An update on brain imaging in parkinsonian dementia

Disturbances of cognition are frequent in Parkinson's disease (PD). Unlike severe loss of dopamine early in PD, extensive cholinergic losses have been consistently reported in PD with dementia. Cholinergic imaging suggests that basal forebrain cholinergic system degeneration appears early in PD and worsens with dementia development. Cortical cholinergic denervation is similar in PD with dementia and dementia with Lewy bodies, supporting a common disease spectrum, at least with respect to cholinergic pathology. Presence of cerebral amyloidopathy in the setting of parkinsonism may accelerate cognitive decline. Novel MRI techniques illustrate the widespread presence of neurodegeneration in PD with dementia, affecting white matter tracts and connectivity functions. This review will outline current concepts regarding dementia development in PD and discuss their correlation with functional and structural neuroimaging including PET and MRI.

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Cognitive dysfunction in Parkinson's disease

Disturbances of cognition are frequent findings in Parkinson's disease (PD) patients with point prevalence estimates of frank dementia (PD with dementia [PDD]) being reported in 40% and more subtle cognitive impairment affecting over 60% of PD patients [1–3]. Older age and duration of disease are associated with increased risk of dementia, with development of dementia in 75% and over 80% of PD patients who survive for more than 10 and 20 years, respectively [4,5].

An arbitrary but generally accepted distinction is made using current consensus diagnostic criteria between patients presenting with parkinsonism prior to the onset of dementia (PDD) versus those with concurrent development of parkinsonism and dementia or with dementia preceding parkinsonism (dementia with Lewy bodies [DLB]). Using the so-called '1-year rule', patients with L-Dopa responsive parkinsonism who develop dementia more than 1 year after their initial PD motor symptoms are classified as PDD. Patients with onset of dementia and parkinsonism within 1 year or with dementia preceding parkinsonism are classified as DLB [6].

Mild selective cognitive deficits in PD are frequently present in the absence of a clinical diagnosis of dementia [3]. Although impairments of executive functions have long been considered the cognitive signature of mild cognitive impairment (MCI) in PD, it is now widely recognized that cognitive impairments in early PD are heterogeneous, with a number of patients exhibiting deficits on posterior cortically based cognitive tasks. For example, the meta-analysis by Aarsland et al. on MCI in PD suggested that memory and visuospatial impairments were more common than executive impairment in nondemented PD [7]. MCI in PD may represent a precursor state to dementia but is qualitatively distinct from the amnestic-type MCI seen in association with Alzheimer's disease (AD). In this respect, the longitudinal study by Williams-Gray et al. suggests that posterior cortical deficits herald the dementia of PD [8].

The mixed pattern of cognitive decline in PD is probably secondary to a combination of different neuropathological processes, which worsen and become more complex and intertwined with disease progression. The pathological hallmark of parkinsonian dementia is the presence of extranigral Lewy bodies [9,10], but can be accompanied by other pathologies, such as AD-type findings [11], including β-amyloid plaques and hyperphosphorylated tau tangle pathology. In addition, comorbid vascular pathology, manifesting as leukoaraiosis on imaging studies, may also contribute to PDD [12,13]. These different neuropathological changes may not only result in local or regional neuronal and/or synaptic dysfunction but can also interrupt neuromodulator projection networks, including the cholinergic, noradrenergic and dopaminergic systems.

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This review will: discuss current evidence and theory on the etiology of cognitive impairment and dementia in PD; outline alterations in cerebral blood flow (CBF) and glucose metabolism in PDD using SPECT, and [18F] Fluorodeoxyglucose (FDG) PET and MR perfusion techniques; review brain PET imaging findings regarding abnormalities in the dopaminergic and cholinergic systems, as well as amyloid deposition in the setting of PD-related cognitive impairment; and provide an overview of MR findings in PD-associated cognitive impairment.

Post-mortem findings of parkinsonian dementia

There are numerous pathologic changes in PDD dementia, including degeneration of subcortical dopaminergic and cholinergic projection systems, as well as direct cortical involvement. Cortical Lewy bodies and Lewy neurites as well as AD-type changes with β-amyloid plaques, and in some instances neurofibrillary tangles, are present in PDD subjects [14–20]. Some neuropathology studies suggest that limbic and neocortical Lewy body deposition is the main determinant of cognitive decline in PD [10,21–24], whereas others suggest an important role for amyloid plaques and neurofibrillary pathology [25–27]. Striatal amyloid deposition is also reported in the setting of PD and cognitive impairment [20,28]. Interestingly, a recent post-mortem study found a greater frequency of striatal β-amyloid deposition in PDD compared with PD [28], and may thus confer increased risk of dementia. A recent pathologic study by Compta *et al.* suggests that the combination of Lewy bodies, amyloid plaques and neurofibrillary tangles is the crucial determinant of dementia in PD [29]. The complex interplay between amyloid deposition and Lewy body pathology may become clearer in the era of *in vivo* fibrillary amyloid imaging. *In vitro* evidence suggests an interaction between PD-type (α-synuclein) and AD-type (i.e., tau) pathologies [30].

