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In vivo cholinergic basal forebrain degeneration and cognition in Parkinson's disease: Imaging results from the COPPADIS study

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ABSTRACT

Introduction: We aimed to assess associations between multimodal neuroimaging measures of cholinergic basal forebrain (CBF) integrity and cognition in Parkinson's disease (PD) without dementia.
Methods: The study included a total of 180 non-demented PD patients and 45 healthy controls, who underwent structural MRI acquisitions and standardized neurocognitive assessment through the PD-Cognitive Rating Scale (PD-CRS) within the multicentric COPPADIS-2015 study. A subset of 73 patients also had Diffusion Tensor Imaging (DTI) acquisitions. Volumetric and microstructural (mean diffusivity, MD) indices of CBF degeneration were automatically extracted using a stereotactic CBF atlas. For comparison, we also assessed multimodal indices of hippocampal degeneration. Associations between imaging measures and cognitive performance were assessed using linear models.
Results: Compared to controls, CBF volume was not significantly reduced in PD patients as a group. However, across PD patients lower CBF volume was significantly associated with lower global cognition (PD-CRS_{total}:

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$r = 0.37$, $p < 0.001$), and this association remained significant after controlling for several potential confounding variables ($p = 0.004$). Analysis of individual item scores showed that this association spanned executive and memory domains. No analogue cognition associations were observed for CBF MD. In covariate-controlled models, hippocampal volume was not associated with cognition in PD, but there was a significant association for hippocampal MD ($p = 0.02$).

Conclusions: Early cognitive deficits in PD without dementia are more closely related to structural MRI measures of CBF degeneration than hippocampal degeneration. In our multicentric imaging acquisitions, DTI-based diffusion measures in the CBF were inferior to standard volumetric assessments for capturing cognition-relevant changes in non-demented PD.

1. Introduction

Although Parkinson's disease (PD) is primarily perceived as a movement disorder, progressive cognitive deficits typically emerge as the disease progresses, eventually resulting in a characteristic PD-associated dementia syndrome [1]. In recent years, structural neuroimaging proxies of cholinergic system integrity could provide indirect in vivo evidence for the critical role of cholinergic degeneration in PD-associated cognitive decline [2]. Although the cholinergic nuclei are not directly visible on structural MRI contrasts, volumetric analysis of regions-of-interest (ROI) focussed on the cholinergic basal forebrain (CBF) revealed marked atrophy of this region in both PD dementia (PDD) and pathologically related dementia with Lewy bodies (DLB) [3–6]. However, CBF degeneration in the predementia phase of PD and its relevance for the emergence of subtle cognitive deficits is less well explored. A previous manual volumetry study found reduced CBF volumes in PD patients with mild cognitive impairment (PD-MCI) to be predictive of progression to dementia [7], but others found no differences between PD-MCI and PD with normal cognition at the group level [4].

More recent studies used automated CBF morphometry techniques based on stereotactic mappings of the cholinergic nuclei that may provide a more comprehensive, and potentially more sensitive, in vivo analysis of CBF degeneration [5,8–11]. Using this approach it could be demonstrated that although CBF volumes were not significantly reduced in de novo PD patients as a group, reduced CBF volumes could be detected in a subset of patients [9,10]. These patients also showed a significantly increased risk for imminent cognitive decline, suggesting that cognition-relevant changes in CBF volume are already present at this early disease stage.

In addition to the recent in vivo research on CBF degeneration in PD, previous neuroimaging studies had implicated other cognition-relevant brain structures in PD-related cognitive impairments, particularly the hippocampal memory system [12–14], and the relative contributions of these different neuroanatomic systems to cognitive decline in PD remain largely unknown. Moreover, recent multimodal MRI studies indicated that microstructural diffusion alterations as measured by diffusion tensor imaging (DTI) may be more sensitive markers of cognition-relevant neurodegenerative processes in PD compared to volumetric measurements on structural MRI [11,14,15].

In the present study we aimed to comprehensively assess the relation of MRI-measured CBF and hippocampal volumes with cognitive differences in a well-characterized multicentric cohort of non-demented PD patients, and to further explore the utility of DTI-based diffusion alterations for detecting cognition-relevant tissue changes in these structures.

