns in neuronal activity. However, fMRI has a poor signal-to-noise ratio in comparison to radiotracer imaging.[2] The BOLD signal can at times consist of spontaneous fluctuations which reflect functional brain connectivity in certain areas of the brain. These spontaneous fluctuations can be measured by the resting-state fMRI.[3] BOLD signals from a particular region of interest or seed are used to calculate correlations with other brain voxels, providing a more precise look at detailed connectivity in the brain.[3] Because of the limitations of single-seed based analysis, other approaches such as creating a correlation matrix via multiple seeds also known as hierarchical clustering, or independent component analysis (ICA),[4] have been used to examine different brain regions and their corresponding functional connectivity. As observed in figure 1, single seed functional images demonstrating regions with increased connectivity with the striatal seed in PD patients.[5] Other fMRI methods, such as regional homogeneity, [6] can only measure local activity rather than connectivity. As of recent literature, limited resting-state studies have been used in the diagnosis of PD.[7]

Radiotracer Imaging

PET and SPECT imaging utilize radiotracers for assessment of brain function, and have been used to study the dopaminergic neuronal system. Furthermore, radiotracer imaging can also visualize cerebral blood flow and glucose utilization via radio-labeled fluids.[9] In comparison to PET, SPECT is readily available and less expensive. However, SPECT lacks the higher sensitivity and superior spatial resolution observed in PET. SPECT spatial resolution restricts the separation of the stratum's caudate and putamen in reference to its use in

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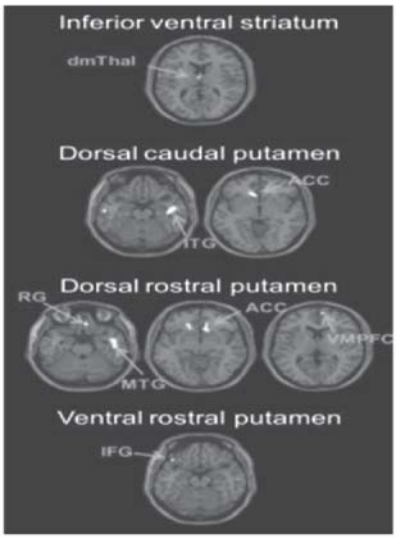
Figure 1 : Functional Magnetic Resonance Imaging[8]

(Figure 1 shows the single seed functional images demonstrating regions with increased connectivity with the striatal seed in PD patients. dmThal, dorsomedial thalamus; ACC, anterior cingulate cortex; VMPFC, ventromedial prefrontal cortex; IFG, inferior frontal gyrus; RG, rectal gyrus; MTG, middle temporal gyrus.)



PD.[9] In PET, the higher sensitivity allows for production of shorter imaging times with less motion artifacts.[9] PET also employs radiotracers with a shorter half-life, making it possible to perform multiple same day studies.

In terms of the practical application of PET/SPECT to PD, the dopaminergic imaging can be used to assess the severity of the disease. The mechanism of radiotracer function is related to the pathways of the dopamine production, release, and uptake.[9] Radiotracers can be used to assess pre- or post- synaptic dopaminergic function, using radioligand imaging of the dopaminergic neurons to study PD. As a result the severity of the disease and the characteristic motor symptoms of PD are shown to have a functional correlation to the pathology seen at the dopaminergic neurons in the substantia nigra. Although applications have been limited in PD, radioligand imaging can possibly visualize pathology in neurodegenerative disorders. For an example, PD is associated with Lewy bodies, and can be visualized using a- synuclein ligands such as 2- (1- [6 - [(2 -[^{18}F] fluoroethyl) (methyl) amino] - 2 - naphthyl] ethylidene) malononitrile (FDDNP),[10] or [^{18}F] -BF22.[11] However, the radiotracer ligands are not specific to -synuclein, and can also bind to - amyloid.

The dual binding of the ligands, requires separate imaging and image subtraction with ligands specific for - amyloid, such as [^{11}C] benzothiazole-aniline (Pittsburgh Compound B, PIB).[11]

[^{18}F]-fluorodeoxyglucose (FDG) PET can be used for imaging cerebral glucose metabolism, reflecting synaptic activity. In PD, cerebral perfusion and cerebral metabolism play an important part, allowing for this linked association to be used in PET and SPECT imaging as well (e.g., [^{15}O]-water PET or [^{56}mTc]-technetium-ethylene cysteinate dimer SPECT).