Loss of mesencephalic dopaminergic neurons in the substantia nigra pars compacta and nerve terminals in the striatum is the pathological hallmark of PD. Significant nigrostriatal dopaminergic cell loss occurs early in symptomatic PD. Its severity and universal prevalence early in the disease course may explain why subsequent emergence and worsening of non-motor symptoms are increasingly attributed to non-dopaminergic degenerations in advancing PD. Despite this, post-mortem cell loss in the medial substantia nigra is seen more commonly in PDD as opposed to PD without dementia, suggesting an association between dementia, duration of disease and the integrity of nigrostriatal dopaminergic pathways [31]. Striatal α-synuclein pathology is also seen more commonly in PDD than in PD without dementia or DLB [32,33]. Although duration of disease may be a confounding factor in PD to account for the more severe striatal pathology, this argument may be less valid in DLB.

In addition to nigrostriatal denervation, there is evidence for alterations in cholinergic neurotransmission in PD. Loss of cholinergic neurons in the nucleus basalis of Meynert has been reported in both PD and AD brains [34–39]. Interestingly, neuronal forebrain loss may be even more profound in PD compared with AD [34]. Similarly, a post-mortem study found greater reductions of acetylcholinesterase (AChE) in the frontal cortex of PDD compared with non-demented patients with PD [40]. The reduction in cortical nicotinic cholinergic receptor number in PD parallels the degree of dementia observed with progression of the disease [41,42]; it is hence believed that degeneration of the cholinergic system may play a significant role in the development of dementia in PD.

Imaging global cerebral cortical dysfunction in parkinsonian dementia: FDG-PET & CBF imaging

FDG-PET and ^{99m}Tc-ECD, ^{99m}Tc-HMPAO or [123I]-iodoamphetamine-SPECT can be used to estimate cerebral glucose metabolism and CBF, both of which serve as surrogate markers for regional cortical health and metabolism in neurodegenerative diseases. More recently, Arterial spin labeling (ASL) MRI has been used to study perfusion changes [43]. Each of these techniques has relative advantages and disadvantages in the assessment of cerebral perfusion and/or metabolism. FDG-PET is both precise and accurate but can be expensive and time consuming to perform. SPECT is less costly but offers poorer spatial resolution. ASL does not involve the use of ionizing radiation or contrast injection but does carry potential for a low signal-to-noise ratio.

FDG-PET has been studied extensively in AD where it shows characteristic parietotemporal and posterior cingulate glucose hypometabolism [44,45]. While similar findings of posterior cingulate hypometabolism are also seen in PDD, the presence of anterior cingulate hypometabolism may be more characteristic

of DLB than PDD [45,46]. Our group recently reported results of a prospective study involving FDG-PET in 23 nondemented individuals with PD and 27 controls [47]. The six out of 23 PD subjects who went on to develop incident clinical dementia by the 2–6-year clinical follow-up displayed significant baseline reductions in FDG-PET metabolism in the occipital–visual association cortex (especially, Brodmann area 18) and posterior cingulate cortex (Figure 1). Early involvement of the visual association cortex is interesting given the prominent visual hallucinations seen in advanced PDD. Mild metabolic reductions were also seen in the caudate nucleus.

In five out of six subjects who developed dementia, repeat FDG-PET imaging after 2 years showed significant interval changes in the thalamus (-11.4%), posterior cingulate (-9%), occipital (-7%), parietal (-7%) and frontal cortices (-7%), and mild reductions in temporal cortices (-5%) and hippocampi (-3%) compared with study entry scans [47]. An example of serial FDG-PET imaging over 4 years in a PD subject converting from MCI to dementia is shown in Figure 2.

These findings are in agreement with a cross-sectional study by Jokinen *et al.* who also reported occipital FDG hypometabolism in PD without dementia compared with more extensive cortical, thalamic and caudate nucleus hypometabolism in PDD subjects [48]. Findings of mixed cortical and subcortical pathology on imaging are also consistent with the current paradigm of mixed pathological substrates leading to dementia in the context of PD (Table 1) [49]. Additionally, the presence of both posterior (parieto–occipital) and anterior cortical (frontal) changes may reflect distinct cognitive syndromes in PD and cognitive impairment. For example, Williams-Gray and colleagues reported that more posterior cortically based cognitive defects evolved into later dementia, whereas frontostriatal executive deficits were not associated with subsequent dementia risk [8].

Regional CBF (rCBF) can be estimated using SPECT imaging and may help differentiate between different types of dementia. Sawada *et al.* found no significant difference between rCBF in nondemented subjects with PD and normal controls in a [^{123}I]-iodoamphetamine-SPECT study [50], but did report bifrontal and biparietal hypometabolism in PDD subjects compared with healthy controls. Biparietal CBF was most strongly associated with poor selective performance on neuropsychological testing. These findings are in agreement with other studies

and suggest that the pattern of rCBF seen in PDD is relatively similar to AD [51,52]. rCBF studies may also differentiate DLB from AD on the basis of occipital hypoperfusion in DLB [53]. Increased severity of frontal rCBF abnormalities can also be seen in DLB compared with AD [54], although DLB with motor symptoms of parkinsonism is associated with reduced rCBF in primary motor and supplementary motor cortices compared with DLB without parkinsonism [55]. These findings all suggest that DLB may manifest with a regionally distinct pattern of cortical blood flow alterations compared with AD.