2. Methods

2.1. Participants

This study included a total of 180 non-demented PD patients and 45 healthy controls from the COPPADIS-2015 (Cohort of Patients with Parkinson's Disease in Spain, 2015) cohort. COPPADIS-2015 is an ongoing prospective, multi-center, non-interventional, long-term study on PD progression that includes detailed clinical evaluations as well as assessments of serum biomarkers, genetics, and neuroimaging data [16]. The participants selected for the current cross-sectional study correspond to a subset of COPPADIS-2015 participants from five different centers who underwent a 3D T1-weighted structural MRI scan at the baseline evaluation. A subsample of 73 PD patients also underwent a baseline DTI acquisition. Patients were excluded if they met screening criteria for dementia (Mini Mental State Examination (MMSE) < 26 and inability of performing basic activities of daily living as determined by clinical interview). Detailed inclusion and exclusion criteria for the COPPADIS-2015 study have been detailed before [16] and are summarized in the supplement.

This study was approved by the local ethics committees on human experimentation of the different participating centers. Written informed consent was obtained from all subjects participating in this study.

2.2. Clinical and neuropsychometric evaluation

Disease stage and motor symptom severity were evaluated by the Hoehn and Yahr (H&Y) scale and the Unified Parkinson's Disease Rating Scale-Part III (UPDRS-III), both assessed in "off" condition.

Neuropsychological performance was evaluated in "on" condition using the Parkinson's Disease – Cognitive Rating Scale (PD-CRS) [17], including individual item scores for tests of sustained attention, working memory, alternating and action verbal fluency, immediate and delayed verbal memory, naming, as well as drawing and copy of a clock. Although all patients were non-demented according to clinical screening criteria, eight patients had PD-CRS total scores ≤ 64 indicative of dementia-level cognitive impairment [17] and were excluded from further analyses.

2.3. MRI acquisition

Structural MRI data were acquired on different clinical MRI scanners (one 1.5 T and four 3 T machines) using scanner-specific 3D T1-weighted structural imaging sequences with approximately 1 mm isotropic spatial resolution. For a subsample of the PD patients scanned on 3 T MRI scanners additional diffusion-weighted images were acquired using scanner-specific echo-planar imaging sequences. Detailed center-specific acquisition parameters for the T1-and diffusion-weighted scans are listed in Supplementary Table 1. Average time between MRI acquisition and cognitive evaluation was 75 ± 67 days (IQR: 24–104 days).

2.4. Processing and analysis of structural MRI and DTI data

Automated CBF and hippocampus volumetry on T1-weighted structural MRI scans followed procedures that have been described in detail previously [5,9,18,19], and were implemented using statistical parametric mapping software (SPM12, Wellcome Trust Center for Neuroimaging) and the CAT-toolbox (http://www.neuro.uni-jena.de/cat/) implemented in Matlab R2018a (MathWorks, Natick, MA, USA). Briefly, MRI scans were segmented into gray matter (GM), white matter, and

cerebrospinal fluid partitions and high-dimensionally registered to Montreal Neurological Institute (MNI) standard space using the highly accurate DARTEL algorithm [18,19]. GM volumes of the CBF and hippocampus were then automatically extracted by summing up the modulated GM voxel values within respective ROIs in MNI standard space. The total intracranial volume (TIV), as a measure of head size, was calculated as the sum of total volumes of the GM, white matter, and cerebrospinal fluid partitions [19].

The CBF ROI was based on our previous methodological study characterizing functionally homogeneous subdivisions within the human CBF as defined by combined information from existing stereotactic atlases of basal forebrain cholinergic nuclei in MNI space [20]. In our primary analyses we used the total anatomic CBF space as an overall measure of CBF degeneration, but in secondary analyses we also considered the functionally-defined anterior-medial (aCBF) and posterior-lateral (pCBF) subdivisions separately (Supplementary Fig. S1). The hippocampus ROI was based on a recently developed MNI standard space template of international consensus criteria for hippocampus outlines on structural MRI [18].