Figure 2 : Radiotracer imaging [12]

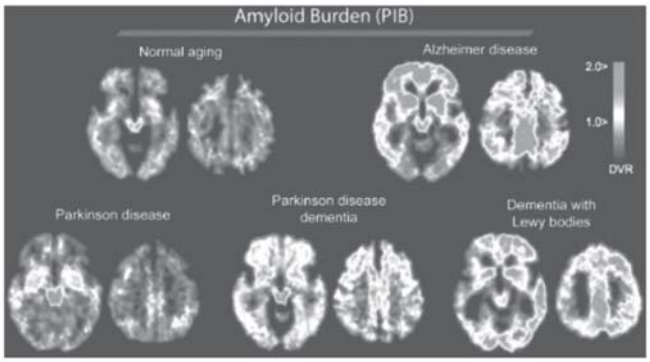


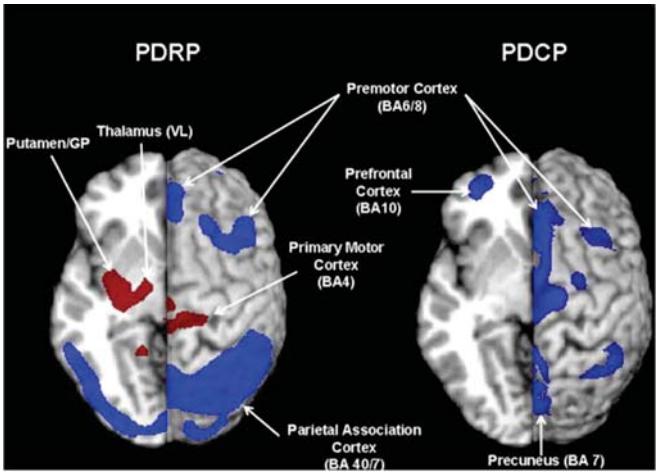
Figure 2: Retention and regional distribution of [^{11}C] benzothiazole-aniline (Pittsburgh Compound B, PIB) as seen on PET images of patients with Alzheimer's disease (top right), Parkinson's disease (lower left), Parkinson's disease with dementia (lower middle), and dementia with Lewy bodies (lower right). DVR = distribution volume ratio.

Parkinson Disease-Related Pattern (PDRP) and FDG PET

FDG PET scans are used to identify changes in cerebral glucose metabolism during disease states. Thus, spatial covariance analysis can identify network-level functional abnormalities in CNS disorders, such as PD.[13] In this method, a scaled subprofile model (SSM), a double-centered log-normalized principal component analysis, is applied to multivoxel metabolic imaging data from healthy patients in order to determine a pattern.[13] The data is then compared to resting-state FDG PET scans from PD patients, and is used to establish an

abnormal disease-related spatial covariance pattern involving elements of the corticostriatopallid othalamocortical (CSPTC) circuitry.[14] By using the covariance and an established pattern, a specific Parkinson's diease-related pattern (PDRP) is quantifiable. The PDRP is characterized by increased pallido-thalamic and pontine metabolic activity, and reduced activity in premotor cortex, supplemental motor area, and parietal association regions. Patients with elevated PDRP patterns correlate mainly with bradykinesia and rigidity, rather than tremors.[15] This data can be used to suggest that the abnormally functioning PDRP may be related to the degeneration of nigrostriatal dopaminergic pathways.[15] Thus, PDRP expression can be used to distinguish between PD and atypical parkinsonian syndromes.[16] PDRP can be measured in imaging modalities of resting cerebral perfusion obtained with [^{15}O]H2O PET, ^{56}mTc-ethylcysteinate dimer (ECD) SPECT or with arterial spin labeling MRI methods.

Figure 3 : Parkinson Disease-Related Pattern (PDRP) and FDG PET (metabolic networks and the PD related Motor Patterns) [17]



Left: Parkinson's disease motor related spatial covariance pattern. Right: Parkinson's disease cognition related spatial covariance pattern. Relative increases in metabolic activity are shown in red, whereas relative decreases are shown in blue.