Kamagata *et al.* recently used ASL-MRI to study posterior perfusion changes in a small group of PDD subjects compared with PD subjects and healthy controls. They found significant reductions in rCBF in the posterior cortex (occipital, inferolateral and medial parietal) in PDD subjects compared with PD subjects who in turn had significantly lower posterior cortical rCBF compared with healthy controls [43]. As this study did not examine other cerebral regions of interest, it remains unclear whether their disease-specific ASL-MRI findings may have been equally severe or even more profound in other cortical regions of interest.

Imaging neurochemical changes in parkinsonian dementia: dopamine & cholinergic imaging

Degeneration in dopamine projection systems within the CNS can be assessed *in vivo* using dopamine SPECT and PET imaging techniques. PET methods include the use of [^{18}F]-fluorodopa
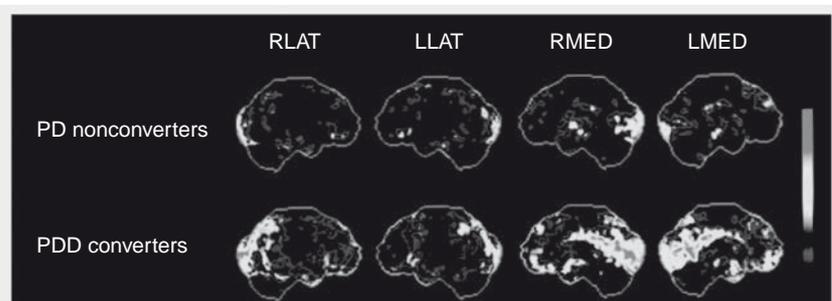
Figure 1. Metabolic reduction in Parkinson's disease. 3D-SSP t-statistic maps comparing PD dementia nonconverters and converters based on voxel-based comparison to normative data from healthy controls at baseline. The most prominent metabolic reduction in the prospective PDD converters is evident in the cuneus (especially Brodmann area 18) and precuneus. Mild-to-moderate reductions are also present in the mesiofrontal lobes. In addition, the PD dementia converter subjects demonstrate relative sparing of the primary sensorimotor cortex, a pattern similar to Alzheimer's disease. In PD nonconverter subjects, metabolic reduction in the posterior calcarine cortex (Brodmann area 17) is evident, while there is relative sparing of Brodmann areas 18, 19 and the precuneus.
LLAT: Left lateral; LMED: Left medial; PD: Parkinson's disease; PDD: Parkinson's disease with dementia; RLAT: Right lateral; RMED: Right medial.
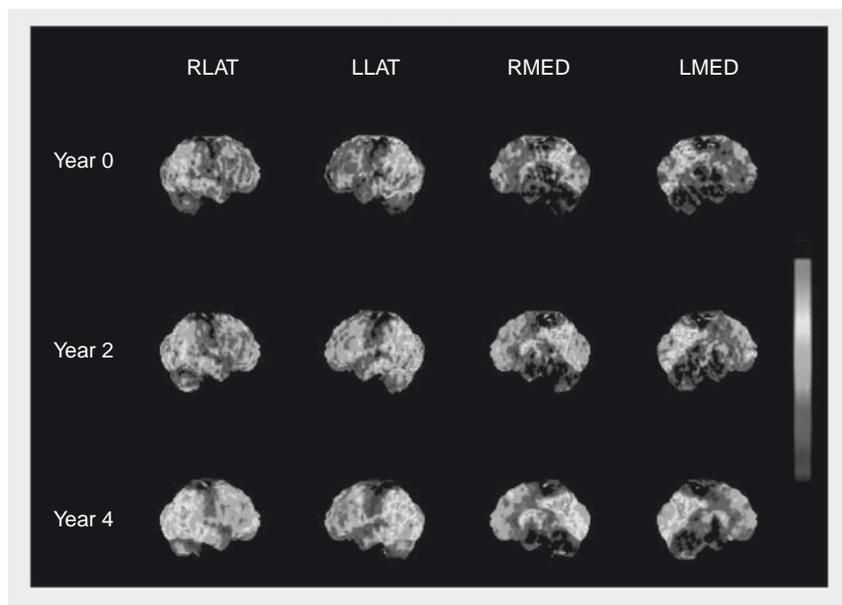
Figure 2. Progressive metabolic reduction from minimal cognitive impairment to clinical diagnosis of dementia in a single patient. Voxel-based statistical maps demonstrate regional cerebral glucose metabolic reductions relative to a database of normal subjects. Progressive metabolic reductions in the cuneus and precuneus occur before less severe, but more widespread, cortical reductions. Sparing of the primary sensorimotor cortical strip is present.
LLAT: Left lateral; LMED: Left medial; RLAT: Right lateral; RMED: Right medial.

(FDOPA)-PET along with other measures of dopaminergic terminal integrity, such as the presynaptic dopamine transporter (DAT; e.g., [11C]-methylphenidate) and the mono-aminergic ligand [11C]-dihydrotetrabenazine. Dihydrotetrabenazine is a vesicular mono-amine transporter type 2 (VMAT2) that binds to VMAT2 terminals in the striatum and serves as a reliable marker for dopamine terminal integrity. SPECT methods include DAT tracers, such as [123I]-2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl)-N-nortropane ([123I]-FP-CIT) and [23I]-2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl) nortropane ([I123]-β-CIT). [123I]-FP-CIT (known as Ioflupane or DaTscan™) has been approved to assist in the clinical evaluation of patients with

parkinsonism and its distinction from essential tremor. The ligand is also approved in Europe to assist with the clinical diagnosis of DLB in its distinction from prototypical AD.

Similar to imaging findings in PD without dementia, PDD and DLB show reduced presynaptic dopaminergic tracer uptake in the striatum [56,57]. Figure 3 shows VMAT2 binding losses in patients with PD, PDD and DLB as determined by [11C]-dihydrotetrabenazine PET.

The caudate nucleus and associated ventral striatum are thought to play a more significant role in cognition in comparison to the more motor-related putamen [58]. These differential roles are supported by dopaminergic studies in PD showing that poor performance on memory and executive functioning is closely correlated to reduced FDOPA tracer uptake in the caudate [59]. Interestingly, poor performance on attentional measures, such as the Stroop test, have been shown to correlate negatively with an increased FDOPA-PET signal in the medial frontal cortex and anterior cingulate in drug-naive PD subjects. A possible explanation is that extrastriatal, frontal lobe dopaminergic systems may also be modulated in early PD [60], probably based on a compensatory mechanism [61].

Cross-sectional dopaminergic studies have failed to show a difference between PDD and DLB in nigrostriatal dopaminergic denervation [62]. Similarly, a longitudinal DAT-SPECT imaging study revealed similar rates of decline between PDD and DLB over time [63]. This study also found that dementia and motor symptom severity correlated with dopaminergic decline, suggesting that dopaminergic loss may play an important role in cognitive as well as motor function in the context of PD. While nigrostriatal dopaminergic denervation is a near-universal phenomenon in PD with and without dementia, it occurs early in PD and thus cannot completely account for the subsequent full-blown development of dementia.

Table 1. Glucose metabolic differences between Parkinson's disease without dementia, Parkinson's disease with dementia/dementia with Lewy bodies and Alzheimer's disease.

| Brain region	PD without dementia	PDD/DLB	Alzheimer's disease
Striatum	Preserved to ↑	↓ (especially caudate nucleus)	Preserved
Thalamus	Preserved	↓	Preserved
Parietotemporal cortices	Preserved	↓	↓↓
Posterior cingulate cortex	Preserved	↓↓	↓↓
Frontal cortex	Preserved	Variable ↓	Variable ↓
Occipital cortex	Brodmann area 17 ↓	Brodmann areas 17, 18 and 19 ↓↓	Preserved
↑: Increased; ↓: Decreased; ↓↓: Severely decreased; DLB: Dementia with Lewy bodies; PD: Parkinson's disease; PDD: Parkinson's disease with dementia.			

Post-mortem studies have shown significant cholinergic losses in PDD compared with PD without dementia [34,40]. Vesicle-associated acetylcholine transporters (VAChT) are responsible for transporting acetylcholine into intracellular vesicles from the cytoplasm and, when radiolabelled *in vivo*, can provide a surrogate marker of presynaptic terminal density. There are several radioligands that target the VAChT [64], but only one of these, [(−)-5-^{123}I]-iodobenzovesamicol ([^{123}I]-IBVM), a SPECT radiotracer, has been used to image the living human brain [64]. [^{123}I]-IBVM, an analog of vesamicol, binds to the acetylcholine vesicular transporter and has a demonstrated relative distribution in the human brain, which corresponds well with post-mortem values reported for choline acetyltransferase [64]. A potential clinical advantage of the VAChT ligand is that it may allow *in vivo* assessment of integrity of cholinergic nerve terminals despite patients taking cholinesterase inhibitor drugs. Radioligands have also been developed to measure cholinergic enzymes, including AChE localized in both pre- and post-synaptic targets. Cholinergic receptor ligands are selective for either muscarinic or nicotinic receptors.

Previous *in vivo* imaging studies have shown reduced cortical AChE and VAChT activity in PDD and DLB compared with PD without dementia [56,65–67].

Previous VAChT imaging studies have reported cholinergic deficits in PD and PDD patients [65]. In PD without dementia, [^{123}I]-IBVM binding was reduced modestly in the average cortex (-9%) with more extensive reductions noted in the parietal (-19%) and occipital (-21%) cortices. Demented PD subjects had extensive cortical binding decreases that were most prominent in the occipital (-39%) and posterior cingulate (-45%) cortices. Furthermore, cortical VAChT losses were greater in PDD compared with AD of the late-onset type and comparable to AD of early onset [65]. Using AChE-PET, we also reported that *in vivo* cortical AChE levels were more severe and widespread in PDD compared with AD of similar dementia severity [66].

FIGURE 4 shows AChE-PET imaging findings in subjects with PDD and DLB.

Several studies have correlated performance on cognitive tests with cortical cholinergic activity. Shinotoh *et al.* noted significantly lower cortical AChE activity in PD subjects with visual hallucinations but did not find a correlation between cortical AChE activity and scores on the Mini-Mental State Examination
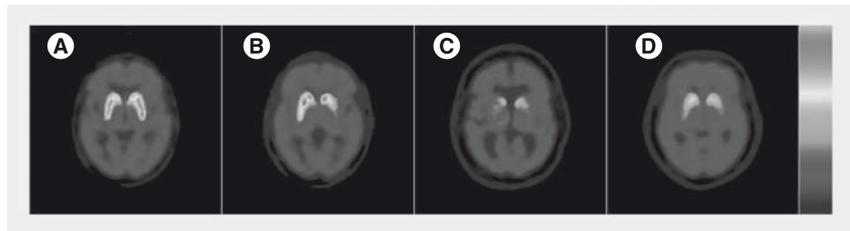

Figure 3. Vesicular monoamine transporter type 2 binding images.
(A) Binding in a normal subject. **(B)** Binding in a patient with early Parkinson's disease without dementia who has predominant asymmetric loss. **(C)** Parkinson's disease with dementia and **(D)** dementia with Lewy bodies as determined by [^{11}C]-dihydrotetrabenazine PET. More significant striatal losses are present in the Parkinson's disease with dementia and dementia with Lewy bodies subjects.

(MMSE) or the Wisconsin Card Sorting Test in a predominantly nondemented PD population [68]. We recently reported a modest inverse correlation between cortical AChE activity and MMSE scores in a larger series of PD subjects without dementia (r = 0.36, p = 0.02) [69]. In a different study, we found that performance on the WAIS-III Digit Span, a test of working memory and attention, correlated well with cortical AChE activity (r = 0.61, p < 0.005) in a combined study of PD, PDD and DLB patients. There were also significant correlations between cortical AChE activity and additional tests of attentional and executive functions, such as the Trail Making Test and Stroop Color Word Test [70]. No significant correlations were seen between AChE activity and delayed verbal learning in this study. Shimada *et al.* found an inverse correlation between cortical AChE activity and MMSE scores in a combined PD/PDD/DLB cohort (r = -0.47, p < 0.005) [67]. Subgroup analysis revealed a more robust inverse correlation between posterior cingulate AChE activity and MMSE scores in the DLB subjects in this study [67].

These findings suggest that attentional and executive cognitive domains in PD may be regulated in part by cholinergic projection neurons arising from the basal forebrain. This theory is
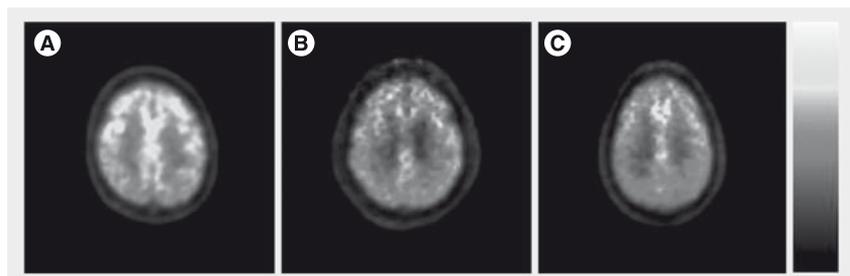
Figure 4. Acetylcholinesterase PET imaging. Findings in healthy elderly control **(A)**, Parkinson's disease with dementia **(B)** and dementia with Lewy bodies subject **(C)**. Significant reductions are present in both the Parkinson's disease with dementia and dementia with Lewy bodies subjects.

corroborated by observational data on anticholinergic medications, which have been shown to specifically worsen performance on tests of executive function and attention in PD, including the Digit Span test and the Wisconsin Card Sorting Task [71–74]. PD patients may also have a disease-specific vulnerability to the harmful cognitive side effects of anticholinergic medications [74,75]. Taken together, these data suggest that the 'cholinergic model' classically associated with AD may provide an even more robust explanation of progressive cognitive dysfunction in the setting of PD. Cognitive impairment in PD is probably the result of a combination of pathologic changes that include degeneration of the dopaminergic, noradrenergic and cholinergic systems. For example, Klein *et al.* did not observe a difference in striatal FDOPA reductions between PD and PDD groups, whereas the PDD group did show a greater reduction in cortical AChE compared with the PD group without dementia (Table 2) [76]. These findings confirm the current view that, unlike early stage PD, where there is evidence of uniform and severe dopaminergic denervation, the appearance of dementia in PD is associated with progressive cholinergic denervation. These findings are also concordant with reports of MRI volumetric measurements of the substantia innominata showing mild volume loss in early stage PD but more profound losses in PDD [77].

Imaging proteinopathies: amyloidopathy

The recent developments of radioligands that target fibrillary β-amyloid offer a novel opportunity to study *in vivo* amyloid protein aggregation [78,79]. ^{11}C-Pittsburgh compound B (PiB) is a widely used PET β-amyloid ligand; studies with ^{11}C-PiB show robust neocortical binding in AD subjects [78,80].

Previous *in vivo* imaging studies indicate lower levels of neocortical PiB binding in PD and PDD patients when compared with AD patients [81–85]. By contrast, patients with DLB may exhibit elevated, but variable, neocortical PiB binding, an interesting observation as the distinction between PDD and DLB is made on clinical grounds based on the relative timing of the onset of dementia and parkinsonism [84,85]. For example, Edison *et al.* found evidence of elevated cortical PiB binding in most DLB subjects but activity levels were generally lower and more variable compared with AD [84]. They found high global cortical amyloid burden in DLB but low global cortical amyloid burden in PDD subjects. By contrast, Maetzler and colleagues found abnormal cortical PiB binding in two out of ten PDD subjects [86]. Foster *et al.* used β-amyloid PET imaging to examine subjects with a variety of Lewy body disorders, including DLB (n = 6), PD (n = 8) and PDD (n = 15), and found no significant differences between any of these disease groups in average PiB binding in any cortical regions of interest [81]. A post-mortem case series of three patients with PDD who had *in vivo* PiB imaging found elevated cortical PiB ligand uptake in two of the three patients. At autopsy, all three individuals had abundant cortical Lewy bodies and were classified as low-probability AD based on National Institute on Aging-Reagan criteria [87]. The two PiB-positive individuals had abundant diffuse β-amyloid plaques but only sparse neuritic plaques and intermediate neurofibrillary tangle pathology. The PiB-negative individual had rare diffuse plaques, no neuritic plaques and low neurofibrillary tangle burden. These data indicate that PiB-PET is specific for fibrillar β-amyloid molecular pathology but not for pathologic diagnosis of comorbid AD in patients with PDD. Findings of generally higher global cortical amyloid burden in DLB but lower global cortical amyloid burden in PDD suggest that cortical fibrillary β-amyloid deposition is not a requisite for PD dementia but may differentially contribute to the temporal manifestation and/or nature of the neurobehavioral phenotype of parkinsonian dementia. Whether a combination of amyloid and Lewy body pathology exacerbates the memory and cognitive problems in DLB is unclear but it is likely that it accelerates the

Table 2. Results of combined [^{18}F]-fluorodopa and acetylcholinesterase studies in Parkinson's disease and Parkinson's disease with dementia.

|	PD	PDD
Striatal FDOPA uptake	↓↓	↓↓
Cortical AChE activity	Normal to mild ↓	↓(↓)

The data shows prominent nigrostriatal dopaminergic denervation both in PD and PDD but significant cholinergic decreases in PDD only.
↑: Increased; ↓: Decreased; ↓↓: Severely decreased; ↓(↓) AChE: Acetylcholinesterase; FDOPA: [^{18}F]-fluorodopa; PD: Parkinson's disease; PDD: Parkinson's disease with dementia.
Data taken from [76].

dementia process, whereas Lewy body pathology alone may lead to a slower dementing process in PDD [25].

FIGURE 5 shows PiB-PET findings in a patient with PD (no abnormal binding) and abnormal elevated binding in a PDD subject.

Structural MRI findings in parkinsonian dementia

A number of MRI studies have reported cortical atrophy in PD. Studies using a region of interest approach have demonstrated atrophy of the hippocampus and the amygdala in PD patients with and without dementia [88–91]. Furthermore, studies have shown correlations between atrophy in these structures and cognitive performance in PD patients [89–93]. Voxel-based morphometry (VBM), a fully automated whole-brain measurement technique that maps out the statistical probability of differences in regional tissue volume or density between groups has also been used in the study of PD patients. VBM brain MRI studies have shown that PDD subjects present with limbic and widespread neocortical gray matter loss; PD subjects without dementia mainly present with atrophy in the frontal and temporal regions [94–97]. Nondemented PD subjects at higher risk for dementia also show greater atrophy than PD subjects without these factors. For example, Beyer *et al.* found that patients with PD and MCI had gray matter reductions in temporal and frontal areas when compared with patients without MCI [97]. Nondemented patients with visual hallucinations (and therefore at increased risk for dementia) were also found to have greater occipitoparietal gray matter loss compared with PD patients without hallucinations [96]. A longitudinal study employing ventricular volume as a measure of global brain volume loss showed greater ventricular volumes in PD subjects who developed dementia within a 36-month period versus PD subjects who remained cognitively intact [98]. Furthermore, there was a significant correlation between ventricular volume change and dementia rating scale scores over the 36-month period. Hu *et al.* also found that annual brain volume loss is greater in PD patients compared with controls and that these changes correlated with cognitive decline [99]. Burton *et al.* found higher rates of atrophy in PDD subjects on serial MRI compared with nondemented PD subjects and controls; there was, however, no difference in the rate of atrophy between nondemented PD subjects and healthy controls [100]. A VBM-based study in PDD reported limbic and temporo–occipital
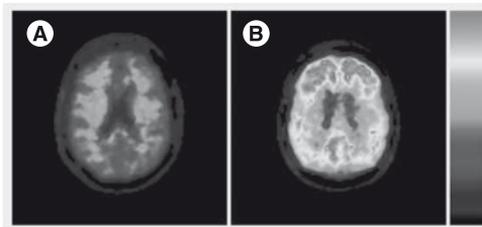
Figure 5. ¹¹C-Pittsburgh compound B PET Images. (A) Findings in a patient with Parkinson's disease with no abnormal binding. **(B)** abnormal elevated binding in a Parkinson's disease with dementia subject.

areas of gray matter reduction after a 25-month follow-up compared to baseline imaging [94]. FIGURE 6 shows an example of global atrophy and dilated ventricles in a PDD subject.

White matter disease is an area of increasing interest in PD. Leukoaraiosis or white matter lesions (WML) are commonly observed on imaging studies in the elderly and may present as signal hyperintensities on T_2-weighted MRI studies. As age-associated WML are associated with cognitive deficits in otherwise normal elderly individuals [101–104], it is plausible that WML may also contribute to cognitive symptoms in PD [12,13,70,105]. For example, Lee and colleagues found that PDD patients had significantly more supratentorial WML, particularly periventricular WML, than the PD group [106]. By contrast, other studies have failed to find significant disease-specific cognitive correlates of WML, at least in early stage disease [107,108]. It is also possible that cognitive effects of comorbid WML may be more prominent in advancing disease where presence of multiple

Figure 6. Transaxial MRI fluid-attenuated inversion recovery image showing global atrophy and enlarged ventricles in a Parkinson's disease with dementia subject.

Table 3. Major MRI findings in Parkinson's disease with dementia.	
Type of MRI	**Findings in PDD**
Structural MRI	Cortical atrophy and ventricular dilatation
	White matter lesions (leukoaraiosis)
MR spectroscopy	Metabolic cortical changes
DTI	Microstructural changes of gray and white matter, including corpus callosum
Resting state functional connectivity fMRI	Disturbances of functional networks, including the default mode network
DTI: Diffusion tensor imaging; fMRI: functional MRI; PDD: Parkinson's disease with dementia.	

neurodegenerations are expected to lower the clinical symptomatic threshold for a single pathological process owing to loss of cerebral reserve capacity.

MR spectroscopy

MR spectroscopy is an advanced MR technique that can provide a noninvasive insight into brain biochemistry and has been used to study PDD. Bowen *et al.* reported elevated lactate levels in the occipital region in PDD subjects compared with nondemented PD patients and healthy controls; this study found no differences in *N*-acetylaspartate (NAA), which is considered a neuronal marker [109]. Summerfield *et al.* reported lower NAA levels in the occipital cortex of PDD subjects compared with PD subjects without dementia but no difference between PDD subjects and healthy controls [110]. A more recent study looking at the posterior cingulate gyrus with MR spectroscopy reported lower NAA:creatine (Cr) ratios in PDD
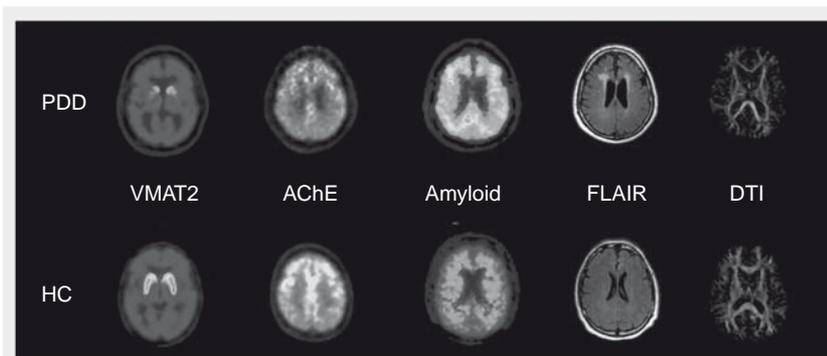
subjects compared with healthy controls and to PD subjects without dementia [111]. MR spectroscopy abnormalities in PDD and AD were different. Both PDD and AD subjects showed a reduced NAA:Cr in the posterior cingulate. PDD subjects also showed reduced glutamate:Cr in the same region compared with both controls and AD subjects. AD subjects showed increased choline (Cho):Cr and elevated myoinositol compared with healthy controls, a finding that was not seen in PDD subjects [112].

Diffusion tensor imaging

Diffusion tensor imaging (DTI) is an MRI technique that examines the local microstructural characteristics of water diffusion and is used to evaluate the integrity of white matter fiber tracts. DTI measures of the magnitude and direction of water diffusion are termed mean diffusivity (MD) and fractional anisotropy (FA) where MD is a measure of water diffusivity and FA of tract directionality and integrity [113]. There is little data regarding DTI changes in PDD. A DTI study by Matsui *et al.* employed region of interest analysis and showed reduced FA values in frontal, temporal and occipital white matter in both PD and PDD patients [114]. Reduced FA values were also noted in the posterior cingulate white matter of PDD versus PD patients. A study of DLB subjects showed decreased FA and increased MD in the corpus callosum and pericallosal regions [115]. A similar study in PDD and nondemented PD subjects did not show any group differences in MD and FA values of the corpus callosum and cingulum. There was, however, significant correlation between MD values and MMSE scores [116].