Processing of DTI data was implemented using the DTI toolbox of FSL (Version 5.0, FMRIB, Oxford, UK), and included correction for eddy current effects and head motion, skull stripping, and fitting of diffusion tensors to the data to derive scalar maps of mean diffusivity (MD). MD maps were spatially normalized to MNI standard space using the deformation fields derived from normalization of the co-registered T1-weighted MRI scans. Individual CBF and hippocampal MD indices were calculated by extracting average voxel values within the respective ROIs from the normalized MD maps [11].

All images passed initial visual quality assessments for gross image artefacts, as well as subsequent assessments of overall tissue type segmentation and global spatial normalization accuracy. Mean absolute and relative inter-volume head displacement during the DTI acquisitions were 1.76 ± 2.04 mm and 0.61 ± 0.71 mm, respectively.

2.5. Statistical analysis

Differences in ROI volumes between groups were assessed with analysis of covariance (ANCOVA) models controlled for acquisition site, TIV, age, sex, and education. Associations of volumetric and diffusivity indices of CBF degeneration with cognitive deficits in PD were assessed using linear regression models with PD-CRS total score ($PD\text{-}CRS_{total}$) as the primary outcome. Separate linear regression models were calculated for CBF volume and CBF MD as predictor variables, and for significant models the added value of combining volumetric and microstructural information was assessed in combined multimodal regression models. Secondary analyses assessed the domain specificity of CBF-cognition associations across individual PD-CRS item scores, as well as the regional specificity of the cognition associations across aCBF and pCBF subdivisions. All regression models were controlled for acquisition site, and TIV in the case of volumetric measures, and the robustness of significant CBF-cognition associations was assessed in additional models further controlling for several potential confounding variables, including age, sex, education, disease duration, motor symptom severity (UPDRS-III scores), total levodopa equivalent doses, and offset between MRI acquisition and cognitive evaluation. Analogous models were calculated using volumetric and diffusivity indices of hippocampal degeneration. In a complementary analysis we additionally assessed associations between neuroimaging markers and cognition separately for each acquisition site, followed by a meta-analysis of the center-specific outcomes (see supplementary material). Statistical analyses were performed using the computing environment R (version 3.5.1). Following recommendations described in the statistical literature [21], we primarily report uncorrected p-values in this hypothesis-driven study with a limited number of planned comparisons focused on the association between neuroimaging measures of CBF degeneration and cognitive deficits in PD. However, for transparency we also report p-values corrected using the False Discovery Rate (FDR).

Table 1
Sample characteristics.

	HC (N = 45)	PD (N = 180)	Cohen's *d*	Group Difference Statistic value (*P* value)
Demographics				
Sex (M/F)	30/15	113/67		$X^2 = 0.10$ (0.755)
Age, years	59.4 (5.7)	61.7 (9.6)	−0.26	$t = -2.07$ (0.041)
Education (primary/secondary/university)	14/19/12	95/44/41		$X^2 = 7.78$ (0.020)
Clinical variables				
Age at onset, years		57.6 (10.1)		
Disease duration, years		4.5 (4.3)		
UPDRS-III "Off" score		21.1 (10.1)		
Hoehn & Yahr stage		2 (2–2)		
Anticholinergic treatment (No/Yes)		175/5		
Total levodopa equivalent doses		517 (430)		
Cognitive characteristics				
Total MMSE	29.7 (0.5)	29.5 (0.8)	0.33	$t = 2.57$ (0.012)
Total PD-CRS	100.1 (8.3)	94.4 (13.2)	0.45	$t = 3.57$ (0.001)
Fronto-subcortical items				
Immediate verbal memory	8.3 (1.4)	7.6 (1.9)	0.36	$t = 2.57$ (0.012)
Sustained attention	9.3 (0.8)	8.8 (1.6)	0.37	$t = 3.15$ (0.002)
Working memory	8.4 (1.5)	8.0 (1.8)	0.26	$t = 1.70$ (0.093)
Clock copy	9.9 (0.3)	9.6 (0.8)	0.40	$t = 3.71$ (<0.001)
Delayed verbal memory	5.2 (1.9)	4.9 (2.6)	0.14	$t = 0.98$ (0.328)
Alternating verbal fluency	12.9 (3.5)	11.8 (3.8)	0.31	$t = 1.94$ (0.057)
Action verbal fluency	16.4 (4.2)	15.2 (5.5)	0.22	$t = 1.53$ (0.129)
Posterior-cortical items				
Naming	19.8 (0.5)	19.3 (1.6)	0.37	$t = 3.75$ (<0.001)
Clock drawing	9.8 (0.4)	9.3 (1.6)	0.38	$t = 4.19$ (<0.001)
Regional MRI Volumes				
Cholinergic basal forebrain	585.9 (45.9)	587.9 (49.4)	−0.04	$F = 0.0002$ (0.988)
Hippocampus	1151.1 (121.1)	1150.6 (118.4)	0.003	$F = 0.14$ (0.71)

The descriptive values presented are: number for categorical variables; median (IQR) for Hoehn & Yahr stage; and mean (standard deviation) for all other continuous variables. Statistic values correspond to chi-squared test for categorical variables, *t*-test for continuous variables, and ANCOVA models controlled for acquisition site, TIV, sex, age and education for regional MRI volumes. Disease duration was defined as the time passed since initial symptoms were noticed by the patient, irrespective of the time of clinical diagnosis.
Abbreviations: HC = Healthy controls; PD = Parkinson's disease; TIV = Intracranial volume; MMSE = Mini Mental State Examination; UPDRS-III = Unified Parkinson's Disease Rating Scale-Part III; PD-CRS = PD-Cognitive Rating Scale.

3. Results

3.1. Patient characteristics

Demographic and clinical characteristics of the participants are detailed in Table 1. Although all PD patients were non-demented by inclusion criteria, they showed a large variability in global cognitive performance (PD-CRS$_{total}$: mean = 94 ± 13, range = 68–135). According to a previously established cut-off of PD-CRS$_{total}$ ≤ 81 [17], 34 patients (19%) would classify for a categorisation as PD-MCI.

In covariate-controlled comparisons to the healthy controls, neither CBF nor hippocampal volume was significantly reduced in the PD group as a whole (p > 0.71).

3.2. MRI-measured cholinergic basal forebrain and hippocampus volume in relation to cognition in PD

Table 2 summarizes the results of linear regression models for the association of CBF and hippocampus volume with PD-CRS scores. After accounting for TIV and acquisition site, lower CBF volume was significantly associated with lower PD-CRS$_{total}$ ($r_{partial}$ = 0.37, p < 0.001), and this association also remained significant after controlling for confounding variables (p = 0.004). Among individual PD-CRS item scores, CBF volume was most strongly associated with immediate memory, but covariate-controlled models were also significant for delayed memory, working memory, and alternating verbal fluency. In subregion-specific analyses all associations were slightly more pronounced for the pCBF than for the aCBF, but none of the differences were statistically significant (p > 0.83; Supplementary Table S2).

In the basic regression models (only controlling for TIV and acquisition site) hippocampal volume was also associated with PD-CRS$_{total}$ ($r_{partial}$ = 0.24, p = 0.002) and particularly with delayed and immediate verbal memory scores, but none of these associations remained significant in the fully covariate-controlled model (Table 2).

For comparison, we also assessed associations of CBF and hippocampus volumes with cognitive performance in the healthy control group using identical linear regression models. In analyses controlled for TIV and acquisition center, neither PD-CRS total score nor any of the individual item scores were significantly associated with CBF or hippocampal volume in this group (p > 0.18).

3.3. DTI-based diffusion measures of cholinergic basal forebrain and hippocampal integrity in relation to cognition in PD

In the subsample with DTI data, CBF volume showed a comparable association with PD-CRS$_{total}$ as in the full sample (Fig. 1A; Supplementary Table S3), but CBF MD was not significantly associated with PD-CRS$_{total}$ (Fig. 1C, Table 3; $r_{partial}$ = −0.10, p = 0.42) or any individual item scores (Table 3). Combining both volumetric and diffusivity measurements of CBF integrity into a multimodal regression model for PD-CRS$_{total}$ did not increase the fit compared to the model based on CBF volume alone (ΔR^2=0.003, p = 0.60).

Associations between hippocampal volume and PD-CRS scores remained nonsignificant in the subsample with available DTI data (Fig. 1B; Supplementary Table S3), but hippocampal MD did show a significant association with PD-CRS$_{total}$ ($r_{partial}$ = −0.43, p < 0.001; Fig. 1D), which also remained significant in fully covariate-controlled models (p = 0.02), and was mainly driven by associations with alternating verbal fluency scores (Table 3). Combining volumetric and diffusivity measurements of hippocampus integrity into a multimodal regression model for PD-CRS$_{total}$ did not significantly increase the fit compared to the model based on hippocampal MD alone (ΔR^2=0.034, p = 0.23).

Table 2
Linear model stats for the association of volumetric imaging markers with cognitive scores.

Cognitive scores	Volume					
	Cholinergic Basal Forebrain			Hippocampus		
	Part. r	T value (P value)	P(FDR)	Part. r	T value (P value)	P (FDR)
PD-CRS$_{total}$	0.37	5.20 (<0.001)	<0.001	0.24	3.20 (0.002)	0.002
	0.22	2.91 (0.004)	0.012	0.05	0.61 (0.541)	0.541
Fronto-subcortical items						
Sustained attention	0.19	2.48 (0.014)	0.016	0.13	1.70 (0.091)	0.102
	0.10	1.25 (0.214)	0.244			
Working memory	0.33	4.56 (<0.001)	<0.001	0.18	2.41 (0.017)	0.028
	0.19	2.49 (0.014)	0.054	−0.01	−0.08 (0.94)	0.94
Clock drawing	0.2	2.75 (0.007)	0.01	0.18	2.41 (0.017)	0.028
	0.10	1.33 (0.184)	0.244	0.06	0.81 (0.417)	0.488
Alternating verbal fluency	0.27	3.75 (<0.001)	0.001	0.18	2.37 (0.019)	0.028
	0.15	2.00 (0.047)	0.094	0.06	0.81 (0.418)	0.488
Action verbal fluency	0.20	2.70 (0.008)	0.01	0.02	0.32 (0.747)	0.747
	0.09	1.14 (0.257)	0.257			
Immediate verbal memory	0.37	5.27 (<0.001)	<0.001	0.27	3.66 (<0.001)	0.001
	0.28	3.69 (<0.001)	0.002	0.15	1.96 (0.052)	0.26
Delayed verbal memory	0.31	4.29 (<0.001)	<0.001	0.29	3.95 (<0.001)	0.001
	0.17	2.22 (0.027)	0.073	0.14	1.8 (0.074)	0.26
Posterior-cortical items						
Naming	0.05	0.59 (0.554)	0.554	0.16	2.07 (0.04)	0.052
				0.08	1.03 (0.306)	0.488
Clock copy	0.23	3.16 (0.002)	0.003	0.23	3.16 (0.002)	0.006
	0.10	1.32 (0.19)	0.244	0.10	1.24 (0.218)	0.488

Linear model stats are presented as (partial) r and T value (P value). For each cognitive item score, results from single predictor linear regression models (controlled for acquisition site and TIV) are indicated in the first row, and for significant models fully covariate-controlled regression results are indicated in the second row.
Abbreviations: PD-CRS = PD-Cognitive Rating Scale.

4. Discussion

In this study we analyzed multimodal neuroimaging measures of CBF degeneration in relation to cognitive performance in a well-characterized multicentric sample of PD patients without dementia, and further assessed the specificity of the CBF-cognition associations in relation to imaging markers of hippocampal degeneration. We found that lower cognitive performance among PD patients was robustly associated with structural MRI-based volume measures of CBF degeneration, but not with volumetric measures of hippocampal degeneration. In a subset analysis of DTI data, diffusivity measures of the CBF were not associated with cognition, but diffusivity measures of the hippocampus were more sensitive to cognition-relevant tissue changes than hippocampal volume.

While severe CBF degeneration is an established neuropathologic feature of dementia in PD that can be readily detected on structural MRI

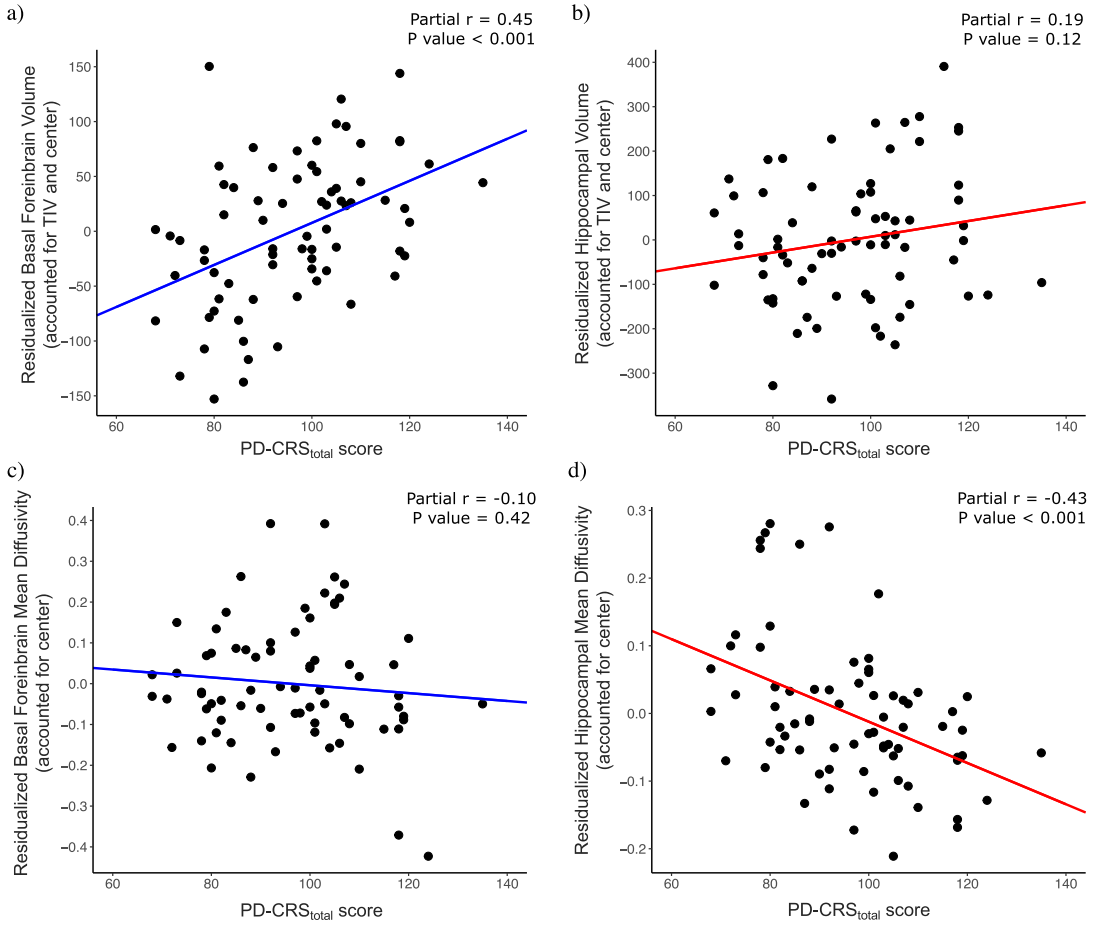

Fig. 1. Associations of volumetric and diffusion-based imaging markers with PD-CRS total scores. (A) Residualized cholinergic basal forebrain volume accounted for TIV and acquisition site plotted against PD-CRS$_{total}$ score. (B) Residualized cholinergic basal forebrain mean diffusivity accounted for acquisition site plotted against PD-CRS$_{total}$ score. (C) Residualized hippocampal volume accounted for TIV and acquisition site plotted against PD-CRS$_{total}$ score. (D) Residualized hippocampal mean diffusivity accounted for acquisition site plotted against PD-CRS$_{total}$ score. For visualization purposes mean diffusivity scores were scaled by a factor of 1000. For better comparability between volumetric and diffusion-based imaging markers, all imaging-cognition associations were plotted for the subset of PD patients who had both imaging modalities available.

scans, the degree to which CBF degeneration also relates to more subtle cognitive deficits that emerge in the predementia phase of PD is less well known [2–5,22]. A previous study on the de novo PD cohort of the Parkinson's Progression Marker Initiative (PPMI) did not observe significant differences in MRI-measured CBF volume between healthy controls and the PD group as a whole, but found reduced CBF volume in a subset of PD patients, and these were at a significantly higher risk for future cognitive decline [9]. A subsequent study further showed that lower CBF volume was also associated with worse cognitive performance in non-demented PD patients at a cross-sectional level [10]. Here we add further evidence for a robust association between MRI-measured CBF volume and cognitive performance in PD without dementia by analysing an independent, multicentric sample of well-characterized PD patients and using strict control of several possible confounding variables.

