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 associated with levodopa.

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. 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. 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. 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. 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. 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), 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. Other fMRI methods, such as regional homogeneity, can only measure local activity rather than connectivity. As of recent literature, limited resting-state studies have been used in the diagnosis of PD.

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. 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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In PET, the higher sensitivity allows for production of shorter imaging times with less motion artifacts. 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. 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 α-synuclein ligands such as 2-(1-[6-[(2-[18F] fluoroethyl) (methyl) amino]-2-naphthyl ethylidene) malononitrile (FDDNP), or [18F] -BF22. However, the radiotracer ligands are not specific to α-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 [14C] benzothiazole-aniline (Pittsburgh Compound B, PIB).

[18F]-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., [18O]-water PET or [99mTc]-technetium-ethylene cysteinate dimer SPECT).

![Figure 1: Functional Magnetic Resonance Imaging](image)

(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.)

![Figure 2: Radiotracer imaging](image)

Figure 2: Retention and regional distribution of [14C] 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. 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. 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 corticostriatopallidal thalamocortical (CSPTC) circuitry. By using the covariance and an established pattern, a specific Parkinson’s disease-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. This data can be used to suggest that the abnormally functioning PDRP may be related to the degeneration of nigrostriatal dopaminergic pathways. Thus, PDRP expression can be used to distinguish between PD and atypical parkinsonian syndromes. PDRP can be measured in imaging modalities of resting cerebral perfusion obtained with \(^{15}O\)H2O PET, \(^{55}m\)Tc-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)

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. 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. 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. 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. Another marker related to LID pathophysiology is alteration in the postsynaptic dopamine D2 receptor availability as measured with \(^{11}C\)-raclopride PET imaging. 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. 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. 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. Another factor involved in severity of LID is the level of dopamine found in the synapse as determined by $^{[1]}C$-raclopride PET. Furthermore, a multitracer study of VMAT and DAT binding revealed relative down-regulation of dopamine reuptake compared to nerve terminal loss. 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, 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.

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. Additional areas of hypometabolism in the frontal, occipital and lateral parietal cortices are also seen in PD patients with mild cognitive impairment (MCI). Analysis of the spread of hypometabolism suggests that the topography of malfunction reflects the degree of cognitive impairment in these patients.

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. 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. 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.

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. 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.

**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 DCP 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 $[^{11}\text{C}]$-methyl-4-piperidinly propionate
(PMP) and $[^{11}\text{C}]$-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 $[^{80}\text{I}]$-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 tropean
based tracers with SPECT (tracers:$[^{123}\text{I}]$- CIT (Dopascan),
$[^{11}\text{C}]$-FP-CIT (ioflupane, DaTSCAN), $[^{18}\text{F}]$-alatropane, $[^{18}\text{F}]$-IPT,
$[^{18}\text{F}]$-PE2I, and $[^{56}\text{mTc}]$ - TRODAT - 10) or PET (tracers:11
C-CFT, 12F-CFT, 18F-FP-CIT, and 18 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 dyskinasias 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:


