Imaging, Cognition, and Parkinson's Disease—An Overview

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Abstract

Although the clinical diagnosis of Parkinson's disease (PD) is defined by motor symptoms, cognitive dysfunction is a common manifestation of this disease and an important contributor to functional disability. Functional brain imaging tools have proved valuable in the study of cognitive impairment in PD. Recent advances in imaging methodology and analysis have provided novel insights into the pathophysiology of cognitive decline in these patients. This review summarizes how positron emission tomographic (PET) imaging of metabolic activity in the rest state has enhanced understanding of cognitive dysfunction in PD. This tool has also created the basis for an objective biomarker for use in clinical trials of new therapeutic agents for this disease manifestation. Moreover, insights gained from the use of specific radiotracers targeting the dopaminergic and cholinergic neurotransmitter systems will be discussed, as well as findings from *in vivo* detection of amyloid-beta.

Parkinson's disease (PD) is characterized by motor symptoms including resting tremor, rigidity, and bradykinesia. However, cognitive and behavioral problems in PD are common[1] and can have a significant effect on quality of life.[2,3] The prevalence of dementia in patients with PD has conservatively been estimated to range between 24 and 31%.[4] The cognitive profile observed in PD patients with dementia (PDD) is substantially different from that of the primarily cortical dementia of Alzheimer's disease (AD). Patients with PDD typically exhibit difficulties with executive functions, the retrieval aspects of memory, and visuospatial skills.[4] They do not exhibit clear aphasia, apraxia, or agnosia, which are common features of AD. The onset of dementia in PD is insidious, typically occurring years after the onset of motor symptoms. However, cognitive difficulties have been observed even in early PD.[5] Although debated, the pattern of early cognitive dysfunction in PD is believed to be generally similar to that of PDD.[6,7]

The pathophysiology of cognitive symptoms in PD is believed to be different from that of the motor symptoms.[8–10] Several theories exist regarding the origins of this particular clinical manifestation. It is possible that cognitive dysfunction in PD is related to the depletion of striatal dopamine and its effect on non-motor cortico–striato–pallidal–thalamocortical (CSPTC) circuits.[6] Nevertheless, other dopaminergic systems may mediate these cognitive changes, including mesocortical dopamine projections to the prefrontal cortex.[11,12] Other pathological processes, such as regional cortical Lewy body formation, are also likely to contribute to PD cognitive decline,[13] as well as abnormalities of other neurotransmitter systems.[14]

Metabolic Imaging

18F-fluorodeoxyglucose (FDG) PET imaging has revealed widespread cortical hypometabolism in advanced PD patients relative to healthy controls.[15] Among patients with PD, those with dementia exhibit relatively greater metabolic reductions in both frontal and parietal regions.[16] Although not widely investigated, several imaging studies support the idea that multiple cortical regions are associated with changes in cognition. For example, performance on a complex spatial conceptual task (Raven's Colored Progressive Matrices) was found to be associated with reduced metabolic activity in the dorsolateral prefrontal cortex (DLPFC) and in the right retrosplenial region and posterior cingulate region.[17] Furthermore, changes in mesial frontal activity observed in normal controls performing a gambling task was not present in non-demented PD patients.[18]

To identify metabolic brain networks associated with PD, we have applied a voxel-based spatial covariance approach to the analysis of PET data.[19] This approach allows for the identification of abnormal disease-related metabolic patterns (i.e. brain networks) and the quantification of the expression of known patterns (i.e. network activity) in individual subjects. Specific metabolic networks have been found to mediate the

motor and cognitive aspects of PD (see *Figure 1*).[7,19] These networks have been demonstrated to be robust descriptors of disease processes.