Motor Complications of Therapy – Dyskinesias

The primary and most well established current treatment for PD is with levodopa. However, prolonged treatment with levodopa leads to increased brain sensitivity in the dopaminergic pathways leading to both motor and nonmotor complications in the majority of patients. The prevalence of levodopa-induced dyskinesia (LID) is up to 90% in patients receiving treatment for nine years or more. [18, 19]

As with other components of PD pathophysiology, we understand the main pathway that leads to the manifestations of LID. The major pathophysiology seems to be related to the over activity of the direct striatal pathway. [20 - 22] The development of LID is known to be related to both duration and intensity of levodopa dosing. Studies have shown that a pulsatile dosing of levodopa with high intensity drug pulses increases risk of LID developing in both animal models and PD patients.[23 - 26] The LID that develops in these cases is then also resistant to recovery even after prolonged cessation of levodopa dosing.

With FDOPA imaging, the relation of LID to levodopa dosing has been used to study the development of dyskinesias. A reduced presynaptic FDOPA uptake is associated with increased dyskinesia severity.[27,28] Another marker related to LID pathophysiology is alteration in the postsynaptic dopamine D2 receptor availability as measured with [^{11}C]-raclopride PET imaging.[29] More importantly, the production of dyskinesias through treatment was studied in a longitudinal fashion which revealed that the use of dopaminergic agonists such as ropinirole produced a smaller reduction in putaminal FDOPA, a marker for disease severity. Consequently, these patients were less likely to develop LID.[30] It has been shown that patients treated with low-dose levodopa and high-dose levodopa both have an equivalent reduction in striatal DAT binding, which suggests the presence of other implicating factors. This may be due to high dopamine metabolism and turnover rates. During early disease, the turnover rate is high, and this is even more pronounced in patients presenting at younger ages. In these cases, the rate of turnover was estimated by kinetic modeling of FDOPA time-activity curves (TACs) that were used with prolonged scan times.[31] Due to high rates of turnover in younger patient and during early disease, these populations have greater susceptibility to motor complications related to

increased fluctuation of neurohormone levels in relevant PD pathways. [32] Another factor involved in severity of LID is the level of dopamine found in the synapse as determined by [^{11}C]-raclopride PET. Furthermore, a multitracer study of VMAT and DAT binding revealed relative down-regulation of dopamine reuptake compared to nerve terminal loss.[33] It is noteworthy that early PD is also often seen to have decreased dopamine reuptake in relation to neuron loss. This adaptation allows an increase in dopamine availability to off-set the reduction of dopaminergic neurons. However, this can also be maladaptive as it results in oscillatory synaptic dopamine and concomitant motor complications as the disease progresses. Though animal studies have shown an additional upregulation of D1 receptors in response to levodopa treatment [34]; which would be consistent with aberrant response to dopamine levels related to treatment and dyskinesia development, no such upregulatory response has been shown in human patients with PD. [34]

Functional Imaging of Nonmotor Symptoms

Resting Metabolism

Functional imaging with FDG PET show abnormalities in cortical metabolism which are related to manifestation of multiple abnormalities including motor and cognitive dysfunctions. Using these studies to compare healthy controls and patients with varying levels of cognitive defect in PD, one can observe that there is hypometabolism seen in the frontal and occipital cortices of PD patients without gross cognitive defects.[35] Additional areas of hypometabolism in the frontal, occipital and lateral parietal cortices are also seen in PD patients with mild cognitive impairment (MCI).[35] Analysis of the spread of hypometabolism suggests that the topography of malfunction reflects the degree of cognitive impairment in these patients.[35]

Applying a spatial covariance analysis to the FDG PET data revealed a specific pattern of cognitive-defect-related-brain-hypometabolism in PD patients. This pattern is characterized by hypometabolism in frontal and parietal areas with hypermetabolism in the cerebellar vermis and dentate nucleus. Such a pattern is described as PD-related cognitive pattern (PDCP) and is distinct from the expression of PDRP even though both are progressive over time and expression levels are predictive of disease severity. That being said, these patterns are independent with PDCP expression related simply with cognitive decline whereas PDRP expression is related to striatal pathway functioning.

Another differentiating feature between the PDCP and PDRP is their changes in response to PD treatment with levodopa or Deep Brain Stimulation (DBS). Unlike PDRP, the PDCP is more resistant to change with levodopa treatment. As expected without improvement in PDCP there is little change in cognitive function in response to levodopa treatment. In patients where some improvement in cognitive function is seen, there is also decreased expression of PDCP maintaining the correlation between clinical observation and functional imaging results.[36] The same study observed variable changes in PDCP expression related to cognitive changes with treatment in PD patients without dementia. However, the inclusion of treatment in the study further demonstrated the independent changes in PDCP and PDRP expression with levodopa treatment. [36] Though PDRP was more likely to change with therapy, cognitive changes and PDCP expression modulation was different in patients who were determined to be responders and non-responders in regards to their baseline verbal learning, used as a measure of cognitive ability. Patients were found to be more likely to respond cognitively to treatment and improve verbal learning performance with levodopa if they initially had higher PDCP expression. In contrast, patients who had low PDCP baseline expression could actually be seen to worsen with treatment with levodopa. [36]

The beneficial and detrimental effects of PD treatment may be related to dopaminergic variation throughout the striatum, which, in the individual, is based on disease severity, treatment and individual genetics. Using DBS, a series of studies revealed that GPi and STN stimulation were associated with improved motor learning, whereas levodopa was not.[36] However, as mentioned above, the improvement was once again dependent on baseline performance where patients who benefited had poor baseline performance.[37] This effect was associated with suppression of normal deactivation seen in ventromedial prefrontal cortex (vmPFC) during motor learning sequence. Patients who were abnormal learners had the activity of vmPFC depressed by levodopa therapy to cause improvement

in learning status. However, good learners who had normal vmPFC activity initially, suffered an abnormal suppression of activity related to worsening learning performance. In addition to use of FDG PET, additional studies with use of fMRI or [15O]H2O PET have also found similar results. [37]

Imaging of Specific Neurotransmitters in PD Cognition

Dopaminergic dysfunction in the striatum of PD patients may be related to the development of cognitive defects. Specifically looking at dopaminergic function of the caudate reveals that reduced activity in this area is related to cognitive defects in PD patients. Additionally, there is a normal correlation between caudate dopaminergic activity and learning-related activation in dorsolateral and ventral prefrontal cortices that is seen in healthy controls but lost in PD patients. [37] Interestingly, this relation of cognitive function, which is functionally related to PDCP expression, is correlated to caudate activity but not with DAT binding in the putamen.[37]

In vivo imaging studies of cholinergic defects can be conducted with the use of tracers targeting the components of cholinergic neurons such as acetylcholinesterase (AChE), cholinergic receptors (nAChR and mAChR) and vesicular transporter (VAChT). Both [^{11}C]-methyl-4-piperidinly proprionate (PMP) and [^{11}C]-methyl-4-piperidyl acetate (MP4A) can be used to assess AChE function.[37,38] Using these markers it was discovered that cortical AChE is decreased in PD and related disorders such as Pervasive Developmental Disorder (PDD) and diffuse Lewy body disease (DLB). This reduction is more severe in PD patients with dementia and is even more widespread than in Alzheimer's disease. It is worth noting that the cholinergic activity in PD is related to cognitive function but less so with the severity of the motor symptoms. [39] PDD has similar decreases in neurotransmitter activity to PD. However, PDD has lower levels of MP4A binding.[39] Although, this decline in cortical MP4A and striatal FDOPA binding are still related suggesting a role for both in the pathophysiology seen in these patients. [39]

Similar studies with [80I]-iodobenzovesamicol (IBVM) allow observation of the VAChT system showing cortical reductions predominating in the parietal and occipital cortices of nondemented PD patients. Studies of nAChR also show consistent subcortical reductions in binding in PD patients.[39] However, in contrast to the nicotinic receptors, studies directed at mAChR have actually shown increased frontal and occipital receptor activity in patients with PD and PDD. [39] Overall it seems clear that cholinergic dysfunction is a prominent feature of cognitive impairment seen in PD.

DAT (DOPAMINE TRANSPORTER) SCAN

DaT scan is an imaging technology designed to help determine the availability of dopamine in a patient's brain. It achieves this by using small amount of tropane based tracers with SPECT (tracers:^{80}I- CIT (Dopascan), ^{80}I-FP-CIT (ioflupane, DaTSCAN),^{80} I-altropane, ^{80} I-IPT, ^{80}I-PE2I, and ^{56} mTc - TRODAT - ^{10}) or PET (tracers:^{11} C-CFT, ^{18}F-CFT, ^{18}F-FP-CIT, and ^{11} C-PE2I).[40] Of these tracers, ioflupane shows clinical promise because of faster kinetics allowing adequate image acquisition as early as three hours following its injection.[40] Ioflupane along with TRODAT are the only currently commercially available tracers, with TRODAT being a cheaper alternative. TRODAT has the advantage of coming in kit form (easy application for daily clinical use) however it also has the disadvantage of easy washout from the CNS. [40, 41]

