Published in final edited form as:

Behav Brain Res. 2011 August 10; 221(2): 564–573. doi:10.1016/j.bbr.2009.12.048.

The Cholinergic System and Parkinson Disease

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Abstract

Although Parkinson disease (PD) is viewed traditionally as a motor syndrome secondary to nigrostriatal dopaminergic denervation, recent studies emphasize non-motor features. Non-motor comorbidities, such as cognitive impairment, are likely the result of an intricate interplay of multi-system degenerations and neurotransmitter deficiencies extending beyond the loss of dopaminergic nigral neurons. The pathological hallmark of parkinsonian dementia is the presence of extra-nigral Lewy bodies that can be accompanied by other pathologies, such as senile plaques. Lewy first identified the eponymous Lewy body in neurons of the nucleus basalis of Meynert (nbM), the source of cholinergic innervation of the cerebral cortex. Although cholinergic denervation is recognized as a pathological hallmark of Alzheimer disease (AD), *in vivo* neuroimaging studies reveal loss of cerebral cholinergic markers in parkinsonian dementia similar to or more severe than in prototypical AD. Imaging studies agree with post-mortem evidence suggesting that basal forebrain cholinergic system degeneration appears early in PD and worsens coincident with the appearance of dementia. Early cholinergic denervation in PD without dementia appears to be heterogeneous and may make specific contributions to the PD clinical phenotype. Apart from well-known cognitive and behavioral deficits, central, in particular limbic, cholinergic denervation may be associated with progressive deficits of odor identification in PD. Recent evidence indicates also that subcortical cholinergic denervation, probably due to degeneration of brainstem pedunculopontine nucleus neurons, may relate to the presence of dopamine non-responsive gait and balance impairments, including falls, in PD.

Keywords

Acetylcholine; Alzheimer disease; Dementia with Lewy bodies; cognition; dopamine; motor; olfaction; Parkinson disease; Parkinson disease with dementia; positron emission tomography; single photon emission tomography

1. Introduction

Although Parkinson disease (PD) is viewed traditionally as a motor syndrome secondary to nigrostriatal dopaminergic denervation, recent studies emphasize non-motor features. Non-motor comorbidities, such as cognitive impairment, are explained better by multi-system

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neurodegeneration that extends beyond the loss of dopaminergic nigral neurons [73]. Several decades of neuropathology research has generated considerable evidence for altered cholinergic neurotransmission in PD, even in the absence of dementia. Lewy first identified the eponymous Lewy body in neurons of the nbM [77], the source of cholinergic innervation of the cerebral cortex. Cholinergic denervation may occur early in PD. In the Braak *et al.* staging scheme of PD pathology, nigral and basal forebrain pathology occur simultaneously [18]. More recently, neurochemical PET (positron emission tomography) and SPECT (single photon emission computed tomography) imaging studies have complemented neuropathology studies by allowing *in vivo* assessment of the regional distribution and quantitative measurement of cholinergic terminal markers or receptors in the brain of patients with PD or related syndromes. These imaging technologies offer the opportunity to study cholinergic innervation *in vivo* at early stages of PD and other neurodegenerative disorders.

2. Pathology of the cholinergic system in Parkinson disease and parkinsonian dementia

2.1. Cholinergic system anatomy and markers

There are three major sources of cholinergic projections in the brain. The basal forebrain complex provides the principal cholinergic input of the entire cortical mantle and degenerates in PD [91]. The pedunculopontine nucleus-laterodorsal tegmental complex (PPN-LDTC; hereafter referred to as the PPN), a brainstem center, provides cholinergic inputs to the thalamus, cerebellum, several brainstem nuclei, some striatal fibers, and the spinal cord [55]. The striatum contains a population of cholinergic interneurons. While striatal cholinergic interneurons are only a small fraction (1-2%) of striatal neurons, the high density of striatal cholinergic markers indicates a robust role for cholinergic neurotransmission in striatal function. Small populations of cholinergic neurons are present in the cortex, the medial habenula, and parts of the reticular formation [29,38,74,90].

Neurochemical, histochemical, immunohistochemical, and radiotracer imaging identification of cholinergic neurons and pathways depends on cholinergic neuron expression of proteins dedicated to acetylcholine synthesis, storage, and degradation. Acetylcholine is synthesized via acetylation of choline by the cytosolic enzyme Choline Acetyltransferase (ChAT) and then pumped into synaptic vesicles by the vesicular acetylcholine transporter (VACHT). After exocytosis, acetylcholine is degraded within the synapse by acetylcholinesterase (AChE) located on both pre- and postsynaptic membranes. The free choline can be recycled back into cholinergic neuron terminals via a plasmalemmal high affinity choline transporter. Cholinergic terminals also express some subtypes of nicotinic cholinergic receptors as presynaptic autoreceptors and ligand binding to these receptors has been used also as a marker for cholinergic terminals.

2.2. Early emphasis of the cholinergic pathology research paradigm on Alzheimer disease

Most of the original pathologic research on neurodegeneration of the cholinergic system in neurodegeneration was performed in AD. Substantial loss of cholinergic innervation in the cerebral cortex is accepted universally as an aspect of advanced AD [43]. Losses are most severe in the temporal lobes, including the entorhinal cortex, where up to 80% of cholinergic axons are depleted [44]. Depletion of cholinergic axons is associated with neurofibrillary degeneration and cell loss in the nbM [45]. Neuronal loss is most severe in the posterior sector of the nbM, where neurons preferentially innervating parts of the temporal lobes are located [45,91]. In contrast to the degeneration of the basal forebrain complex, the cholinergic innervation of the striatum (mainly originating from striatal interneurons) and of the thalamus (mainly originating from the brainstem) remain relatively intact. Therefore,

there is no general cholinergic lesion in AD [89], but rather, selective cholinergic denervation of the cerebral cortex, most severe in the temporal lobes as well as in adjacent limbic and paralimbic areas [89]. Although the initial neuropathology studies indicated profound cortical reduction of ChAT activity and cholinergic nbM neuronal loss in patients with AD [16,27,105,136], more recent evidence indicates that cholinergic deficits are not severe in mild AD, and become significant only in more advanced stages of AD [28,30,94,128,129].

2.3. Cholinergic pathology in Parkinson disease and parkinsonian dementia

A key pathologic hallmark of PD is loss of midbrain dopaminergic neurons of the substantia nigra, pars compacta, and of their terminals in the striatum. In addition to the well-known reductions in dopamine, there is convergent evidence for early alterations in cholinergic neurotransmission in PD. Braak *et al.* note early accumulation of α -synuclein deposition within basal forebrain cholinergic neurons in PD, apparently coincident with the occurrence of Lewy bodies and neuronal loss in the substantia nigra [18].

2.3.1. Cholinergic forebrain pathology—Significant loss of nbM cholinergic neurons is reported in PD brains [19,97,111,126,134]. Arendt *et al.* found greater neuronal loss of nbM neurons in PD compared to AD [3], suggesting that cholinergic deficits may be at least as prominent in PD as in AD. Dysfunction of the basal forebrain cholinergic system is accompanied by a consistent loss of presynaptic cholinergic markers in cortex, sometimes accompanied by loss of muscarinic receptor binding sites. For example, muscarinic binding and ChAT activity are reduced in the pars compacta of the substantia nigra [112], hippocampus, and especially in the neocortex in PD [72].

Dementia associated with parkinsonism is an imprecisely defined entity [80,87] and has been attributed to co-existent AD pathology [79]. Reported pathologic changes in PD with dementia, however, also include direct cortical involvement as evidenced by the presence of cortical Lewy bodies and Lewy neurites, nigrostriatal and ventral tegmental area-mesocortical dopaminergic degeneration, noradrenergic denervation of the locus ceruleus, and cholinergic deficits from nbM atrophy [21,46,80,84]. One post-mortem study found greater reductions of AChE in frontal cortices of demented (−68%) compared to non-demented (−35%) patients with PD [113]. Cognitive impairment correlates with cortical ChAT levels, but not with the extent of plaque or tangle formation in PD [83,102]. Mattila *et al.* found that cognitive decline in PD was associated with lower cortical ChAT levels, even in the absence of AD pathology [83]. The reduction in cortical nicotinic cholinergic receptors (nAChR) in PD subjects appear to parallel the degree of dementia observed with progression of the disease and as with AD may result from degeneration of cholinergic projection neurons in the basal forebrain [6,135]. Impairment or degeneration of the basal forebrain cholinergic system may thus play a significant role in the cognitive decline in PD [68,102].

An arbitrary but generally accepted distinction is made in current consensus diagnostic criteria between patients presenting with parkinsonism prior to the onset of dementia (PDD) versus those developing parkinsonism and dementia concurrently or with dementia preceding parkinsonism (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 [87].

DLB is characterized neuropathologically by neuronal loss and Lewy body inclusions in midbrain dopaminergic nuclei (as in PD), but with limbic and neocortical Lewy body – Lewy neurite deposition as well [87,140]. Histopathologic findings, however, are generally

similar in DLD and PPD, suggesting that these entities occupy different parts of a single spectrum of Lewy Body diseases [68,130]. Many cases of DLB have significant amyloid plaque deposition in addition to cortical Lewy bodies, and some express additionally the neurofibrillary pathology and senile plaque deposition characteristic of AD. DLB and patients with a clinical diagnosis of AD with post-mortem evidence of co-morbid Lewy bodies (Lewy body variant of AD) brain show greater central cholinergic deficits relative to patients with pure AD [103,104,114,129,130].

2.3.2. Cholinergic brainstem pathology—The PPN is located in the dorso-lateral part of the ponto-mesencephalic tegmentum [99], and is composed of two groups of neurons: a pars compacta predominantly containing cholinergic projection neurons and a pars dissipata containing glutamatergic projections. The PPN is continuous with a more medial group of cholinergic neurons in the central gray matter, the laterodorsal tegmental complex, which has similar morphology. The PPN sends profuse ascending cholinergic efferent fibers to several thalamic nuclei, particularly the intralaminar complex that is also reciprocally connected with the basal ganglia [75]. The PPN is a brainstem locomotor center and also degenerates in PD [75]. PPN dysfunction is associated with dopamine-resistant akinesia in PD [123]. Low frequency deep brain stimulation (DBS) of the PPN is emerging as a treatment for dopamine replacement resistant postural and gait disorders in PD and other parkinsonian disorders such as Progressive Supranuclear Palsy [123].

Neuropathological studies on humans have reported that about 50% of the large cholinergic neurons of the lateral part of the PPN, pars compacta, degenerate in PD [42,59,62,141]. No reductions in PPN cholinergic neurons in AD were found [42]. Table 1 provides an overall summary of post-mortem findings of forebrain and brainstem cholinergic studies in AD and PD and dementia.

3. *In vivo* imaging findings of the cholinergic system in Parkinson disease and parkinsonian dementia

3.1. *In vivo* cholinergic imaging

PET or SPECT imaging provides the means to study neurochemical processes *in vivo*. These methods have been applied to examine cholinergic changes in neurodegenerative disorders. Cholinergic neurons and their synaptic connections provide molecular targets suitable for radiolabeling. These include ligands for markers cholinergic neuron terminals and cholinergic receptors.

3.2.1. Choline acetyltransferase, acetylcholine vesicular transporter and acetylcholinesterase—The ability to measure cholinergic synapses in the living brain would provide an important investigative tool for assessing the integrity of cholinergic nerve terminals. The most specific presynaptic marker expressed by cholinergic neurons is ChAT, but there is no tracer available for *in vivo* imaging of this enzyme. There are radiolabelled ligands for VACHT or AChE that have been shown to map cholinergic pathways in brain and have a good correspondence with ChAT distribution [92,132].

VACHTs are localized within cholinergic terminals on synaptic vesicle membranes and translocate acetylcholine from the cytoplasm into vesicles. (–)-5-[I-123]iodobenzovesamicol ([I-123]IBVM), a SPECT VACHT radioligand, has been used to image human brain *in vivo* [71]. The distribution of [I-123]IBVM retention in the human brain correspond well with postmortem measurements of regional ChAT activity [71].

AChE has been recognized for decades as a reliable marker for brain cholinergic pathways [120]. AChE is localized predominantly in cholinergic cell bodies and axons. In neocortex, AChE is present in cholinergic axon afferents from the basal forebrain complex [115]. There is some AChE activity in intrinsic cortical neurons and low levels of AChE are probably present in the non-cholinergic structures post-synaptic to the nucleus basalis innervation [56]. AChE is anchored in presynaptic membranes of cholinergic neurons as well as in postsynaptic membranes and within the intersynaptic space. AChE activity has a very good correspondence with the regional distribution of ChAT activity. The distribution of AChE activity is highest in the basal ganglia and the basal forebrain nucleus, intermediate in the cerebellum and lower in the cortex [5]. The most commonly used method of AChE PET imaging utilizes radio-labeled lipophilic acetylcholine analogues that diffuse readily into brain. These analogues are metabolized by AChE to produce hydrophilic metabolites that are trapped at the site of production [61]. Examples include methyl-4-piperidyl acetate (MP4A) and methyl-4-piperidinyl propionate (PMP) esters [61,65]. Radiotracer distribution measured with AChE PET imaging conforms to post-mortem measurements of regional AChE activity (Figure 1).

AChE PET imaging allows assessment of two major cholinergic projection systems in the brain; the cortical system originating from the basal forebrain and a subcortical system originating from the brainstem PPN and laterodorsal tegmental nucleus (Figure 2). Cortical AChE activity reflects basal forebrain cholinergic neuron integrity and thalamic AChE activity represents PPN integrity. AChE PET, however, is a less robust method for quantifying striatal cholinergic neuron integrity. Striatal AChE activity is high, such that regional blood flow, rather than pure radiotracer catabolism, affects striatal tracer retention.

In vivo cholinergic imaging studies report cholinergic deficits in PD and PDD patients [70,119]. In PD without dementia, retention of the SPECT VAcHT ligand [I-123]-IBVM was reduced only in parietal and occipital cortex, but demented PD subjects had extensive cortical retention decreases [70]. The Chiba group reported reduced AChE activity in the cerebral cortex in PD, greater in patients with dementia [98,119]. Hilker *et al.* reported significant reductions of cortical AChE in PD without dementia (10.7%) but severe reductions in PDD (29.7%) [57]. We reported previously that cortical AChE deficits were greatest and more extensive in PDD when compared to AD of approximately equal dementia severity [13]. In our study, cortical AChE activity was also significantly reduced in a PD without dementia group when compared to the control subjects.

Shimada *et al.* report *in vivo* imaging of cerebral AChE in a series of patients with PD without and with dementia (PDD), and in patients defined clinically as DLB [117]. These authors specifically evaluated whether brain cholinergic deficits occur in early PD, antedating the occurrence of dementia. They also studied possible differences in cholinergic denervation between demented patients clinically defined as PDD or DLB. The authors describe prominent and widespread reductions in cortical AChE in both demented subject groups. Their data confirmed our previous observations that average cortical cholinergic denervation generally does not differ between PDD and DLB subjects, supporting the view that PDD and DLB lie on a common disease spectrum, at least with respect to degree of basal forebrain cholinergic neuron pathology [13]. Although DLB and PDD may have similar degrees of cholinergic denervation, the time of the initial onset and degree of cholinergic denervation may be a significant determinant of the temporal manifestation of neurobehavioral symptoms in Lewy body parkinsonism.

Shimada *et al.* made also an important observation of significant reductions in cortical AChE activity in early drug naïve PD subjects [117]. The most prominent AChE reductions in PD subjects with early disease occurred in medial occipital secondary visual cortex

(Brodmann area 18). These results correlate well with prior post-mortem data indicating that this region (the cuneus) experiences the greatest degree of cholinergic denervation in PD [102]. Taken together, these observations agree with post-mortem evidence suggesting that basal forebrain cholinergic system degeneration appears early in PD and worsens with the appearance of dementia [113]. These results, for example, are consistent with the Braak *et al.* description of relatively early α -synuclein deposits in basal forebrain neurons [18].

3.2.2. Cholinergic receptor radioligand imaging—Radioligands have also been developed to measure cholinergic receptors. These receptors are localized in both presynaptic and postsynaptic targets. Cholinergic ligands are selective for either muscarinic or nicotinic receptors.

Nicotinic (nAChR) receptors are ligand-gated heteropentameric ion channels [101]. Neuronal nAChR subunits assemble according to a general $2\alpha 3\beta$ stoichiometry, with the possibility of more than one α subunit subtype within a pentamer [23]. It appears that the majority of high affinity nAChRs in the brain comprise the $\alpha 4\beta 2$ subtype [39].

Muscarinic (mAChR) receptors are G-protein coupled receptors mediating metabotropic actions of acetylcholine [37], and include pharmacologically-defined M1 – M3 subtypes. On a molecular level, there are 5 distinct receptor subtype gene products designated m1 – m5. Dense concentrations of muscarinic cholinergic receptors are associated with the termination of the basal forebrain projections to the neocortex, hippocampus, olfactory tubercle, and amygdala [40,67]. The highest concentration of muscarinic receptors is found in the striatum, in association with similarly concentrated markers of presynaptic cholinergic terminals. The M1 subtype (including the m1 and m4 molecular subtypes) is post-synaptic and accounts for 80% of cortical muscarinic receptors, occurring in high concentration in limbic and paralimbic areas including the cingulate gyrus [82].

While a majority of cholinergic receptors are post-synaptic, some cholinergic receptors are expressed on presynaptic terminals. A high proportion of nicotinic cholinergic receptors in some regions are located presynaptically on both cholinergic and non-cholinergic terminals. A post-mortem autoradiography study of the nAChR ligand 5-[I-125]-A-85380 demonstrated loss of striatal binding that closely paralleled the loss of nigrostriatal dopaminergic markers [106]. *In vivo* reductions of $\alpha 4\beta 2$ nAChR binding in the striatum and substantia nigra has also been reported in PD without dementia [64]. A [I-123]-5-I-A-85380 $\alpha 4\beta 2$ nAChR SPECT study found widespread significant decrease (10%) in not only subcortical but also cortical regions in PD patients without dementia [41]. Recently, Meyer *et al.* reported widespread *in vivo* loss of $\alpha 4\beta 2$ nAChR binding in PD without dementia, including the midbrain and cerebellum [93].

Imaging muscarinic receptors, which are the dominant postsynaptic cholinergic receptors in the brain, has also been pursued. A muscarinic receptor PET study using the radioligand [C-11]NMPB demonstrated increased mAChR binding in the frontal cortex in non-demented PD patients [4]. This finding may reflect denervation hypersensitivity caused by loss of the ascending cholinergic input to that region from the basal forebrain.

4. Cholinergic functions in atypical parkinsonian disorders

Although idiopathic PD accounts for the majority of patients who have parkinsonian symptoms, parkinsonism is seen also with other neurodegenerative disorders, such as progressive supranuclear palsy (PSP), spinocerebellar ataxias (SCA), multiple system atrophy (MSA), or corticobasal degeneration (CBD).

4.1. Progressive supranuclear palsy and corticobasal degeneration

PSP is an atypical parkinsonian syndrome with severe gait and balance impairments occurring at early stages of disease, and characteristic supranuclear gaze palsy. Pathological changes consist of neurofibrillary tangle formation and neuronal loss in the superior colliculi, brainstem nuclei, peri-aqueductal gray matter, and basal ganglia [122]. A neurochemical post-mortem study found reduced VAcHt expression and ChAT activity in striata of patients with PSP, consistent with selective loss of striatal cholinergic interneurons [124].

Cholinergic imaging in patients with PSP has been performed using the AChE ligand MP4A [119]. Shinotoh and colleagues reported a modest reduction in cortical AChE activity in patients with PSP with greater reductions in thalamus. These results indicate significant loss of brainstem cholinergic PPN neurons. PPN degeneration or dysfunction may play an important role in the characteristic gait, eye movement, and postural motor impairments of PSP. A muscarinic receptor PET study using [C-11]NMPB demonstrated no abnormal cortical mAChR binding in PSP [4]. Cerebral cholinergic system impairment may have more relevance to motor than cognitive impairments in PSP. Table 2 provides a global summary of *in vivo* imaging findings of forebrain and brainstem cholinergic studies in PD, PDD/DLB, mild and advanced AD and PSP illustrating disease-specific involvement of forebrain versus brainstem cholinergic systems.

In related disorder characterized by neurofibrillary pathology, CBD, Shinotoh *et al.* report asymmetric cortical loss of AChE activity in the fronto-parietal cortex [118f].

4.2. Multiple system atrophy and cerebellar ataxia

MSA is an atypical parkinsonian syndrome covering a clinical spectrum of parkinsonism in variable combination with features of cerebellar ataxia and dysautonomia. The pathology of MSA is distinct from PD and consists of neuronal loss in the substantia nigra, striatum, cerebellum, brainstem and spinal cord with argyrophilic and glial inclusions [100]. Gilman *et al.* found evidence of reduced thalamic [I-123]IBVM binding, indicative of decreased pontine cholinergic projections, in MSA that may be related to symptoms of obstructive sleep apnea [47]. Shinotoh *et al.* reported reduced cerebellar AChE activity in patients with MSA [118]. Gilman *et al.* presented preliminary findings of cerebral AChE functions in different parkinsonian syndromes, including MSA of the parkinsonian type, PSP, PD and DLB [48]. Striatal activity was reduced in MSA, PSP and DLB. Cerebellar reductions were present in MSA and DLB. Pons/thalamic reductions were present in MSA and DLB. However, cortical AChE was relatively preserved in PSP and MSA.

Cerebellar ataxia syndromes represent heterogeneous etiologies, including genetic conditions such as SCAs. Hirano *et al.* reported reductions in thalamic AChE in the SCA3 syndrome (Machado-Joseph disease) [58].

5. Clinical correlates of cholinergic denervation in Parkinson disease and parkinsonian dementia

5.1. Cognition, mood and behavior

Disturbances of cognition are frequent findings in PD patients with point prevalence estimates of dementia (PDD) ranging up to 40% of patients and (executive) cognitive disturbances in over 60% [51,81,85,86,107]. The cumulative prevalence is very high, at least 75% of the PD patients who survive for more than 10 years will develop dementia [1]. In PD, selective cognitive deficits are often present in the absence of clinically diagnosable dementia. Early cognitive impairment in PD patients is characterized mainly by executive

dysfunction with difficulties planning, innovating, and sequencing [9]. Because of the primary basal ganglia involvement in PD, it has generally been asserted that executive impairment is mainly attributable to a striatal dopaminergic loss. The contribution of dopamine to the working memory processes in PD has been emphasized [49]. While dopaminergic therapy in PD patients is found to improve functions of working memory and cognitive sequencing, more pure measures of executive functioning do not show significant benefit with dopaminergic agents [26,50]. Interpretation of some of these studies, however, is complicated by the fact that striatal dopamine denervation is not uniform in PD. In early PD, particularly, there is more dorsal than ventral striatal dopamine terminal loss. Dopamine replacement therapy may improve performance in tasks mediated by fronto-dorsal striatal circuits and worsen performance in tasks mediated by fronto-ventral striatal circuits where there is no prominent dopaminergic denervation, so-called “dopamine over-dose hypothesis” [24,25]. Executive dysfunction in PD is likely a cumulative effect of striatal dysfunction, dopaminergic abnormalities within prefrontal cortex, and dysfunction within other neurochemical systems, such as the basal forebrain cholinergic projection, important for prefrontal cortex function.

Pharmacological studies demonstrate that anti-cholinergic drugs have disproportionately adverse effects on attentional and executive processes in PD subjects with mild cognitive symptoms [9,26]. Dubois *et al.* reported that anti-cholinergic medications in patients with PD led to severe impairment on attentional and executive tests, such as the Digit Span test and the Wisconsin Card Sorting Task [33,34]. Anti-cholinergic drug administration caused a transient dysexecutive syndrome in PD patients, but not in normal controls, indicating specific anti-cholinergic vulnerability in PD [8,9]. Anti-cholinergic sensitivity may indicate the presence of cholinergic denervation in PD. In addition to the well-known dopaminergic reductions, cholinergic system degeneration is also an early feature of PD and worsens with the appearance of dementia [113,117]. For example, significant loss of cholinergic forebrain neurons has been reported in PD brains [134]. We determined *in vivo* cortical AChE activity with PET imaging in patients with mild AD, PDD, and PD without dementia. We found reductions in cortical AChE levels were greater and more extensive in PDD compared to AD of similar dementia severity [13]. A novel finding was that patients with PD without dementia had less severe but significant reductions in cortical AChE activity most prominent in temporal cortices [13]. The degree of cognitive impairment correlated with cortical AChE activity [12]. Analysis of the cognitive data within patient groups demonstrated that scores on the WAIS-III Digit Span, a test of working memory and attention, had most robust correlation with cortical AChE activity. There were significant correlations between cortical AChE activity and other tests of attentional and executive functions, such as the Trail Making and Stroop Color Word tests [12]. These findings support the hypothesis that cholinergic system degeneration and/or dysfunction is a significant contributor to cognitive impairment in PD. Such a cholinergic component likely further augments cognitive deficits caused by prefrontal dopaminergic changes in PD [137].

Other non-motor correlates of cortical cholinergic denervation include symptoms of depression and/or apathy [11], and impaired activities of daily living [15]. We previously reported that the presence of depressive symptoms and apathy was significantly associated with the severity of cortical cholinergic denervation in PD and PDD [11]. A relatively unique feature of depression in PD is that mood disturbance is associated with quantitative but not qualitative worsening of cognitive deficits [131]. This modulatory effect of depression on cognitive impairment in PD suggests that a common mechanism might underlie both types of symptoms. Meyer *et al.* reported *in vivo* reductions of $\alpha 4\beta 2$ nAChR, another possible presynaptic cholinergic marker, in PD that correlated also with increased presence of depressive symptoms [93]. Cholinergic dysfunction as a mechanism underlying depression-modulated cognitive impairment may explain why depression is a risk factor for

dementia in PD [78]. A cholinergic component of PD depression may also explain the limited efficacy of serotonergic anti-depressant drugs in this disorder [133].

5.2. Olfaction

Impairment of olfaction is reported in 70–100% of patients with PD [31,54,95], with a recent analysis of pooled datasets indicating a prevalence of over 95% [52]. The pathophysiology of hyposmia in PD is understood incompletely. It may be related to neuronal degeneration with deposition of α -synuclein within the olfactory bulb and anterior olfactory nucleus [17,53]. There is evidence also of α -synuclein pathology within the limbic rhinencephalon [121]. Deficits in olfactory function in PD are described in odor identification, odor discrimination, threshold detection and odor recognition memory [88]. Some studies show preferential decline in odor identification rather than odor detection, suggesting impairment in odor memory [109], possibly involving hippocampal formation dysfunction [63]. Hyposmia occurs also in AD [32], and increases with severity of dementia [96,116]. Higher density of entorhinal cortex and hippocampal neurofibrillary tangles correlate with greater deficits of odor identification, suggesting a role for hippocampal dysfunction in AD hyposmia [138]. As loss of basal forebrain cholinergic neurons is an important feature of AD [139], in particular with early involvement of septohippocampal projections [76], we tested the hypothesis that limbic cholinergic denervation may be a contributory factor to PD hyposmia. [69]. Using a previously defined selective hyposmia measure found to be predictive of conversion of subjects with mild cognitive impairment to AD [125], we found robust correlations of this measure with limbic (hippocampal and amygdala) AChE activity in PD subjects. These preliminary data suggest that olfactory tests may be used to detect central cholinergic dysfunction. Future research is needed to determine whether lower smell performance predicts development of dementia in PD.

5.3. Motor

Falls and postural instability represent the most severe motor problems in Lewy body parkinsonism and these balance impairments are least responsive to dopaminergic pharmacotherapy. We showed recently that PD fallers did not differ in the degree of nigrostriatal dopaminergic denervation but had significantly decreased thalamic cholinergic innervation compared to non-fallers [14]. Thalamic AChE activity derives mainly from terminals of brainstem PPN neurons that play a central role in the control of movement [75]. The PPN is located in the dorsolateral part of the ponto-mesencephalic tegmentum [99], and sends profuse ascending cholinergic efferent fibers to several thalamic nuclei, particularly the intralaminar complex. PPN neurons also innervate several basal ganglia nuclei. The PPN, basal ganglia, and intralaminar thalamic nuclei form a complex web of circuits because the intralaminar thalamic nuclei are reciprocally connected with the basal ganglia [75]. Loss of thalamic AChE is likely to reflect PPN neuron dysfunction or degeneration. Our results are consistent with a key role for the PPN in the maintenance of balance in humans and with PPN dysfunction/degeneration as a cause of impaired postural control and gait in PD.

Coincident subcortical and cortical cholinergic system degeneration or dysfunction may provide a conceptual framework to explain why patients with higher postural instability and gait disturbances in Lewy body parkinsonism are at an increased risk of developing dementia. Unlike isolated cortical cholinergic denervation in AD, the additional but variable subcortical cholinergic system degeneration may be unique to Lewy body parkinsonism.

These findings and prior work raise the question as to whether cholinergic therapy may have a place in the management of mobility problems in PD. Preliminary data of a small placebo-

controlled clinical trial showed that treatment with the AChE inhibitor donepezil for 6 weeks reduced the frequency of falls about 50% in frequently fallings PD subjects [20].

6. Future directions

6.1. Heterogeneity of cortical and subcortical cholinergic denervation in PD: Implications for clinical phenotyping

An unexpected finding in the recent study of Shimada *et al.* is that some subjects described as advanced PD without dementia appear to have less cholinergic denervation than some subjects described as early drug-naïve PD [117]. If basal forebrain cholinergic system degeneration appears early in PD, one would predict slowly progressive decline over time. The data presented by Shimada *et al.* suggest that their cognitively intact but advanced subjects with PD do not appear to have more motor impairment than some of the reported early PD subjects, despite the longer duration of disease. Rates of progression are quite variable among PD patients. Patients with tremor-predominant disease, for example, tend to progress more slowly than patients with postural instability and gait disturbances (PIGD). Some studies indicate an association between the PIGD motor phenotype in PD and increased risk of dementia [127]. An association between the PIGD phenotype and a greater degree of cholinergic cortical denervation is plausible. These data indicate that cholinergic denervation is heterogeneous in PD with some subjects having preserved and others decreased cortical and/or subcortical activity. For example, figure 3 is a group scatter plot of the distribution of thalamic AChE activity in our study of PD and falls showing that at least half of the subjects have normal thalamic AChE activity. PD is a multi-system neurodegeneration and differences in the degree of or rate of degeneration of different CNS systems may account for differences in phenotypic features. Further studies are needed to determine the relationship between specific motor and cognitive phenotypes in PD, and degree and regional distribution of cholinergic denervation.

6.2. Sub-cortical dopamine-acetylcholine interactions

The remarkably high density of cholinergic markers in the striatum suggests an important role for cholinergic neurotransmission in striatal function. Current views of basal ganglia motor dysfunction emphasize striatal dysfunction, where dopamine and acetylcholine interact. Based on clinical observations demonstrating that anticholinergic drugs and dopamine agonists were both effective in ameliorating the symptoms occurring in PD, a hypothesis of opposing actions for dopamine and acetylcholine in striatal function was proposed [7,35,60].

The classic clinical hypothesis is that the reduced dopaminergic input to the striatum causes a relative cholinergic hyperactivity [35]. This idea is used to explain the improvement of some motor signs, such as tremor, after muscarinic receptor blockade [22]. A major defect of the striatal dopamine/acetylcholine antagonist theory is that anti-muscarinic agents have little effect on the bradykinesia and rigidity characteristic of PD. The role of cholinergic neurotransmission in striatal function remains poorly understood.

Striatal cholinergic interneurons comprise about 1%-2% of striatal neurons. These cholinergic interneurons have some distinctive features. They have larger perikarya than other striatal neurons and exhibit tonic, spontaneous activity. In the electrophysiology literature, striatal cholinergic interneurons are identified as tonically active neurons (TANs). Striatal cholinergic interneurons give rise to abundant widely arborizing axons but form surprisingly few typical synaptic contacts on other striatal neurons. This morphological feature suggests striatal cholinergic interneurons may have a predominantly "volume" neurotransmission or paracrine function. It is likely that striatal cholinergic striatal interneurons have widespread effects on the behavior of virtually all other striatal neuron

populations [108]. Synaptic plasticity, for example, at corticostriate synapses is modulated by striatal cholinergic interneurons.

While the overall role of striatal cholinergic neurotransmission is not understood, there are hints that it plays important roles in a variety of behaviors. Striatal cholinergic interneuron activity is modulated by rewarding and aversive stimuli and may play a role in learning or conditioning of responses to these stimuli [2,10,66].

In animal models of PD, striatal cholinergic interneuron activity does increase, consistent with a hypercholinergic state within the striatum of PD subjects. Perhaps more important, the activity of striatal cholinergic interneurons becomes synchronized across the striatum, which may be part of abnormal circuit oscillations in parkinsonian states [110]. Much remains to be learned about striatal cholinergic dysfunction in PD and related disorders, and the development of better probes for striatal cholinergic neurotransmission may be useful in unraveling alterations of striatal cholinergic neurotransmission.

6.3. Presence of comorbid amyloidopathy in parkinsonian dementia and cholinergic denervation

A major criterion to clinically distinguish PDD from DLB is the 1-year rule where dementia onset later than 1 year after onset of motor symptoms constitutes PDD and onset of dementia prior to or coincident with motor features constitutes DLB. Although apparently arbitrary, the clinical 1-year rule may reflect differences in the probability of co-morbid cortical amyloidopathy in parkinsonian dementia. For example, recent beta-amyloid PET imaging studies show that global cortical amyloid burden is high in DLB but low in PDD [36]. Although this may indicate some overlap of DLB and AD, available few *in vivo* imaging studies have shown comparable cholinergic losses in both DLB and PDD [13,117]. Further research is needed to further evaluate the relationship between nbM cholinergic denervation and the presence of co-morbid amyloidopathy.

Acknowledgments

The authors gratefully acknowledge research support from the NIH-NINDS, the Department of Veterans Affairs and the Michael J. Fox Foundation.

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Figure 1. Transaxial, slices of [C-11]PMP AChE PET images (summed radioactivity images 0-25 minutes post-injection) showing normal AChE biodistribution with most intense uptake in the basal ganglia, followed by the cerebellum, with lower levels in the cortex.

Figure 2. Schematic overview of the major cholinergic cerebral projections. The major cortical input originates from cholinergic forebrain neurons (in blue) whereas thalamic inputs have significant origination from brainstem cholinergic nuclei (pedunculopontine nucleus and laterodorsal tegmental nucleus; in red).

Figure 3. Group scatter plot of distribution of thalamic AChE activity (k_3 hydrolysis rate, min^{-1}) in control and PD subjects.

Table 1

Summary of consensus post-mortem findings of forebrain and brainstem cholinergic studies in AD and PD and dementia

	PD with or without dementia	AD
Forebrain (nbM)	↓ ↓	↓ ↓
Brainstem (PPN)	↓	preserved

Table 2

Summary of consensus *in vivo* imaging findings of forebrain and subcortical cholinergic studies in PD, PDD/DLB, MSA, PSP, and AD. There is a relative lack of data regarding striatal and cerebellar *in vivo* cholinergic imaging changes and the listed observations should be considered preliminary in nature.

	nbM/Cortex	PPN/Thalamus	Striatum	Cerebellum
PD	variable ↓	variable ↓	variable	variable
PDD/DLB	↓↓	variable ↓	variable ↓	variable
MSA	preserved	↓	↓	↓
PSP	preserved	↓↓	↓	preserved
AD (mild)	↓↓	preserved	preserved	preserved
AD (severe)	↓↓	preserved	preserved	preserved