REVIEW

Cholinergic Basal Forebrain Integrity and Cognition in Parkinson's Disease: A Reappraisal of Magnetic Resonance Imaging Evidence

Nicola M. Slater, PhD,[1,2,3*] Tracy R. Melzer, PhD,[1,2,3] Daniel J. Myall, PhD,[2] Tim J. Anderson, MD, FRACP,[2,3,4] and John C. Dalrymple-Alford, PhD[1,2,3]

[1]*School of Psychology, Speech and Hearing, University of Canterbury, Christchurch, New Zealand*
[2]*New Zealand Brain Research Institute, Christchurch, New Zealand*
[3]*Department of Medicine, University of Otago Christchurch, Christchurch, New Zealand*
[4]*Department of Neurology, Christchurch Hospital, Te Whatu Ora Waitaha Canterbury, Christchurch, New Zealand*

ABSTRACT: Cognitive impairment is a well-recognized and debilitating symptom of Parkinson's disease (PD). Degradation in the cortical cholinergic system is thought to be a key contributor. Both postmortem and in vivo cholinergic positron emission tomography (PET) studies have provided valuable evidence of cholinergic system changes in PD, which are pronounced in PD dementia (PDD). A growing body of literature has employed magnetic resonance imaging (MRI), a noninvasive, more cost-effective alternative to PET, to examine cholinergic system structural changes in PD. This review provides a comprehensive discussion of the methodologies and findings of studies that have focused on the relationship between cholinergic basal forebrain (cBF) integrity, based on T1- and diffusion-weighted MRI, and cognitive function in PD. Nucleus basalis of Meynert (Ch4) volume has been consistently reduced in cognitively impaired PD samples and has shown potential utility as a prognostic indicator for future cognitive decline. However, the extent of structural changes in Ch4, especially in early stages of cognitive decline in PD, remains unclear. In addition, evidence for structural change in anterior cBF regions in PD has not been well established. This review underscores the importance of continued cross-sectional and longitudinal research to elucidate the role of cholinergic dysfunction in the cognitive manifestations of PD. © 2024 The Author(s). *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: Parkinson's disease; cholinergic system; cognition; Parkinson's disease dementia; cholinergic basal forebrain

*__Correspondence to:__ Dr. Nicola M. Slater, New Zealand Brain Research Institute, 66 Stewart Street, Christchurch 8011, New Zealand; E-mail: nicky.slater@nzbri.org

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Nonmotor symptoms in Parkinson's disease (PD) are an integral part of the disease process.[1-3] Changes in olfaction, sleep, neuropsychiatric symptoms, and especially cognitive impairment are prevalent manifestations. Cognitive decline often progresses to formal dementia (PD dementia [PDD]) in most long-term patients and thereby has a significant negative effect on patients' quality of life.[4] Cognitive decline may reflect a diversity of neurobiological changes.[5] However, a common theme in recent literature is a focus on the integrity of brain cholinergic systems and cognition in PD.[6-8] Early investigations using postmortem analyses noted fewer cholinergic perikarya in the cholinergic basal forebrain (cBF) of patients with PDD.[9-12] This association was supported by in vivo evidence from positron emission tomography (PET) of cholinergic function changes in PD.[13-16] Structural magnetic resonance imaging (MRI) is more accessible than

functional PET and has the benefit of allowing for observation of longitudinal changes not possible with postmortem structural analysis. This review summarizes the burgeoning literature on the structural integrity of the cBF in PD, beyond an earlier summary of six studies provided by Pasquini et al.[17] We explicitly focus on MRI studies that investigated the association between cBF integrity and cognition in PD. For context, we first outline the neuroanatomical structure of the cBF and its projections, and summarize the postmortem evidence of cBF changes in PD and in vivo cholinergic PET studies in PD.

cBF Structure and Projections

Situated inferior to the anterior commissure and predominantly anterior to the striatum, the human basal forebrain comprises four diffuse cell clusters (Fig. 1).[21,22] Cholinergic neurons within these clusters, described by the widely adopted "Ch" nomenclature, reflect diverse functional autonomy because of their different patterns of neural connectivity.[21,23-27] The Ch1 cluster resides within the medial septum, and Ch2 within the vertical limb of the diagonal band of Broca (DBB; vlDBB) rostral to the anterior commissure. Ch1 and Ch2 project to the hippocampus, most densely to the CA2 subregion, via the precommissural fornix.[28-31] Ch3, which lies within the horizontal limb of the DBB (hlDBB), projects primarily to the olfactory bulb.[21,30] Ch4 is the largest cluster and is regarded as synonymous with the nucleus basalis of Meynert (NBM), which has been the primary focus of most studies on the cBF. The significance of this focus is that Ch4 provides cholinergic input to the entire human cortical mantle (Fig. 2) and amygdala.[21,29,30,32,36,37] Notably, the NBM can be further segmented into anterior, intermediate, and posterior divisions (Fig. 1). The axonal branches of individual NBM neurons project extensively. Extrapolation from studies in mice suggests that the axonal territory of individual NBM cholinergic neurons may cover a length of 100 meters, and that the total cholinergic axonal projections from the human NBM may cover 1000 kilometers.[38] These NBM projections travel in discrete organized bundles following three primary pathways (Fig. 2).[32] Ninety percent of neurons in the NBM have been estimated to be cholinergic, in contrast with 70% in the vlDBB, only 10% in the medial septum, and 1% to 2% in the hlDBB.[30] In vivo MRI assessment of the basal forebrain may therefore reflect more than changes related to cholinergic neuronal integrity, most especially when regions other than the NBM are assessed.

Postmortem Evidence of cBF Degeneration in PD

Cholinergic neurons can be easily delineated in histological sections, given their large size.[7] Using postmortem histological analysis on human brain tissue, several studies have found cholinergic neuron degeneration in PD.[22] The level of degeneration varies across the cell clusters of the cBF, with evidence suggesting a posterior–anterior pattern of degeneration across the whole cBF in PD, as has been found in Alzheimer's disease.[7,18,20,39] As such, Ch4 perikarya may be preferentially impacted relative to the anterior cBF regions (Ch1, Ch2, Ch3) in PD.

In the Ch4 region, modest cell loss has been recorded in patients with PD without dementia, with more pronounced cholinergic cell loss in patients with PDD.[9-12,40-43] These findings support the inference that Ch4 integrity is reduced in PDD but remains largely unaltered in PD with normal cognition (Fig. 3). No histological studies have differentiated PD patients experiencing some cognitive impairment, but not yet reaching a diagnosis of dementia. As such, the timing and extent of cell loss in patients with PD with mild cognitive impairment (PD-MCI) remain unclear.

The structural integrity of cholinergic projection pathways and/or cholinergic functional integrity may play a more important role than Ch4 cell loss in cognitive impairment in PD. This hypothesis is supported by postmortem evidence of an association of cortical cholinergic function, measured with acetylcholinesterase (AChE) histochemistry, with cognitive impairment[10] and by evidence that cholinergic axon degeneration, assessed using choline acetyltransferase (ChAT) immunohistochemistry, precedes cholinergic cell loss.[45]

Histological evidence of pathology in the Ch1 and Ch2 regions in PDD has been inconsistent, with one study reporting decreased cholinergic neuron count and another finding no significant differences when compared with control samples.[28,45] No evidence for reduced neuron counts in patients with PD with normal cognition or MCI (PD-MCI) has been found in these cell clusters.[43,45-47] Given the high proportion of cholinergic neurons in the Ch2 region (approximately 70%) and the prominence of afferent and efferent connections with the hippocampus, further research into this cell cluster is warranted.[28,31]

In Vivo Evidence of Cholinergic Functional Activity Changes in PD

PET has been used to assess cholinergic function from the perspective of acetylcholine enzyme, receptor, and transporter activity, significantly advancing our understanding of cholinergic dysfunction. In PD, PET assessment has shown brain-wide cholinergic system alterations, which illustrate downstream cortical and subcortical dysfunction that may be related to neuropathology in the cBF and/or cholinergic axon terminals.[8,13-16,48-51] For example, even PD without dementia has been associated with reductions in vesicular acetylcholine transporter (VAChT) and AChE activity in cortical regions.[49,50,52]