Figure 7. Multimodal imaging in a single Parkinson's disease with dementia subject (upper row) and comparative normal control subject (healthy control) images (lower row). The multitracer PET studies show significant nigrostriatal dopaminergic losses (VMAT2-PET), cholinergic denervation (AchE-PET), mildly elevated but abnormal amyloid binding (^{11}C-Pittsburgh compound B PET), leukoaraiosis (FLAIR-MRI) and microstructural white matter tract changes (DTI-MRI). The imaging findings illustrate the multifactorial and heterogeneous nature processes of parkinsonian dementia.
AchE: Acetylcholinesterase; DTI: Diffusion tensor imaging; FLAIR: Fluid-attenuated inversion recovery; HC: Healthy control; PDD: Parkinson's disease with dementia; VMAT 2: Vesicular monoamine transporter 2.

Functional MRI techniques

Functional MRI (fMRI) is based on measuring and analyzing the blood-oxygen-level-dependent (BOLD) effect. While the exact relationship between neural activity and changes in BOLD signal are still under investigation, the BOLD

signal appears to be indirectly linked to neural activity [117]. There are no task-based fMRI studies in PDD subjects, presumably owing to difficulties with task execution in the MR scanner by subjects with both significant motor and cognitive impairment. There have been a number of fMRI studies examining PD subjects with no cognitive impairment or isolated executive dysfunction [118]; these are beyond the scope of the current review.

A newer fMRI method, termed 'functional connectivity', has been developed that has the potential to assess brain activity at rest that is not in response to a predefined task. A resting connectivity study in a small number of PD patients with mild executive deficits showed reduced deactivation of the posterior cingulate cortex and the precuneus regions of the default mode network compared with healthy controls [119]. Two recent PET studies in PD, measuring CBF during cognitive tasks before and after the administration of the dopamine agonist apomorphine and before and after levodopa, suggest possible dopaminergic modulation of the default mode network [120,121].

Table 3 summarizes the major MRI findings in PDD.

Conclusion

Functional and anatomic imaging studies confirm the heterogeneous nature of parkinsonian dementia syndromes. Differences in the degree or rate of degeneration within different brain systems may account for differences in phenotypic features, such as temporal differences, in the clinical course of PDD versus DLB. Imaging studies demonstrate evidence of combined subcortical and cortical processes in parkinsonian dementia. Distinct posterior and anterior cortical changes may also reflect specific pathologies. Unlike early stage PD, where there is evidence of uniform and severe dopaminergic denervation, subcortical and cortical cholinergic denervation is more prominent in patients with PDD and DLB. Advances in MRI techniques as well as amyloid PET imaging allow for improved characterization of specific gray and white matter contributions to parkinsonian dementias, such as comorbid amyloidopathy and neural system-wide degenerations in the white matter and functional brain networks. The multisystem changes in parkinsonian dementia are illustrated in a PDD subject who underwent multitracer PET and MRI (Figure 7).

Future perspective

Further studies are needed to determine the differential contribution of heterogeneous patterns of monoaminergic and cholinergic denervation and proteinopathies, such as amyloidopathy, to the cognitive and neurobehavioral phenotype of the Parkinson syndrome. It is conceivable that the multiple lesions seen in different neural systems in parkinsonian dementia may not simply evolve in parallel, but instead may be additive or may potentiate one another in terms of functional expression. There is also a need for the development of new PET ligands that are specific for neurofibrillary tau or α-synuclein protein aggregation, which help to improve our understanding of the overlap between AD-type pathology and dementia in parkinsonian disorders.

New MR sequences, such as DTI and resting state functional connectivity fMRI are expected to demonstrate widespread neurodegeneration in both white and gray matter areas in PDD and DLB that extend far beyond the degeneration of monoaminergic and cholinergic neurons.

Executive summary

Parkinsonian dementia pathophysiology
- Dementia is frequent in the advanced stages of Parkinson's disease. Its underlying pathology is complex and probably results from a variety of processes, including dopaminergic, noradrenergic and cholinergic neuron degeneration, degeneration associated with widespread α-synuclein deposition and neurodegeneration associated with β-amyloid deposition.

Amyloid deposition & parkinsonian dementia
- Comorbid amyloidopathy may contribute to the complex dementia syndrome in Parkinson's disease and dementia with Lewy bodies and may possibly interact with the α-synucleinopathy process.

Neuroimaging & parkinsonian dementia
- Imaging techniques provide a noninvasive way to interrogate brain functions, such as glucose metabolism, perfusion and neurochemistry of dopaminergic and cholinergic neurotransmission. Novel MRI sequences are providing a new perspective on the extent of neurodegeneration that is present in parkinsonian dementia and will help to better understand disturbances in functional network connectivity and white matter tracts and cortical integrity.

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