The motor manifestations of PD are associated with a highly reproducible disease-related spatial covariance pattern (PDRP) characterized by relative metabolic increases in pallidal, ventral thalamic, and pontine areas, associated with reductions in premotor and posterior cortical association regions.[20] PDRP has been shown to be consistently correlated with standardized ratings of motor disability, and has been extensively validated as a treatment biomarker.[21–23] A separate cognition-related spatial covariance pattern (PDCP) has also been identified and validated in non-demented PD patients.[10] This pattern is characterized by metabolic reductions in frontal and parietal association areas, associated with relative metabolic increases in the cerebellum. Both the PDRP and PDCP have excellent test–re-test reproducibility. The PDCP has been demonstrated to correlate with neuropsychological measures specifically associated with subcortical dementia syndrome.[10] Network expression is most strongly associated with performance on tests of memory and executive functioning. A relationship with visuospatial and perceptual motor speed has also been found.[10]

The PDCP does have some regional overlap with the PDRP. However, these network biomarkers are dissociable in multiple ways.[7,10,23,24] In a longitudinal study[7] we documented that PDRP expression is elevated in early disease, whereas a significant degree of PDCP network expression cannot be discerned until approximately six years after symptom onset. In other words, network expression parallels symptom onset, with the motor manifestations preceding cognitive dysfunction. In addition, PDRP expression is sensitive to pharmacological and surgical therapies directed at the motor manifestations of the disease.[22,25] On the other hand, PDCP expression remains stable with these interventions, consistent with the lack of a treatment effect on cognitive functioning based on repeated psychometric testing.[10,23]

Subsequent studies have suggested that the PDCP is sensitive to early cognitive decline, as characterized by mild cognitive impairment (MCI).[26,27] PDCP activity was found to increase in a stepwise fashion, with worsening cognitive categorization (see *Figure 2*). Healthy control subjects had lower PDCP expression than PD patients without MCI, who in turn had lower values than those with cognitive impairment. Moreover, patients with single-domain MCI maintained an intermediate position between those with involvement of multiple cognitive domains and those without cognitive impairment. PDD patients exhibit further PDCP elevations than MCI subjects.

The anatomical regions that contribute most to the PDCP network are the medial aspects of the lateral frontal and parietal association areas, and are therefore somewhat reminiscent of the 'default mode network.'[28] Therefore, it is possible that abnormal elevations in PDCP activity denote reduced capacity to allocate neural resources, as well as a diminution in cognitive reserve. Given the lack of a significant effect of levodopa on PDCP expression,[10] this network is unlikely to be a simple reflection of mesocortical dopaminergic dysfunction. Moreover, PDCP regions do not generally display α-synuclein aggregation until later in the clinical course of disease.[29] It is therefore possible that in early stages of disease, this cognition-related pattern reflects functional

Figure 1: Motor- and Cognition-related Metabolic Patterns in Parkinson's Disease
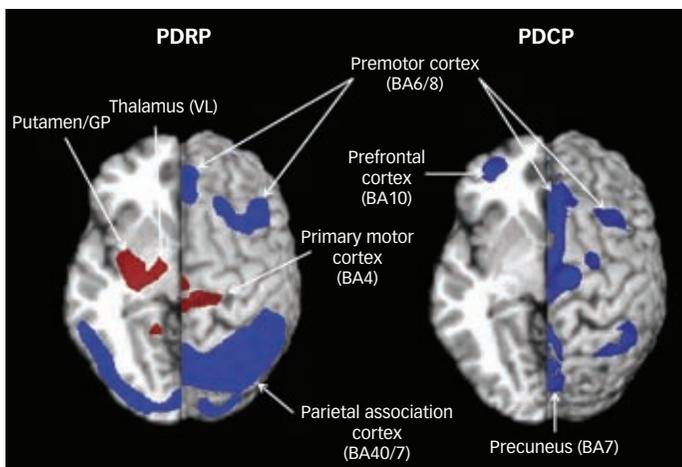
Left: Parkinson's disease motor-related spatial covariance pattern (PDRP)[20] characterized by pallidothalamic, pontine, and motor cortical hypermetabolism, associated with relative metabolic reductions in the lateral premotor and posterior parietal areas. Right: Parkinson's disease cognition-related spatial covariance pattern (PDCP)[10] characterized by hypometabolism of prefrontal cortex, rostral supplementary motor area, and superior parietal regions. Relative metabolic increases are displayed in red; relative metabolic decreases are displayed in blue. Both patterns were overlaid on a standard magnetic resonance imaging (MRI) brain template. The left hemisphere was cut in the transverse plane at z=-5mm. The right hemisphere was displayed as a surface projection on the same brain template. Reprinted with permission of HighWire Press®, a subsidiary of the Stanford University Libraries.

Figure 2: PDCP Expression for Subgroups of Parkinson's Disease Patients with Different Degrees of Cognitive Functioning
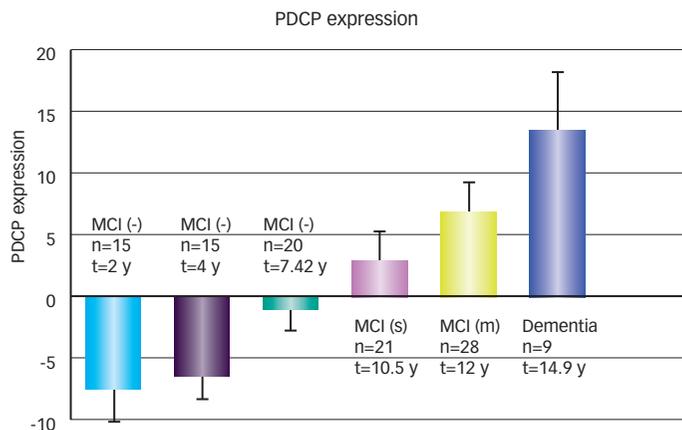
Plots of Parkinson's disease cognition-related spatial covariance pattern (PDCP) expression (mean±SE) for subgroups of PD patients with different degrees of cognitive functioning. (-) is normal cognition; (s) is single-domain mild cognitive impairment (MCI); (m) is multiple-domain MCI. t represents the mean duration of illness for each of the groups. With increasing cognitive impairment there is a concomitant reduction in cortical metabolic activity (positive network values). These metabolic reductions do not appear to be evident prior to seven years after the onset of motor symptoms.

changes in non-dopaminergic systems. Indeed, cholinergic deficits have been documented in multiple PDCP areas.[10,14,30] To date, there has been no direct comparison of PDCP expression and cholinergic functioning.

Dopaminergic Imaging

The development of several ligands for use with PET has helped elucidate the role of different mechanisms associated with cognitive

decline in patients with PD. Indeed, this disease is well suited to PET imaging studies of neurotransmitter function because of the availability of specific radiotracers targeting the dopamine (DA) system.

The use of 6-[^{18}F]fluoro-L-dopa (FDOPA) with PET permits the study of pre-synaptic dopaminergic terminal function in the striatum. This imaging technique has been used extensively to document disease severity in PD, but has more recently been applied to study dementia in PD patients. Indeed, compared with cognitively normal PD patients, those with PDD have exhibited reduced FDOPA uptake bilaterally in the region of the anterior cingulate and ventral striatum, and in the right caudate nucleus.[31] However, reduced cortical uptake of this tracer has not been universally reported as a feature of PDD.[14]

Striatal FDOPA uptake values have also been found to correlate with the degree of cognitive impairment present in non-demented PD patients. For example, when comparing non-demented PD patients with and without executive deficits, Cheesman et al.[32] observed a relationship between striatal dopamine and executive functioning, but not with cortical or limbic dopamine. Similarly, Cropley and colleagues[33] found that in PD patients, putamen uptake predicted performance on the number of categories achieved on the Wisconsin Card Sorting Test. Interestingly, this relationship did not exist for the caudate. This suggests that striatal dopamine denervation may contribute to some degree to frontostriatal cognitive impairment in moderate-stage PD. Overall, based on FDODA uptake, caudate dopamine is believed to be more closely associated with cognition than dopamine in the putamen,[31,34] although it has been suggested that both regions are linked to different aspects of cognition,[35] hypothesizing that the putamen is related to the executive aspect of motor initiation. Others have found that cortical FDOPA uptake in DLPFC and medial PFC is associated with executive functioning[34,36] and conceptualization abilities.[17]

Other radiotracers have been extensively utilized with PET and single-photon-emission computed tomography (SPECT) to measure striatal dopamine transporter (DAT) binding in PD.[37] At our Center, we have utilized [^{18}F]fluoropropyl-βCIT (FPCIT) and PET in early PD to assess rates of change in DAT binding with disease progression.[7] This radiotracer was also used in conjunction with [^{15}O]-labeled water (H$_2$^{15}O) PET to assess the relationship of DAT binding and sequence learning-related activation responses.[38,39] We found a significant correlation between dopamine input to the caudate and cognitive functioning in early PD. This study also revealed a relationship between caudate DAT binding and PFC activation during sequence learning.