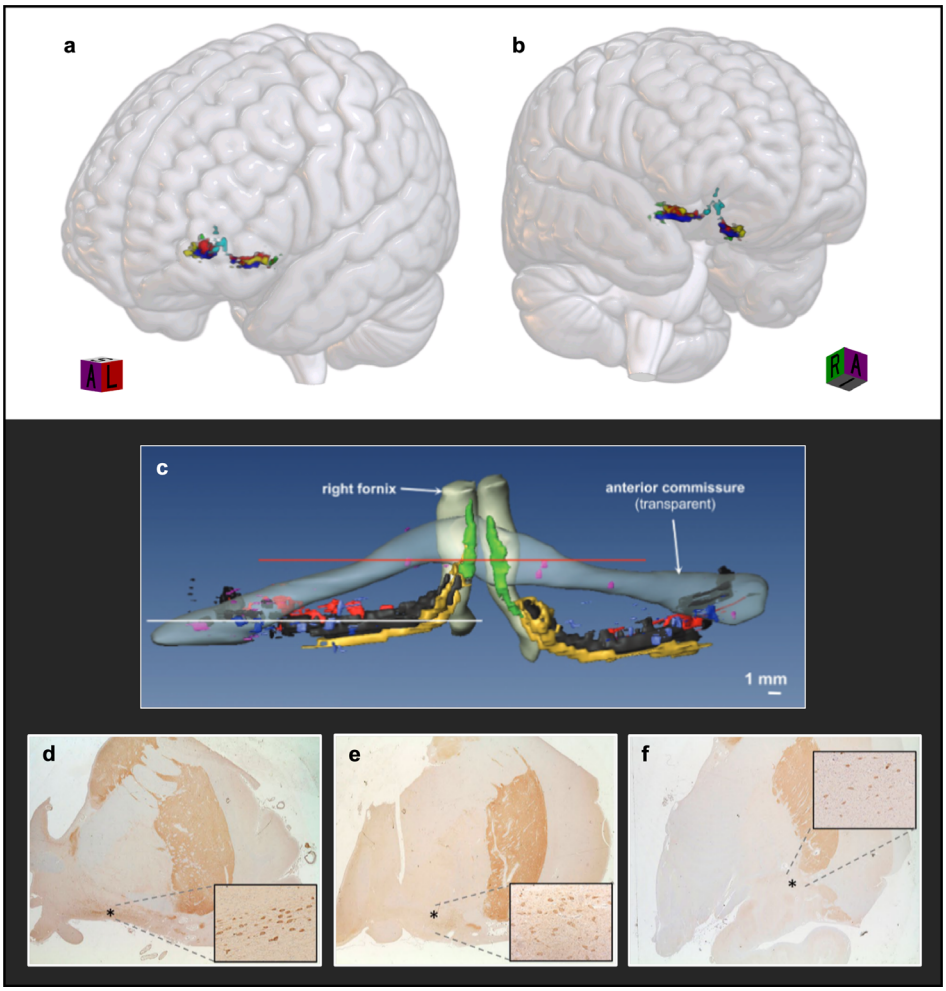

FIG. 1. Cholinergic basal forebrain (cBF) position and structure. (**a**, **b**) In vivo cholinergic basal forebrain atlas, as defined by Kilimann et al.,[18] displayed here on Montreal Neurological Institute (MNI) 152 template brain. cBF regions: cyan, Ch1-2; yellow, Ch3; blue, lateral extension of anterior Ch4; red, anterior and intermediate Ch4; green, posterior Ch4. (**c**) A computer-assisted three-dimensional reconstruction of Ch clusters of the basal forebrain after gallocyanin staining postmortem is shown: green, Ch2; yellow, Ch3; gray, anteromedial-anterolateral Ch4; red, intermediate Ch4; black, posterior Ch4; pink, juxta-commissural cells. Ch1 is not shown. (Reproduced from Grinberg and Heinsen[19] CC BY 4.0 DEED.) (**d–f**) Postmortem formalin-fixed, paraffin-embedded nucleus basalis of Meynert (NBM) sections stained with choline acetyltransferase (ChAT) immunohistochemistry and arranged rostrally to caudally starting from the most caudal aspect of the anterior commissure. Cholinergic neurons are shown in the anterior (**d**), intermediate (**e**), and posterior (**f**) divisions of the NBM. (Reproduced from Liu et al.[20] CC BY.) [Color figure can be viewed at wileyonlinelibrary.com]

In PDD, these reductions appear to be both more prominent and more widespread, consistent with postmortem evidence.[16,48] Conversely, in patients with early PD without cognitive deficits, cholinergic upregulation has been observed in cerebellar and frontal cortical regions and some subcortical structures, including the hippocampus.[49,53,54]

Differential cholinergic innervation patterns appear to distinguish patients with PD from control participants before the onset of dementia. Cholinergic innervation deficits may be more pronounced in the 7% to 12% of patients with PD with a heterozygous *GBA1* mutation,[51] the most prevalent genetic risk factor for PD.[55] In addition, cholinergic changes may be driving deficits in specific cognitive domains in PD, with Crowley et al[56] describing, in a sample of PD patients with varying cognition, an association between VAChT activity in all cortical regions and attention and working memory, executive function, and immediate and delayed memory, but not visuospatial function or language. van der Zee et al,[57] using assessment of covarying VAChT uptake, identified PD-specific cholinergic vulnerability in the centro-cinulate network,[58] a part of a broader cingulo-insular network that recent functional MRI (fMRI) evidence has indicated is a nexus for cortical cholinergic activity during attentionally demanding tasks.[59,60] In addition, right superior parietal lobe-Ch4 functional connectivity activity, assessed using resting-state fMRI, has been positively correlated with cognitive assessment results in PD with a moderate effect.[61]

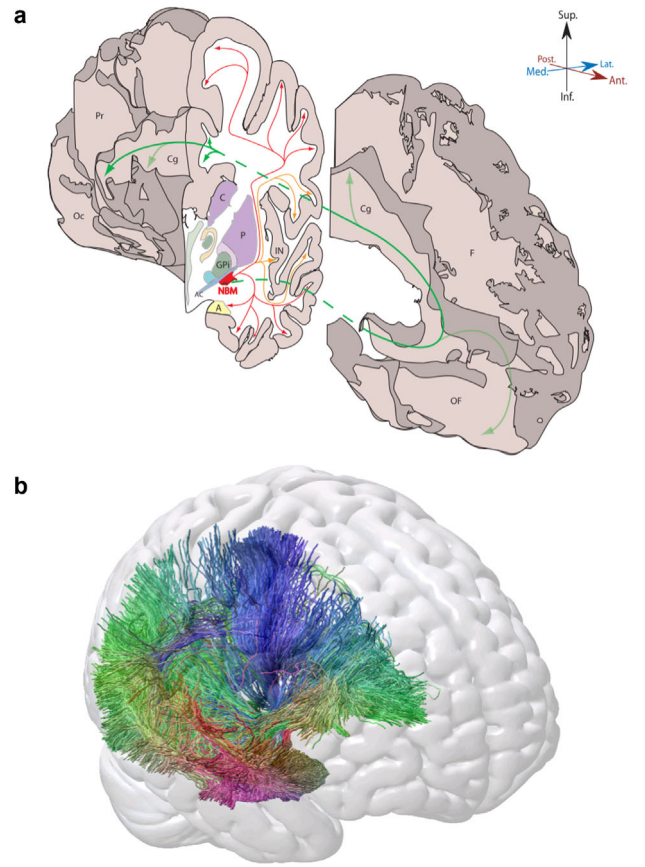

FIG. 2. Pathways connecting the nucleus basalis of Meynert (NBM) and the cortex. (**a**) The main cholinergic pathways in the left hemisphere based on observations by Selden et al[32] and Hong and Jang.[33] Green, medial cholinergic pathway; red, capsular division of the lateral cholinergic pathway; yellow, perisylvian division of the lateral cholinergic pathway; A, amygdala; AC, anterior commissure (lateral aspect); C, caudate; Cg, cingulate gyrus; F, frontal lobe (medial surface); GPi, globus pallidus (internus); IN, insular cortex; NBM, nucleus basalis of Meynert; Oc, occipital lobe (medial surface); OF, orbitofrontal cortex; P, putamen; Pr, parietal lobe (medial surface). The coronal section is presented approximately 6 mm posterior to the midpoint of the anterior commissure. (Reprinted from *Neuroscience and Biobehavioral Reviews*, 37(10), Gratwicke, J., Kahan, J., Zrinzo, L., Hariz, M., Limousin, P., Foltynie, T., Jahanshahi, M., The nucleus basalis of Meynert: A new target for deep brain stimulation in dementia? pp. 2676–2688, Copyright (2013), with permission from Elsevier.) (**b**) Tracks from the right NBM,[18] to all right hemisphere cortical regions,[34] modeled using probabilistic diffusion tractography (via constrained spherical deconvolution [MRtrix3[35]]). Colors indicate fiber orientation: red, left–right; blue, superior (sup.)–inferior (inf.); green, anterior (ant.)–posterior (post.). Med., medial. [Color figure can be viewed at wileyonlinelibrary.com]

In Vivo MRI Evidence of Basal Forebrain Degeneration in PD

Although PET provides an opportunity to investigate cholinergic function in PD, PET is not widely available, is costly, and involves radiation exposure. MRI, in contrast, is noninvasive, generally more affordable, and more widely available. In addition, examination of structural cholinergic system changes will help clarify the relationship between progressive system changes in cBF regions and advancing cognitive decline in PD. Employing different imaging modalities, MRI can provide evidence of variations in cBF macrostructure, that is, changes in gray matter volume or intra-axonal cross-sectional area and microstructure changes to tissue components.

Accurate in vivo cBF definition is required to maximize the utility and validity of MRI-derived structural metrics. Several atlases have been created to delineate the cBF and its components for in vivo assessment.[18,62-66] Different atlases vary in their treatment of cBF regions, ranging from representing the cBF as a single region[63] to segmenting the cBF into as many as five subregions[18] (Fig. 4b). Most follow the Mesulam nomenclature.[21]

Four atlases have been used to define the cBF in PD research (Fig. 4). Two have predominated: the multiregion SPM Anatomy Toolbox atlas[62,67-69] (Fig. 4a), which defines two regions (Ch1-2-3 and Ch4); and an atlas developed by Kilimann et al[18] (Fig. 4b), which includes five cell clusters (Ch1-2, Ch3, and three subregions of Ch4).

Limitations of MRI

Although the utilization of in vivo assessment of cBF structural integrity holds significant potential, it is important to acknowledge the challenge and limitations of accurately delineating the small, diffuse cell clusters of the cBF with MRI. Magnetic field strength (eg, 3 or 7 T) can affect spatial resolution of the underlying imaging data and will have an influence on the creation of different cBF atlases. In addition to the influence of atlas selection outlined earlier, further considerations include probabilistic thresholds applied to delineate cBF structures; thresholding a probabilistic atlas at 0.3 or 0.5 will obviously affect the volume of the resulting regions of interest. Furthermore, specific image preprocessing decisions—for example, selection of processing software, segmentation options, nonlinear warping algorithm—can also influence the volume of the cBF and cBF subregions obtained.[70] These challenges are further confounded by an inability to confirm accurate in vivo atlas placement because of the lack of contrast between subcortical regions in MRI data acquired using commonly adopted protocols.

Although great care has been taken in the generation of the different cBF atlases, a fundamental mismatch in spatial resolution exists between typical clinical MRI resolution (~mm) and gold standard histology (~micron), suggesting an additional source of multiple processing steps (and potential noise) when registering these two types of datasets for atlas generation and labeling. The demographics of a population used in an atlas generation process also needs to be considered. Given cBF volume reduces with age, atlases derived from young, healthy individuals may not provide the

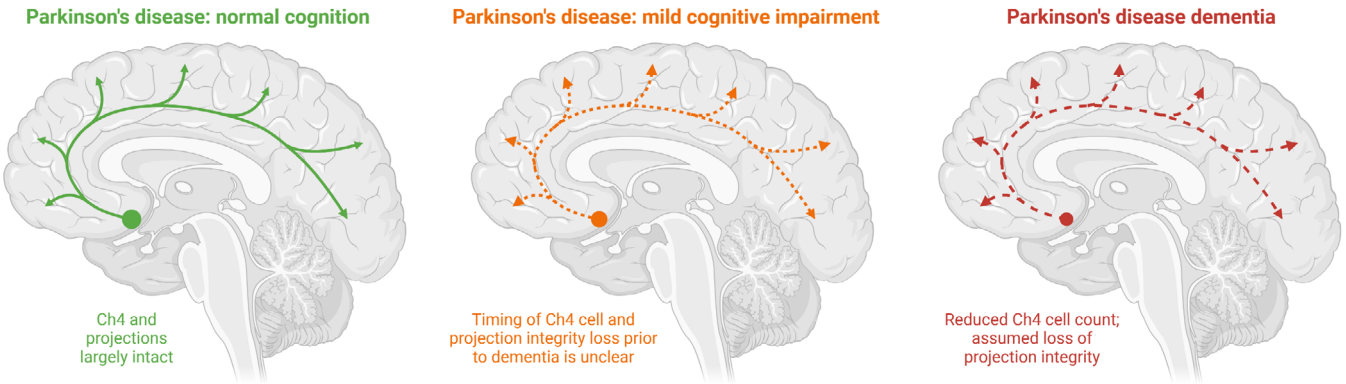

FIG. 3. Summary of postmortem histological evidence and anticipated changes in PD with mild cognitive impairment (PD-MCI) of Ch4 neuron and projection integrity in PD. Adapted from Pepeu et al.[44] Created with BioRender. [Color figure can be viewed at wileyonlinelibrary.com]

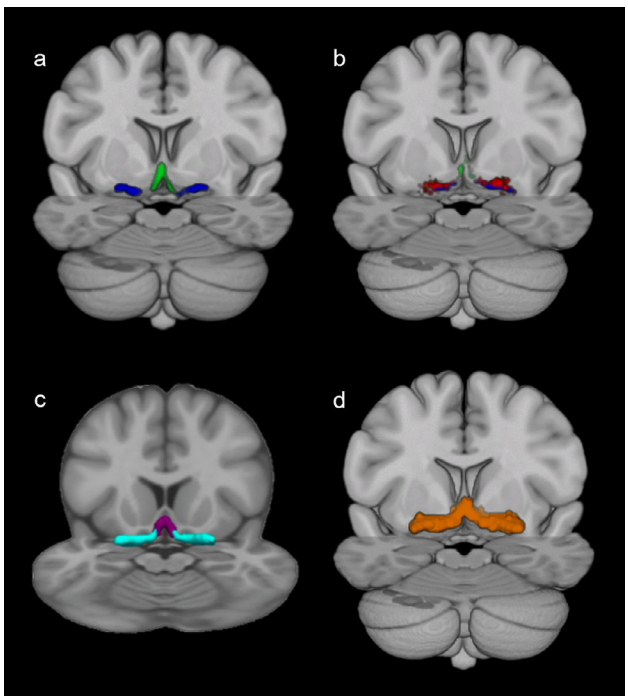

FIG. 4. Representations of cholinergic basal forebrain atlases in a multiplanar view of the Montreal Neurological Institute (MNI) 2009c asymmetric template ($y = 5$ mm; $z = -25$ mm). (**a**) As defined in the SPM Anatomy Toolbox[62,67–69]: green, Ch1-2-3; blue, Ch4. (**b**) As defined by Kilimann et al[18]: green, Ch1-2; blue, Ch3; red, Ch4. (**c**) Purple, Ch1-2; cyan, Ch3-4. (Reproduced from Gargouri et al.[66] CC BY 4.0 DEED.) (**d**) As defined by Fritz et al[63]: cholinergic basal forebrain as one region (orange). [Color figure can be viewed at wileyonlinelibrary.com]

most appropriate canvas in which to study the cBF in neurodegeneration.

Although powerful, atlas selection and decisions made during preprocessing should be borne in mind when evaluating published results of cBF structural changes.

Summary of In Vivo Evidence

Recent studies that have used MRI to assess cBF structure with at least one measure of cognition are summarized in Table 1. These studies have included PD patients with a range of disease durations and cognitive abilities. Most have included a measure of general cognition, for example, the Montreal Cognitive Assessment (MoCA) or Mini Mental State Examination (MMSE); others have included more comprehensive neuropsychological testing. Many have focused on macrostructural changes in specific cBF regions. We have grouped the studies in Table 1 by PD sample size given larger sample sizes may provide a better representation of the effects of PD. Within each sample size, group studies have been ordered alphabetically.

Posterior Basal Forebrain (Ch4) Macrostructural Change

Macrostructural change in the posterior cBF (Ch4) region has been the primary focus of investigations into cBF changes in PD. Cross-sectional studies suggest that Ch4 volume is reduced in cognitively impaired PD patients (PD-CI) when compared with a control sample.[76,80,88] However, this reduction has not been consistently observed when the PD-CI sample was small ($n = 13$[90]), or when the PD sample was not stratified by cognitive impairment.[61,71,72,76,77,80,81,87,90,95,97] Where a cognitively normal PD sample has been compared with a control sample, most studies report preserved Ch4 volume.[61,76,77,80,86,90,97] In comparing a PD-CI group with an unimpaired PD group, the majority of studies have not observed a significant Ch4 volume reduction; however, trends for lower volume in the cognitively impaired group have been noted.[76,86,88,90] Where a reduction in volume has been reported in a PD-CI group, compared with an unimpaired PD group, the effect was often small, even with larger sample sizes (Cohen's d [PD-N—PD-CI] = 0.32[77]). The variability in finding volume reduction in PD-CI may be attributable to the broad spectrum of cognitive abilities within cognitively impaired patient groups, ranging from mild to severe impairment. A larger sample does not appear to

TABLE 1 *Magnetic resonance imaging studies on cholinergic basal forebrain integrity and cognition in Parkinson's disease: cross-sectional comparisons*

			Sample Detail								
PD Sample Size[a]	**Author (year)**	**Atlas Used for cBF**	**Sample Description (n)**[b]	**Age, y, Mean (SD) or *Median* [Range]**	**PD Duration, y, Mean (SD) or *Median* [Range] {IQR}**	**Motor Severity (UPDRS Part III), Mean (SD) or *Median* [Range] {IQR}**	**Mental Status Test and n of Neuropsychological Domains**[c]	**Cross-Sectional Between-Group cBF Differences (● = Significantly "Worse" in Second Group; ○ = Not Significant)**			**Association with Cognitive Measures**
Very large (total n for PD > 149)	Barrett et al (2019)[d71]	Anatomy Toolbox[e]	HC (101)	59.5 (11.0)	–	–	MoCA; five domains	Ch1-2-3 volume[f]	HC—de novo PD	○	Presurgical PD: Ch1-2-3 and Ch4 volume both significantly associated with MoCA, attention, and visuospatial function; de novo PD: Ch4 volume significantly associated with MoCA, but not Ch1-2-3 volume
			De novo PD (MoCA range 26–29) (228)	64.5 (9.7)	0.6 (0.6)	–			De novo PD—presurgical PD	●	
								Ch4 volume[f]	HC—de novo PD	○	
			Presurgical PD (MoCA range 23–28) (125)	63.2 (8.4)	8.3 (4.5)	–			De novo PD—presurgical PD	●	
	Blair et al (2019)[d72]	Anatomy Toolbox[e]	HC (103)	60.2 (11.2)	–	0.7 (1.3)	MoCA	Ch1-2-3 volume[f]	HC—de novo PD	○	Not reported
			De novo PD (MoCA range 17–30) (228)	61.9 (9.5)	0.6 (0.6)	20.7 (8.7)			HC—presurgical PD	○	
									De novo PD—presurgical PD	●	
			Presurgical PD (MoCA range 11–30) (136)	63.5 (8.7)	8.0 (4.8)	35.1 (11.2)		Ch4 volume[f]	HC—de novo PD	○	
									HC—presurgical PD	●	
									De novo PD—presurgical PD	●	
	Franco et al (2023)[73]	Multiatlas segmentation	PD (265)	62.4 (8.9)	9.4 (4.4)	20.2 (10.6)	MMSE or DRS	cBF volume	ET—PD	●	No correlation between basal forebrain volume and cognitive scores for PD patients or ET patients
			Essential tremor (149)	65.6 (10.4)	–	–					
	Grothe et al (2021)[74]	Fritz et al (2019)[63]	HC (45)	59.4 (5.7)	–	–	MMSE; PD-CRS	cBF volume	HC—PD	○	In PD, cBF volume had a significant correlation with PD-CRS, but cBF MD did not
			PD (MMSE > 25; 180)	61.7 (9.6)	4.5 (4.3)	21.1 (10.1)		cBF MD	Not reported		
	Labrador-Espinosa et al (2023)[d75]	Fritz et al (2019)[63]	HC (56)	60 (10.1)	–	–	MoCA; four domains	cBF volume	Not reported		Not reported
			De novo PD (162)	61.5 (9.3)	–	20.9 (8.8)					
	Ray et al (2018)[d76]	Kilimann et al (2014)[18]	HC (76)	59.9 (10.2)	–	–	MoCA; four domains	Ch1-2 volume	HC—all PD	○	Not reported
			De novo PD (168)	61.5 (9.4)	0.6 (0.6)	–		Ch4 volume	HC—all PD	○	
			Divided into PD-no suspected MCI (PD-N) and PD-suspected MCI from baseline results[g]					Ch4p volume	HC—PD-N	○	
									HC—PD-MCI	●	
									PD-N—PD-MCI	○	
	Schulz et al (2018)[d77]	Anatomy Toolbox[e]	HC (167)	59.9 (11.4)	–	1.3 (2.7)	MoCA; five domains; MDS level II	Ch4 volume[f]	HC—PD-N	○	Not reported
			De novo PD (304)	61.4 (9.5)	0.6 (0.6)	20.9 (9.1)			PD-N—PD-CI	●	

(Continues)

TABLE 1 *Continued*

PD Sample Size[a]	Author (year)	Atlas Used for cBF	Sample Detail: Sample Description (n)[b]	Age, y, Mean (SD) or *Median* [Range]	PD Duration, y, Mean (SD) or *Median* [Range] {IQR}	Motor Severity (UPDRS Part III), Mean (SD) or *Median* [Range] {IQR}	Mental Status Test and n of Neuropsychological Domains[c]	Cross-Sectional Between-Group cBF Differences (● = Significantly "Worse" in Second Group; ○ = Not Significant)			Association with Cognitive Measures
			PD-N (MoCA > 25): n = 232; PD-CI (MoCA < 26 and MDS level II): n = 72					Ch4 FA	HC—PD-N	○	
									PD-N—PD-CI	○	
								Ch4 MD	HC—PD-N	○	
									PD-N—PD-CI	●	
	Zhou et al (2023)[78]	Anatomy Toolbox[e]	HC (119)	61.7 (7.3)	–	–	MoCA	cBF FWF	HC—all PD	○	Not reported
			PD (216)	60.5 (8.6)	4.3 (2.8)	22.7 (13.0)			PD subtype 1—subtype 2	●	
			(114 subtype 1; 102 subtype 2)								
			Subtypes determined using SuStain machine-learning algorithm[h]								
Large (total n for PD 100–149)	Crowley et al (2022)[79]	Anatomy Toolbox[e]	HC (62)	68.1 (5.4)	–	4.1 (4.7)	MMSE; four domains	Ch4 FWF	HC—PD-low FWF	○	High FWF PD group had significantly lower general cognitive scores than control group, but the medium and low FWF PD groups did not
			PD-low FWF (36)	63.9 (5.2)	7.1 (5.6)	18.0 (11.8)		Clusters determined using FWF in Ch4 and dorsal caudate nucleus	HC—PD-medium FWF	○	
			PD-medium FWF (57)	68.7 (5.4)	7.1 (4.8)	21.0 (9.9)			HC—PD-high FWF	●	
									PD-low—PD-medium FWF	○	
			PD-high FWF (19)	73.9 (4.8)	5.9 (3.8)	23.4 (10.8)			PD-low—PD-high FWF	●	
									PD-medium—PD-high FWF	●	
	Crowley et al (2023)[56]	Not reported	PD (101)	67.1 (7.5)	6.0 (4.4)	35.6 (12.7)	Five domains	cBF volume	Not reported		cBF volume and FWF were associated with attention, working memory, and executive function; volume also with immediate memory; FWF also with delayed memory
								cBF FWF	Not reported		
	Pereira et al (2020)[80]	Kilimann et al (2014)[18]	HC (42)	*65.7* [41.3–83.2]	–	*1.6* [0–13]	MMSE; three domains	Ch1-2 volume	HC—PD-stable	○	Not reported
			PD-stable (86)	*64.9* [21.4–83.1]	3.2 (3.8)	*12.5* [0–46]			HC—PDD-converters	○	
			PDD-converters[i] (20)	*72.4* [63.7–82.5]	3.5 (4.3)	*16.9* [5–43]			HC—PDD	○	
									PD-stable—PDD	○	
			PDD (19)	*74.0* [61.4–83.6]	8.9 (6.0)	*34.1* [13–56]		Ch4 volume	HC—PD-stable	○	
									HC—PDD-converters	●	
									HC—PDD	●	
									PD-stable—PDD	●	

(Continues)

TABLE 1 *Continued*

PD Sample Size[a]	Author (year)	Atlas Used for cBF	Sample Detail: Sample Description (n)[b]	Age, y, Mean (SD) or *Median* [Range]	PD Duration, y, Mean (SD) or *Median* [Range] {IQR}	Motor Severity (UPDRS Part III), Mean (SD) or *Median* [Range] {IQR}	Mental Status Test and n of Neuropsychological Domains[c]	Cross-Sectional Between-Group cBF Differences (● = Significantly "Worse" in Second Group; ○ = Not Significant)			Association with Cognitive Measures
	Ray, Kanel, and Bohnen (2023)[81]	Kilimann et al (2014)[18]	PD (101; 38 PD-MCI [MoCA < 26])	67.6 (7.7)	0.5 (0.4)	34.2 (12.5)	MoCA	Ch1-2, Ch3, Ch4a-i, Ch4al, Ch4p volume	Not reported		No associations with cognitive measures reported, but Ch4p volume significantly correlated with VChAT tracer uptake in widespread cortical regions
	Schumacher et al (2023)[82]	Consensus ROI based on published maps[j]	HC (52)	64.0 (12.6)	–	–	MoCA; four domains	Total cBF volume	HC—PD AChE+	○	Across PD patients, posterior cBF (Ch4) volume was a predictor of global cognition, memory, and visuospatial function
			PD normocholinergic (AChE+) (94)	64.0 (7.2)	5.3 (3.8)	30.4 (13.6)			HC—PD AChE−	○	
									PD AChE+—PD AChE−	●	
								Anterior cBF (Ch1-2-3) volume	HC—PD AChE+	○	
			PD hypocholinergic (AChE−) (49)	69.0 (7.4)	7.7 (4.8)	37.4 (14.9)			HC—PD AChE−	○	
									PD AChE+—PD AChE−	○	
								Posterior cBF (Ch4) volume	HC—PD AChE+	○	
									HC—PD AChE−	●	
									PD AChE+—PD AChE−	●	
Medium (total n for PD 50–99)	Barrett et al (2021)[d83]	Anatomy Toolbox[e]	PD (97; MoCA > 25)	59.9 (9.8)	*0.3* {0.2–0.6}	–	MoCA; MDS level I	Ch1-2-3 volume	–		Ch4 volume significantly correlated with MoCA score; Ch1-2-3 volume did not
								Ch4 volume	–		
	Batzu et al (2023)[d84]	Kilimann et al (2014)[18]	HC (13)	59.5 (6.1)	–	0.4 (0.7)	MoCA; five domains	cBF volume	HC—LRRK2-UC—iPD—LRRK2-PD	●	Baseline MoCA, executive function, and attention scores were worse for PD than non-PD groups
			LRRK2-UC (13)	59.4 (6.3)	–	1.5 (1.5)					
			De novo iPD (31)	61.8 (9.0)	0.7 (0.6)	25.9 (9.9)			HC—LRRK2-UC	●	
			LRRK2-PD (31)	59.2 (10.3)	3.3 (1.9)	25.2 (13.2)			iPD—LRRK2-PD	●	
	Gang et al (2020)[85]	Anatomy Toolbox[e]	HC (13)	63.0 (4.5)	–	–	MMSE; three domains	Ch4 volume[f]	HC—PD without atrophy	○	Significant differences between PD with and without NBM atrophy for visuoperceptual assessment
			PD (MMSE > 25, CDR 0 or 0.5):						HC—PD with atrophy	●	
			Without NBM (Ch4) atrophy (36)	64.1 (6.0)	4.7 (4.0)	15.4 (7.5)			PD without—PD with atrophy	●	
			With NBM atrophy (20)	67.1 (7.4)	4.7 (4.2)	22.0 (8.7)					

(Continues)

TABLE 1 *Continued*

PD Sample Size[a]	Author (year)	Atlas Used for cBF	Sample Detail: Sample Description (n)[b]	Sample Detail: Age, y, Mean (SD) or *Median* [Range]	Sample Detail: PD Duration, y, Mean (SD) or *Median* [Range] {IQR}	Sample Detail: Motor Severity (UPDRS Part III), Mean (SD) or *Median* [Range] {IQR}	Mental Status Test and n of Neuropsychological Domains[c]	Cross-Sectional Between-Group cBF Differences (● = Significantly "Worse" in Second Group; ○ = Not Significant)			Association with Cognitive Measures
	Gargouri et al (2019)[66]	Manual segmentation[k]	HC (25)	59.8 (8.0)	–	0.6 (0.1)	MMSE; Mattis Dementia Rating Scale; three domains	Ch1-2 FA	HC—PD	○	In PD, Ch1-2 MD and RD correlated with total free recall measure, and MD, AD, and RD correlated with RCFT copy; Ch3-4 MD, AD, and RD correlated with Stroop, and RD correlated with TMT B-A
			PD (52; MMSE > 24)	60.6 (8.8)	8.7 (3.5)	16.4 (8.8)		Ch1-2 MD	HC—PD	●	
								Ch1-2 AD	HC—PD	●	
								Ch1-2 RD	HC—PD	●	
								Ch3-4 FA	HC—PD	○	
								Ch3-4 MD	HC—PD	●	
								Ch3-4 AD	HC—PD	○	
								Ch3-4 RD	HC—PD	●	
	Ray et al (2023)[86]	Kilimann et al (2014)[18]	HC (40)	66.7 (7.6)	–	–	MMSE; MoCA, four domains	Ch1-2 volume	HC—PD-N—PD-CI	○	In PD: Ch1-2 and Ch4 FWF significantly correlated with MoCA and some scores in each cognitive domain; Ch4 cMD significantly correlated with SRM, PAL (TT); Ch4 cAD significantly correlated with MoCA and spatial working memory scores; Ch1-2 cMD significantly correlated with SRM, PAL (MTS); no significant correlations between cAD in Ch1-2 and any cognitive measures
			PD (96)	65.7 (10.7)	0.5 (0.4)	25.1 (10.1)		Ch1-2 FWF	HC—PD-N—PD-CI	○	
			PD-N (MoCA > 25): n = 49; PD-CI (MoCA < 26): n = 41					Ch1-2 cMD	HC—PD-N—PD-CI	○	
								Ch1-2 cAD	HC—PD-N—PD-CI	○	
								Ch4 volume	HC—PD-N—PD-CI	○	
								Ch4 FWF	HC—PD-N—PD-CI	○	
								Ch4 cMD	HC—PD-N—PD-CI	○	
								Ch4 cAD	HC—PD-N	○	
									HC—PD-CI	○	
									PD-N—PD-CI	●	
	Pieperhoff et al (2022)[87]	Anatomy Toolbox[e]	HC (50)	56.9 (12.5)	–	–	MMSE	Ch4 volume	HC—PD	○	Not reported
			PD (50; MMSE > 23)	55.1 (12.1)	3.9 (3.1)	15.4 (11.2)					
	Rong et al (2021)[88]	Anatomy Toolbox[e]	HC (33)	58.4 (7.3)	–	–	MMSE; MoCA, four domains; MDS level I	Ch4 volume	HC—PD-N	●	In PD and in HC, Ch4 volume was not correlated with MMSE, MoCA, or any other assessments
			PD-N (48)	58.6 (7.5)	3.1 (2.3)	26.3 (11.0)			HC—PD-MCI	●	
			PD-MCI (35)	60.4 (8.5)	3.3 (2.6)	28.7 (13.9)			PD-N—PD-MCI	○	
	Wu et al (2023)[89]	FreeSurfer segmentation	HC (82)	59.7 (7.2)	–	–	MMSE; MoCA; four domains	cBF FWF	HC—PD	●	Higher cBF FWF was significantly correlated with TMT-A time, but not other cognitive assessments
			PD (84)	57.8 (8.8)	3.2 [1.1–6.0]	16 [10–26]					