The contrast identifies the dopamine transporter which exists as a protein complex in presynaptic dopaminergic terminals. Therefore, the tagging intensity is proportional to the density of healthy dopaminergic neurons in that area. The distribution and density of these neurons can be determined with the DaT scan and experienced readers can identify PD and Parkinsonian disorders on this basis. Studies using this technique were even able to differentiate between cases of PD and vascular Parkinsonism. [41 - 43]

Conclusion:

Through the review, we were able to summarize information that functional radiologic studies can provide into the understanding of molecular changes in the Parkinson's disease. Data obtained from Functional MRI, FDG PET Brain scans, and DAT (Dopamine activity tracer) scans enables us to better localize the disease activity predominantly to the Caudate nucleus of the brain. We get better information about the PDRP and PDCP. The PDRP (parkinsonism disease related

pattern) is characterized by increased pallido-thalamic and pontine metabolic activity, and reduced activity in premotor cortex, supplemental motor area, and parietal association regions on FDG pet Brain studies. PDCP (Parkinson disease cognitive pattern) is better understood by applying a spatial covariance analysis to the FDG PET data. It revealed a specific pattern, which is characterized by hypometabolism in frontal and parietal areas with hypermetabolism in the cerebellar vermis and dentate nucleus. These functional studies can also explain the molecular basis of the resting symptoms of Parkinson's disease and motor dyskinesias associated with levodopa therapy. A reduced presynaptic FDOPA uptake is associated with increased dyskinesia severity. DAT scans uses the contrast Ioflupane (most commonly), which identifies the dopamine transporter, which exists as a protein complex in presynaptic dopaminergic terminals. Therefore the tagging intensity is proportional to the density of healthy dopaminergic neurons in that area. The distribution and density of these neurons can be determined with the DaT scan and experienced readers can identify PD and Parkinsonian disorders on this basis.

References:

1. Wu T, Long X, Zang Y, Wang L, Hallett M, Li K, Chan P 2009. Regional homogeneity changes in patients with Parkinson's disease. Hum Brain Mapp 30: 1502–1510.
2. Niethammer, Martin, Andrew Feigin, and David Eidelberg. "Functional Neuroimaging in Parkinson's Disease." Cold Spring HarbPerspect Med 2.5 (2012): n. pag. PubMed. Web. 19 Mar. 2014.
3. Moeller JR, Nakamura T, Mentis MJ, Dhawan V, Spetsieres P, Antonini A, Missimer J, Leenders KL, Eidelberg D 1999. Reproducibility of regional metabolic covariance patterns: Comparison of four populations. J Nucl Med 40: 1264–1269
4. Van de Ven VG, Formisano E, Prvulovic D, Roeder CH, Linden DE 2004. Functional connectivity as revealed by spatial independent component analysis of fMRI measurements during rest. Hum Brain Mapp 22: 165–178.
5. Pavese N, Brooks DJ 2009. Review Imaging neurodegeneration in Parkinson's disease. BiochimBiophysActa. 1792:722-9
6. Zang Y, Jiang T, Lu Y, He Y, Tian L 2004. Regional homogeneity approach to fMRI data analysis. Neuroimage 22: 394–400.
7. Achard S, Salvador R, Whitcher B, Suckling J, Bullmore E 2006. A resilient, low-frequency, small-world human brain functional network with highly connected association cortical hubs. J Neurosci 26: 63–72.
8. Kwak Y, Muller ML, Bohnen NI, Dayalu P, Seidler RD 2010. Effect of dopaminergic medications on the time course of explicit motor sequence learning in Parkinson's disease. J Neurophysiol 103: 942–949.
9. Niethammer M, Eidelberg D 2012. Neuroimaging studies in the evaluation of patients with movement disorders. In Tremor, Parkinson's disease and related movement disorders (ed. LeWitt PA.). Cambridge University Press, Cambridge.
10. Smid LM, Vovko TD, Popovic M, Petric A, Kepe V, Barrio JR, Vidmar G, Bresjanac M 2006. The 2,6-disubstituted naphthalene derivative FDDNP labeling reliably predicts Congo red birefringence of protein deposits in brain sections of selected human neurodegenerative diseases.BrainPathol 16: 124–130.
11. Fodero-Tavoletti MT, Mulligan RS, Okamura N, Furumoto S, Rowe CC, Kudo Y, Masters CL, Cappai R, Yanai K, Villemagne VL 2009. In vitro characterisation of BF227 binding to -synuclein/Lewy bodies. Eur J Pharmacol 617: 54–58.
12. Priori A, Foffani G, Pesenti A, Tamma F, Bianchi AM, Pellegrini M, Locatelli M, Moxon KA, Villani RM 2004. Rhythm-specific pharmacological modulation of subthalamic activity in Parkinson's disease. ExpNeurol 189: 369–379
13. Edison P, Rowe CC, Rinne JO, Ng S, Ahmed I, Kemppainen N, Villemagne VL, O'Keefe G, Nagren K, Chaudhury KR, et al. 2008. Amyloid load in Parkinson's disease dementia and Lewy body dementia measured with [11C]PIB positron emission tomography. J NeurolNeurosurg Psychiatry 79: 1331–1338.
14. Vingerhoets FJ, Snow BJ, Lee CS, Schulzer M, Mak E, Calne DB 1994. Longitudinal fluorodopa positron emission tomographic studies of the evolution of idiopathic parkinsonism. Ann Neurol 36: 759–764.
15. Thobois S, Jahanshahi M, Pinto S, Frackowiak R, Limousin-Dowsey P 2004. PET and SPECT functional imaging studies in Parkinsonian syndromes: From the lesion to its consequences. Neuroimage 23: 1–16.
16. Snow BJ, Tooyama I, McGeer EG, Yamada T, Calne DB, Takahashi H, Kimura H 1993. Human positron emission tomographic [18F]fluorodopa studies correlate with dopamine cell counts and levels. Ann Neurol 34: 324–330.
17. Hirano S, Dhawan V, Eidelberg D 2010. PET Imaging in movement disorders. In Encyclopedia of movement disorders (ed. Kompoliti K, Verhagen L), pp. 452–461 Academic Press, New York.
18. Nurmi E, Ruottinen HM, Bergman J, Haaparanta M, Solin O, Sonninen P, Rinne JO 2001. Rate of progression in Parkinson's disease: A 6-[18F]fluoro-L-dopa PET study. MovDisord 16: 608–615.
19. Niethammer M, Feigin A 2011. Imaging applications to Parkinson's disease clinical trials. In Imaging in Parkinson's disease (ed. Eidelberg D.), pp. 181–190 Oxford University Press, New York.
20. Pirker W 2003. Correlation of dopamine transporter imaging with parkinsonian motor handicap: How close is it? MovDisord 18 Suppl 7: S43–S51.
21. Muller U, Wachter T, Barthel H, Reuter M, vonCramon DY 2000. Striatal [123I] - CIT SPECT and prefrontal cognitive functions in Parkinson's disease. J Neural Transm 107: 303–319.
22. Rinne JO, Portin R, Ruottinen H, Nurmi E, Bergman J, Haaparanta M, Solin O 2000. Cognitive impairment and the brain dopaminergic system in Parkinson disease: [18F]fluorodopa positron emission tomographic study. Arch Neurol 57: 470–475.
23. Ribeiro MJ, Vidailhet M, Loc'h C, Dupel C, Nguyen JP, Ponchant M, Dolle F, Peschanski M, Hantraye P, Cesaro P, et al. 2002. Dopaminergic function and dopamine transporter binding assessed with positron emission tomography in Parkinson disease. Arch Neurol 59: 580–586.