In summary, imaging research targeting the dopaminegic system supports the existence of a substantial contribution from the mesocortical and nigrostriatal pathways to cognitive functioning in PD. Nonetheless, these changes do not fully explain the impairment in cognitive functioning seen in these patients. Indeed, the behavioral response to dopaminergic treatment is complex and may involve a variety of phenotypic and genotypic factors.[12]

Cholinergic Imaging
It is not surprising that other neurotransmitter systems have been found to play a role in PD cognitive impairment. N-[^{11}C]-methyl-4-piperidyl acetate (MP4A) and N-[^{11}C]-methyl-4-piperidin-4-yl-propionate (PMP) are PET radioligands that assess the activity of acetylcholinesterase (AChE), the major enzyme for acetylcholine metabolism. Using these tracers, patients with PD have been found to exhibit a global reduction (~10%) in cholinergic activity, with more substantial reductions (20–30%) in those patients with PDD.[14,40] This is consistent with pathological studies in which similar reductions in acetylcholine have been documented.[30] PDD patients are reported to exhibit bilateral widespread reductions in MP4A binding compared with normal control subjects, while those without cognitive dysfunction exhibit reduced binding only in the left cuneus.[14] Compared with PD, PDD patients had lower uptake in multiple cortical regions (left inferior parietal lobule, left precentral gyrus and right posterior cingulate gyrus). Interestingly, cortical MP4A did not correlate with local FDOPA uptake values. By contrast, striatal FDOPA uptake correlated with loss of cholinergic activity in the temporoparietal cortex, suggesting that in PD the dopaminergic and cholinergic systems degenerate in parallel.[14]

Imaging Protein Aggregation
The development of the tracer N-methyl-[^{11}C]2-(4'-methylaminophenyl)-6-hydroxybenzothiazole (Pittsburgh Compound-B or PIB) has allowed for the *in vivo* detection of amyloid-beta (Aβ) burden.[41] This radioligand binds to fibrillar Aβ plaques, one of the two main pathological elements of Alzheimer's disease (AD). Patients with AD have been shown to have marked retention of PIB in association cortices, regions in which amyloid deposits are evident on histopathological studies.[42] Although less frequent than in diffuse Lewy body disease (DLB), cortical Aβ aggregates can be found in approximately one-fifth of PDD patients,[43] and elevated PIB binding on PET imaging has been noted in a similar proportion of these patients.[44–46] Interestingly, PDD patients with and without PIB activity do not appear to differ behaviorally,[44,46] suggesting that focally increased amyloid deposition is not the cause of impaired cognitive functioning in these patients. PIB has been shown to bind to α-synuclein fibrils, although with a much lower affinity than to Aβ.[47] Nevertheless, PIB does not bind to DLB homogenates that are Aβ-plaque-free.[47] Thus, the role of α-synuclein aggregation in PD-related cognitive impairment remains an open issue. Moreover, the relationship between PIB burden and cognitive functioning has not been studied with comprehensive neuropsychological testing, although a clear relationship has been found with brief screening instruments.[44]

Conclusion
Although the clinical diagnosis of PD is based on motor symptoms, cognitive dysfunction is a significant element of this disease and contributes substantially to patient disability. Functional imaging studies have demonstrated that the mechanism of cognitive dysfunction in PD is complex. This manifestation of PD is likely to stem from dopaminergic and/or cholinergic dysfunction, as well as pathological changes intrinsic to the cerebral cortex. Some aspects of these changes are captured by the PDCP network, which can be quantified to assess cognition-related metabolic changes over time and/or with treatment. A detailed understanding of the role of individual regions in this network can be obtained through activation studies with H$_2$^{15}O PET or functional MRI, as well as with specific radioligands to assess the integrity of ascending neurotransmitter pathways or the accumulation of cortical protein aggregates. Thus, PET imaging provides a useful means of testing new therapies for cognitive dysfunction in PD. ∎

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