(Continues)

TABLE 1 *Continued*

PD Sample Size[a]	Author (year)	Atlas Used for cBF	Sample Detail: Sample Description (n)[b]	Age, y, Mean (SD) or *Median* [Range]	PD Duration, y, Mean (SD) or *Median* [Range] {IQR}	Motor Severity (UPDRS Part III), Mean (SD) or *Median* [Range] {IQR}	Mental Status Test and n of Neuropsychological Domains[c]	Cross-Sectional Between-Group cBF Differences (● = Significantly "Worse" in Second Group; ○ = Not Significant)			Association with Cognitive Measures
	Zhang et al (2023)[61]	Anatomy Toolbox[e]	HC (33)	63.3 (5.3)	–	–	MMSE; MoCA, five domains; MDS level II	Ch1-2-3 volume	HC—PD-N—PD-MCI	○	Not reported
			PD-N (42)	64.5 (6.9)	2.9 (2.2)	31.2 (13.2)		Ch4 volume	HC—PD-N—PD-MCI	○	
			PD-MCI (24)	65.8 (6.0)	2.8 (2.3)			34.3 (16.8)			
Small (total n for PD < 50)	Berlot et al (2021)[90]	Anatomy Toolbox[e]	HC (20)	66.4 (7.5)	–	–	MMSE; MoCA; three domains; MDS level I	Ch1-2 volume	HC—PD-N	○	In PD, significant association of Ch1-2 volume and RCFT visual memory performance, but not other assessments; no significant relationship between Ch4 volume and any cognitive measure
			PD (14 PD-N, 13 PD-MCI)	68.1 (5.9)	3.0 (1.9) [0.0–7.0]	27 [12–42]			HC—PD-MCI	○	
									PD-N—PD-MCI	○	
								Ch4 volume	HC—PD-N	○	
									HC—PD-MCI	○	
									PD-N—PD-MCI	○	
	Legault-Denis et al (2024)[54]	Anatomy Toolbox[e]	HC (6)	65.8 (7.7)	–	–	Four domains; MDS level II	Ch1-2 volume	HC—PD-CN—PD-xMCI	○	Not reported
			PD-CN (6)	65.3 (6.7)	8.0 (3.2)	27.0 (8.9)		Ch3 volume	HC—PD-CN—PD-xMCI	○	
			PD-xMCI (6)	68.7 (6.5)	8.7 (7.1)	27.5 (10.6)		Ch4a-i volume	HC—PD-CN—PD-xMCI	○	
			PD-xMCI: PD with dysexecutive single-domain MCI					Ch4p volume	HC—PD-CN—PD-xMCI	○	
								Whole BF	HC—PD-CN—PD-xMCI	○	
	Lench et al (2023)[91]	Anatomy Toolbox[e]	PD (33)	63.7 (7.6)	9.2 (4.8)	41.2 (14.5)	NoMoFA; DRS	Ch4 MD Ch4 FA	Not reported		In those with at least one cognitive symptom that worsened in OFF state, found a significant correlation between Ch4 MD and number of cognitive symptoms
	Okkels et al (2023)[92]	Fritz et al (2019)[63]	HC (15)	75 (6)	–	–	MoCA; five domains	Anterior cBF (Ch1-2-3) volume	HC—PD	○	Not reported in PD
			PD without dementia (15)	70 (7)	8.0 (4.0)	32 (10)			HC—DLB	●	
								Posterior cBF (Ch4) volume	HC—PD	○	
			DLB (25)	74 (5)	–	42 (20)			HC—DLB	●	

(Continues)

TABLE 1 *Continued*

PD Sample Size[a]	Author (year)	Atlas Used for cBF	Sample Detail: Sample Description (n)[b]	Sample Detail: Age, y, Mean (SD) or *Median* [Range]	Sample Detail: PD Duration, y, Mean (SD) or *Median* [Range] {IQR}	Sample Detail: Motor Severity (UPDRS Part III), Mean (SD) or *Median* [Range] {IQR}	Mental Status Test and n of Neuropsychological Domains[c]	Cross-Sectional Between-Group cBF Differences (● = Significantly "Worse" in Second Group; ○ = Not Significant)			Association with Cognitive Measures
	Rea et al (2021)[93]	Kilimann et al (2014)[18]	HC (21)	66.3 (7.3)	–	–	None	Ch1-2 volume	HC—PD—non-PD MCI	○	Not reported
			PD (31; non-PDD)	67.8 (6.3)	–	–	MCI criteria as per Albert et al (2011)[94]	Ch4 volume	HC—PD—non-PD MCI	○	
			Non-PD MCI (21)	70 (7.4)	–	–		Ch4p volume	HC—PD—non-PD MCI	○	
	Rogozinski et al (2022)[95]	Kilimann et al (2014)[18]	HC (29)	61.1 (7.5)	–	–	MMSE; FAB	Ch4 volume	HC—PD	●	No significant correlation between MMSE or FAB and Ch4 volume for probable PD (nor probable PSP, nor MSA)
			Probable PD (26)	64.3 (9.2)	5.1 (3.6)	20 (5.5)	PD MMSE range: 25–30		HC—PSP	●	
			Probable PSP (43)	67.4 (4.6)	3.1 (1.5)	23.2 (5.5)			HC—MSA	○	
			MSA (23)	60.4 (6.9)	3.6 (1.7)	23.6 (5)			PD—PSP	○	
								Ch1-2 volume	Not reported		
	Tan et al (2023)[d96]	Anatomy Toolbox[e]	HC (35)	69.1 (5.8)	–	*0* {0–1}	MoCA; five domains	Ch1-2-3 volume	HC—iRBD	○	Ch4 degeneration in iRBD a predictor of worse working memory
			Prodromal PD with iRBD (35)	69.2 (5.7)	–	*3* {2–7}		Ch4 volume	HC—iRBD	●	
	Zhang et al (2020)[97]	Anatomy Toolbox[e]	HC (22)	57.8 (6.4)	–	–	MMSE; MoCA; five domains; MDS level II	Ch4 volume[f]	HC—PD-N—PD-MCI	○	Not reported
			PD-N (22)	61.2 (8.7)	9.1 (3.5)	28.1 (7.8)					
			PD-MCI (22)	63.9 (9.3)	8.1 (2.7)	27.5 (6.2)					

[a]Very large: PD sample > 149; large: PD sample 100–149; medium: PD sample 50–99; small: PD sample < 50.
[b]At baseline if longitudinal study.
[c]Number of domains assessed with at least one test in each domain and MDS level as per MDS PD-MCI Task Force diagnostic criteria for PD-MCI.[98]
[d]Study used Parkinson's Progression Markers Initiative data.
[e]References 62,67-69.
[f]Have not reported undertaking an intracranial volume (ICV) correction for gray matter volume; dashes indicate not reported, or, in the case of PD duration for non-PD patients, not applicable. Results for the most comprehensive reported models have been presented; for longitudinal studies, baseline sample sizes and results have been reported unless noted otherwise; where UPDRS Part III scores were provided both *on* and *off* medication, the *on* score has been reported.
[g]PD-MCI definition at baseline: at least two of six cognitive task scores >1.5 SD below the control sample's mean; at follow-up: complaint by patient or informant (spouse, family member, or friend), at least two of six scores >1 SD below standardized mean, and no functional impairment as a result of cognitive impairment, labeled as "suspected" MCI in publication.
[h]Subtypes were determined using the SuStain machine-learning algorithm with clinical features, neuromelanin-sensitive magnetic resonance imaging of substantia nigra and locus coeruleus, and FWF of amygdala, hippocampus, entorhinal cortex, and basal forebrain as inputs.
[i]Converted after 10 years; baseline results reported.
[j]Maps included those published by Fritz et al,[63] Kilimann et al,[18] Teipel et al,[99] and Zaborszky et al.[62]
[k]Based on histological sections from Fischl et al.[100]
Abbreviations: PD, Parkinson's disease; cBF, cholinergic basal forebrain; SD, standard deviation; IQR, interquartile range; UPDRS, Unified Parkinson's Disease Rating Scale; HC, healthy control; de novo, had not started PD medication; MMSE, Mini Mental State Examination; NBM, nucleus basalis of Meynert; MoCA, Montreal Cognitive Assessment; Ch4a-i, anterior intermediate nucleus Ch4; Ch4p, posterior Ch4; PD-N, Parkinson's disease with normal cognition; PD-MCI, Parkinson's disease with mild cognitive impairment; ROI, region of interest; DRS, Dementia Rating Scale; ET, essential tremor; PD-CRS, Parkinson's Disease–Cognitive Rating Scale; AChE, acetylcholinesterase; MD, mean diffusivity; MCI, mild cognitive impairment; FA, fractional anisotropy; PD-CI, Parkinson's disease with cognitive impairment; FWF, free water fraction; PDD, Parkinson's disease with dementia; LRRK2-UC, LRRK2 unaffected carriers; iPD, idiopathic PD; MDS, Movement Disorder Society; CDR, clinical dementia rating; RD, radial diffusivity; AD, axial diffusivity; RCFT, Rey Complex Figure Test; SRM, Spatial Recognition Memory; PAL (MTS), mean trials to success from Paired Associate Learning tests from CANTAB; TMT-A, Trail Making Test part A; TMT B-A, Trail Making Test B-A; cMD, free water corrected mean diffusivity; PAL (TT), total trials from Paired Associate Learning tests from Cambridge Neuropsychological Test Automated Battery (CANTAB); cAD, free water corrected axial diffusivity; PD-xMCI, PD with dysexecutive single domain Mild Cognitive Impairment; NoMoFA, Non-Motor Fluctuation Assessment Questionnaire; PSP, progressive supranuclear palsy; MSA, multiple system atrophy; FAB, Frontal assessment battery; iRBD, isolated REM sleep behavior disorder.

correlate with the likelihood of finding reduced Ch4 volume in PD (eg, Grothe et al[74] and Zhou et al[78]).

Significant associations of Ch4 volume with continuous measures of cognition have been reported by several studies. These include positive associations with general measures of cognition, such as the MoCA,[74,82,83] and with assessments of specific domains, including visuospatial function (eg, Benton Judgement of Line Orientation Test,[71,82] overlapping figure identification test[85]), attention (various tests including Trail Making Part A, Symbol Digit Modalities Test[71]), and memory (California Verbal Learning Test[82]). However, given there was considerable variance in the effect sizes of the associations reported and given a number of other studies have assessed for, but not found, significant associations with specific cognitive tests or with specific cognitive domains,[81,88,95] analysis of the existing literature does not yield sufficient evidence to stipulate which cognitive domains are associated with cholinergic system disruption in PD and how significant the effect of these associations are.

Patients with PDD have been included as an exclusive group in only one MRI study.[80] Consistent with postmortem evidence, Pereira et al[80] found reduced Ch4 volume in patients with PDD when compared with both control participants and nonimpaired PD patients.

Differential degradation across Ch4 subregions has received little attention. Posterior Ch4 (Ch4p) volume changes reported by Ray et al[76] and Rea et al[93] mirror results for whole Ch4 volume differences between control and PD-CI participants. Additional assessment is required to determine the extent to which subregional degradation is occurring in PD.

Table 2 summarizes the nine studies that have examined longitudinal changes in the cBF in PD and associations with cognition. Additional information on these studies is provided in Table 1. Two approaches have been used to assess Ch4 volume changes in relation to cognitive impairment over time: use of baseline Ch4 volume in relation to future cognition, and repeated assessment of Ch4 volume. Both approaches have provided evidence of reduced Ch4 volume being associated with cognitive decline. Most studies have assessed future cognition in relation to baseline Ch4 volume.[76-78,83-85] Using Parkinson's Progression Markers Initiative (PPMI) data, this approach has provided evidence of baseline Ch4 volume predicting MoCA score after 2 to 4 years in de novo or newly diagnosed patients.[76,83] In addition, differences in general cognition between those with and without reduced baseline integrity after 3 to 5 years have been reported in both PPMI data[77] and novel data.[78] In contrast, longitudinal investigation of Ch4 volume has been limited.[75,80] Using this approach with novel data, Pereira et al[80] did report that greater reductions in Ch4 volume increased the risk of developing dementia over 10 years in PD.

Posterior Basal Forebrain (Ch4) Microstructural Change

Microstructural integrity can be inferred from diffusion-weighted MRI metrics to assess the structural integrity of tissue components. Although much less commonly investigated than macrostructural changes, increased mean and axial diffusivity in Ch4 have been reported in PD-CI patient samples with medium-sized effects (Cohen's d [PD-N—PD-CI] = −0.65 to −0.66).[77,86] Other studies suggest evidence of both increased diffusivity and free water, which is an indication of isotopically unrestricted extracellular water potentially related to neuronal loss and neuroinflammation, has been associated with lower cognitive scores in PD.[66,79,86] An association with changes in fractional anisotropy in Ch4 has not been observed.[66,77,78,86] Through longitudinal assessment, mean diffusivity in Ch4 has demonstrated potential as an indicator of future cognitive impairment.[77]

Anterior Basal Forebrain (Ch1-2 and Ch3) Macrostructural and Microstructural Change

In cross-sectional studies, there is no evidence for a significant reduction in anterior cBF (Ch1-2-3) volume in PD, and no associations with cognitive assessment scores have been reported.[61,76,80,86,90,93,96] Where Ch4 volume reductions have been reported, corresponding analysis of anterior cBF regions has shown no reductions.[76,80,82,96] Only one study, in a PD sample with no or minimal cognitive impairment (MMSE > 24), reported worse Ch1-2 microstructural integrity, which was based on evidence of increased mean, axial, and radial diffusivity in these regions.[66]

When assessed over 10 years, patients with PDD and PDD-converters had greater Ch1-2 atrophy compared with patients with PD whose cognitive impairment remained stable.[80] However, anterior cBF degeneration has not been seen longitudinally in PD patients without cognitive impairment.[76,83] The Ch3 region, encompassed in the hlDBB, has been assessed only when included with the Ch1 and Ch2 regions.[28]

Structural Assessment of cBF Projections in PD

Any reduction in the structural integrity of axonal projections from cBF neurons will have a considerable impact on the maintenance of normal cholinergic system function (Fig. 3). A more detailed examination of cBF axonal projections is now possible with the application of advanced diffusion tractography methods. Studies on normal aging and in Alzheimer's disease indicate initial cholinergic system degradation may preferentially occur in these axonal projections rather than in the cBF cell clusters.[22,101,102] Moreover, the structural integrity of

TABLE 2 *Longitudinal studies on cholinergic basal forebrain integrity and cognition in Parkinson's disease*

Author, Year	Baseline Sample Description Summary of Longitudinal Results
Barrett et al, 2021[a83]	97 PD (MoCA > 25) Ch4 volume was significantly correlated with rate of change in MoCA score after 4 years of follow-up, but not Ch1-2-3 volume
Batzu et al, 2023[a84]	13 HCs, 13 LRRK2-UC, 31 LRRK2-PD, 31 de novo iPD After 2- and 4-year follow-up, iPD group cBF volume predicted changes in global cognition, memory, and executive function, but this effect was not seen for LRRK2-UC or LRRK2-PD groups. In addition, cBF volume was a significant mediator of differential longitudinal changes in memory and global cognition (MoCA) over 4 years between LRRK2-PD and iPD groups
Gang et al, 2020[85]	13 HCs, 36 without baseline NBM atrophy, 20 with baseline NBM atrophy Significant differences in MMSE and visuoperceptual assessment between PD with and without NBM atrophy after 3 years
Labrador-Espinosa et al, 2023[a75]	56 HCs, 162 de novo PD Four-year follow-up: cBF volume significantly reduced in PD patients, but not in HCs
Pereira et al, 2020[80]	42 HCs, 86 PD-stable, 20 PDD-converters, 19 PDD PD patients with greater Ch4 atrophy over time were at greater risk of developing dementia over 10 years. PDD-converters and PDD patients had greater Ch1-2 atrophy over time compared with PD-stable patients and control subjects
Ray et al, 2018[a76]	76 HCs, 168 de novo PD In PD, Ch4 and Ch4p volumes were significant predictors of MoCA score after 3 years. Smaller than expected (from control range) Ch4 volume independently increased risk of MCI or PDD diagnosis for those without suspected MCI (n = 112) at baseline.
Ray et al, 2023[86]	40 HCs, 96 PD Baseline Ch4 volume associated with change in MoCA, an executive function measure and memory measures, baseline Ch4 FWF associated with change in MMSE and an attention measure, baseline Ch4 cAD with change in an attention measure, baseline Ch1-2 volume associated with change in MMSE, executive function, memory and attention measures, and baseline Ch1-2 FWF with an executive function and an attention measure at 4.5 years
Schulz et al, 2018[a77]	167 HCs, 304 de novo PD (232 PD-N, 72 PD-MCI) In PD, baseline Ch4 volume and MD were significant predictors of cognitive impairment at 3-year follow-up
Zhou et al, 2023[78]	119 HCs, 216 PD (114 subtype 1, 102 subtype 2) Similar progression of cognitive impairment between the two subtypes over 5-year follow-up (subtype 2 had significantly worse cognition and significantly higher FWF at baseline)

Studies have been ordered alphabetically.
[a]Study used Parkinson's Progression Markers Initiative data.
Abbreviations: PD, Parkinson's disease; MoCA, Montreal Cognitive Assessment; HC, healthy control; LRRK2-UC, LRRK2 unaffected carriers; iPD, idiopathic Parkinson's disease; cBF, cholinergic basal forebrain; NBM, nucleus basalis of Meynert; MMSE, Mini Mental State Examination; PDD, Parkinson's disease dementia; MCI, mild cognitive impairment; cAD, free water corrected axial diffusivity; FWF, free water fraction; PD-N, Parkinson's disease with normal cognition; PD-MCI, Parkinson's disease with mild cognitive impairment; MD, mean diffusivity.

cBF projections appear to be more strongly associated with cognitive function than are structural changes within the cBF.[103,104]

Five studies have considered the integrity of projections from Ch4 in PD. Hepp et al[105] and Nazmuddin et al[106] both examined medial and lateral cholinergic pathways from Ch4 using seed regions of interest.[22,33,107] They reported worse projection integrity in PD patients with postural instability and gait disorder subtype than in control participants[106] and in PD patients experiencing visual hallucinations.[105] However, neither study assessed cognition. Crockett et al[108] examined the association between medial and lateral tracts from Ch4 and cognitive function in a sample of 37 PD patients and found those who converted to PD-MCI at 1-year follow-up (n = 16) had worse baseline mean diffusivity in both tracts.

In addition, significant associations were found with some cognitive measures, but these did not survive correction for multiple comparisons. Wu et al[89] found that the free water fraction (FWF) increased in fiber tracts connecting the cBF to the occipital, parietal, and prefrontal cortices in 84 PD participants compared with controls, but FWF was not increased in projections to the limbic, sensorimotor, temporal, and peri-insular cortices. Interestingly, none of these FWF increases were associated with cognitive measures. In addition, Gargouri et al[66] considered the density of fiber tracts, a measure of the probability of fiber tracts connecting two regions, from Ch3-4 to various cortical regions. They reported a decreased probability of tract density in the tracts connecting Ch3-4 with the associative prefrontal, occipital, and peri-insular cortices in PD. Connection density in the tract connecting with the prefrontal cortex was positively associated with general cognitive (MMSE) scores.

Discussion

The contribution of the cBF to cognitive impairment in PD may be more nuanced than often anticipated, especially in the initial stage of cognitive decline. Structural cholinergic integrity may depend on several factors, including functional cholinergic changes, structural or functional changes affecting adjacent neuromodulatory functions, and resulting, potentially highly intricate, brain system- and network-level alterations. The strongest evidence, provided by reduced cortical AChE and VChAT activity measured using PET, has been for functional cholinergic changes in PD,[49,50] which appear to be widespread in PDD.[16,48] Emerging work indicates an association between cBF structural integrity and neocortical cholinergic innervation, with evidence of a relation with Ch4 volume, but not anterior cBF volume, in PD patients without dementia,[82,92] with whole cBF FWF,[56] and with Ch4p volume.[81] Further investigation of associations between cBF structural integrity, cortical cholinergic activity, and cognitive function will greatly enhance our understanding of how structural and functional cholinergic system changes develop as cognitive impairment progresses in PD. Alterations to brainstem cholinergic structures, the pedunculopontine and laterodorsal tegmental nuclei, and projections from these nuclei, especially those to multiple regions of the thalamus and all basal ganglia components, are also likely to be contributing.[109-111]

The heterogeneity of cholinergic alterations across subgroups of patients with PD deserves further attention. A distinct cholinergic phenotype may exist, potentially distinguishing those with MCI who progress to dementia.[7,17,112] Features of PD that are refractory to dopaminergic therapy are often able to be attributed to cholinergic function, indicating the hypothesis of cholinergic involvement in cognitive impairment in PD is well founded.[8,109] However, although acetylcholine is prospectively the primary neurotransmitter modulating cognitive function in the majority of the cerebral cortex and is implicated in impairment in all cognitive domains in PDD, dopaminergic and noradrenergic input to the prefrontal cortex has been proposed to predominate modulation that affects executive function.[113] As such, investigation of structural changes associated with cognitive impairment in PD would likely benefit from a network-level approach rather than consideration of a single neurotransmitter system.[113] In addition, evidence suggests the extent of cholinergic system involvement in PD may be influenced by genetic risk factors, with changes more prevalent in patients presenting with a GBA1 mutation than those with idiopathic PD or a LRRK2 mutation.[114] It is also important to bear in mind disease-related pathology is occurring alongside age-related changes, and the disentanglement of the effect of each is a notable limitation in the investigation of any neurotransmitter or network involvement in PD-related cognitive impairment.[23,115,116]

Although there are several limitations in using MRI to assess cBF structural integrity in vivo, perhaps the most significant is the spatial resolution of most available imaging data. Prospective use of higher-field-strength MRI will offer greater resolution, better definition, and allow for improved accuracy of cBF atlas placement. This offers hope for improved precision of in vivo cBF structural integrity measurement in the future.[117]

Clinical Implications

Identification of cortical cholinergic system structural changes that consistently associate with PD-related cognitive impairment has the potential to inform diagnosis and prognosis, and allow for individualized targeting of treatment. In vivo assessment of cBF volume using MRI may provide the most accessible method of identifying such changes. Treatment may be most effective before extensive degradation of cBF structures has occurred, highlighting a need for an accessible clinical pathway for identifying changes.

Direct deep brain stimulation (DBS) of the NBM has shown potential therapeutic benefit for those with PDD, although with considerable variability.[118,119] However, evidence suggests NBM volume is a strong predictor of the efficacy of subthalamic nucleus DBS,[120] an established treatment for motor symptoms in PD that may have a neuroprotective effect.[121-123] In addition, cholinomimetics may have some efficacy before PD-MCI where cBF structural changes can be identified, but before widespread structural changes have occurred.[124,125]

Conclusions

Evaluation of the contribution of cBF structural integrity to cognitive impairment in PD has seen increasing attention. Postmortem histological analysis

and cholinergic PET indicate loss of Ch4 neurons and increased cortical cholinergic denervation in PDD. Cross-sectional in vivo antemortem evidence suggests an effect of reduced Ch4 volume, but not anterior cBF volume, in PD-CI patients, when compared with unimpaired patients. Longitudinal in vivo assessment has indicated Ch4 volume may be a predictor of future decline.

A more comprehensive understanding of the relationship between cholinergic system degeneration and regression of cognitive ability in PD is needed. This may derive from opportunities to evaluate cBF projection axons, elucidate differential Ch4 subregional involvement, and further investigate longitudinal effects of reduced cBF integrity, alongside investigation of functional cholinergic system changes.[8,126] In addition, although there is no clear evidence of benefit before dementia in PD, the prospective utility of cholinomimetics in amelioration of cholinergic function highlights the potential utility of accessible in vivo biomarkers. Such biomarkers may be crucial for accurate targeting of cholinomimetic treatments for cognitive impairment in PD. ■

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Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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Author Roles

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