24. Dhawan V, Eidelberg D 2006. PET imaging in Parkinson's disease and other neurodegenerative disorders. In Neurobiology of disease (ed. Gilman S.), pp. 821–828 Academic Press, San Diego.
25. Feigin A, Antonini A, Fukuda M, De Notaris R, Benti R, Pezzoli G, Mentis MJ, Moeller JR, Eidelberg D 2002. Tc-99m ethylene cysteinate dimer SPECT in the differential diagnosis of parkinsonism. MovDisord 17: 1265–1270.
26. Ahlskog JE, Muenter MD 2001. Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature. MovDisord 16: 448–458.
27. Cenci MA, Lundblad M 2006. Post- versus presynaptic plasticity in L-DOPA-induced dyskinesia. J Neurochem 99: 381–392.
28. Smith LA, Jackson MJ, Hansard MJ, Maratos E, Jenner P 2003. Effect of pulsatile administration of levodopa on dyskinesia induction in drug-naive MPTP-treated common marmosets: Effect of dose, frequency of administration, and brain exposure. MovDisord 18: 487–495.
29. Linazasoro G, Antonini A, Maguire RP, Leenders KL 2004. Pharmacological and PET studies in patients with Parkinson's disease and a short duration-motor response: Implications in the pathophysiology of motor complications. J Neural Transm 111: 497–509.
30. Whone AL, Watts RL, Stoessl AJ, Davis M, Reske S, Nahmias C, Lang AE, Rascol O, Ribeiro MJ, Remy P, et al. 2003. Slower progression of Parkinson's disease with ropinirole versus levodopa: The REAL-PET study. Ann Neurol54: 93–101.
31. Sossi V, de La Fuente-Fernandez R, Holden JE, Doudet DJ, McKenzie J, Stoessl AJ, Ruth TJ 2002. Increase in dopamine turnover occurs early in Parkinson's disease: Evidence from a new modeling approach to PET 18 F-fluorodopa data. J Cereb Blood Flow Metab 22: 232–239.
32. Sossi V, de la Fuente-Fernandez R, Schulzer M, Adams J, Stoessl J 2006. Age-related differences in levodopa dynamics in Parkinson's: Implications for motor complications. Brain 129: 1050–1058.
33. Turjanski N, Lees AJ, Brooks DJ 1997. In vivo studies on striatal dopamine D1 and D2 site binding in L-dopa-treated Parkinson's disease patients with and without dyskinesias. Neurology 49: 717–723.
34. Rioux L, Frohna PA, Joyce JN, Schneider JS 1997. The effects of chronic levodopa treatment on pre- and postsynaptic markers of dopaminergic function in striatum of parkinsonian monkeys. MovDisord 12: 148–158.
35. Hosokai Y, Nishio Y, Hirayama K, Takeda A, Ishioka T, Sawada Y, Suzuki K, Itoyama Y, Takahashi S, Fukuda H, et al. 2009. Distinct patterns of regional cerebral glucose metabolism in Parkinson's disease with and without mild cognitive impairment. MovDisord 24: 854–862.
36. Mattis PJ, Tang CC, Ma Y, Dhawan V, Eidelberg D 2011. Network correlates of the cognitive response to levodopa in Parkinson disease. Neurology 77: 858–865.
37. Fukuda M, Ghilardi MF, Carbon M, Dhawan V, Ma Y, Feigin A, Mentis MJ, Ghez C, Eidelberg D 2002. Pallidal stimulation for parkinsonism: Improved brain activation during sequence learning. Ann Neurol 52: 144–152.
38. Feigin A, Ghilardi MF, Carbon M, Edwards C, Fukuda M, Dhawan V, Margouleff C, Ghez C, Eidelberg D 2003. Effects of levodopa on motor sequence learning in Parkinson's disease. Neurology 60: 1744–1749.
39. Carbon M, Ghilardi MF, Feigin A, Fukuda M, Silvestri G, Mentis MJ, Ghez C, Moeller JR, Eidelberg D 2003. Learning networks in health and Parkinson's disease: Reproducibility and treatment effects. Hum Brain Mapp 19: 197–211.
40. Argyelan M, Carbon M, Ghilardi MF, Feigin A, Mattis P, Tang C, Dhawan V, Eidelberg D 2008. Dopaminergic suppression of brain deactivation responses during sequence learning. J Neurosci 28: 10687–10695.
41. Cools R, Stefanova E, Barker RA, Robbins TW, Owen AM 2002. Dopaminergic modulation of high-level cognition in Parkinson's disease: The role of the prefrontal cortex revealed by PET. Brain 125: 584–594.
42. Mattay VS, Tessitore A, Callicott JH, Bertolino A, Goldberg TE, Chase TN, Hyde TM, Weinberger DR 2002. Dopaminergic modulation of cortical function in patients with Parkinson's disease. Ann Neurol 51: 156–164.
43. Morrish PK, Sawle GV, Brooks DJ 1996. Regional changes in [18F]dopa metabolism in the striatum in Parkinson's disease. Brain 119 (Pt 6): 2097–2103.