Analysis of the individual item scores of the PD-CRS battery revealed that CBF volume was associated with performance in several neuropsychological functions including both executive and memory domains. This is partly in contrast to predictions from the "dual syndrome hypothesis", which states that the cholinergic deficit in PD may be more closely associated with impairments in mnemonic and visuospatial functions, as compared to more dopamine-dependent executive dysfunctions [1]. Similar to our present findings, previous PET-based imaging studies of cholinergic degeneration in non-demented PD found that cortical cholinergic denervation was associated with reduced performance in several cognitive domains, including attention, executive function, and memory, but not with visuospatial function [23,24]. It could be possible that the relative influence of CBF degeneration on domain-specific cognitive functions may change over the course of disease, where effects on typical cognitive measures of visuospatial performance may only become apparent at more severe degrees of cholinergic degeneration and closer to the time of dementia diagnosis.

A striking finding of our study is that, in contrast to CBF volume, hippocampal volume did not show robust associations with cognition after controlling for confounding variables that are likely to mediate such an association, particularly age and disease severity. Several previous structural MRI studies had reported hippocampal atrophy in PD patients with cognitive impairment and particularly in PDD [12,13]. However, studies investigating the implication of the hippocampus in cognitive impairments among non-demented PD patients have produced mixed results, and a recent meta-analysis of structural MRI findings could confirm significant hippocampus atrophy in PDD but not in PD-MCI [25]. Our combined assessment of hippocampal and CBF volume in the same study sample of non-demented PD patients indicates that cognitive deficits at this stage more closely relate to CBF atrophy than to hippocampal atrophy. Macroscopic hippocampal atrophy as

Table 3
Linear model stats for the association of diffusivity imaging markers with cognitive scores.

Cognitive scores	Mean Diffusivity					
	Cholinergic Basal Forebrain			Hippocampus		
	Part. r	T value (P value)	P (FDR)	Part. r	T value (P value)	P(FDR)
PD-CRS$_{total}$	−0.10	−0.82 (0.418)	0.418	−0.43	−3.98 (<0.001)	<0.001
				−0.29	−2.40 (0.02)	0.029
Fronto-subcortical items						
Sustained attention	0.01	0.05 (0.958)	0.958	0.02	0.20 (0.843)	0.843
Working memory	−0.10	−0.84 (0.404)	0.95	−0.26	−2.22 (0.030)	0.049
				−0.01	−0.08 (0.939)	0.94
Clock drawing	−0.08	−0.63 (0.528)	0.95	−0.26	−2.27 (0.026)	0.049
				−0.15	−1.17 (0.247)	0.371
Alternating verbal fluency	0.04	0.37 (0.710)	0.958	−0.49	−4.72 (<0.001)	<0.001
				−0.44	−3.90 (<0.001)	0.001
Action verbal fluency	−0.01	−0.10 (0.924)	0.958	−0.30	−2.58 (0.012)	0.036
				−0.20	−1.63 (0.108)	0.323
Immediate verbal memory	−0.24	−2.01 (0.048)	0.216	−0.18	−1.53 (0.131)	0.147
	−0.14	−1.10 (0.274)	0.274			
Delayed verbal memory	−0.27	−2.37 (0.021)	0.186	−0.25	−2.18 (0.033)	0.049
	−0.14	−1.14 (0.257)	0.274	−0.03	−0.24 (0.812)	0.94
Posterior-cortical items						
Naming	−0.02	−0.20 (0.846)	0.958	−0.21	−1.80 (0.077)	0.099
Clock copy	−0.09	−0.77 (0.445)	0.95	−0.32	−2.85 (0.006)	0.026
				−0.18	−1.42 (0.161)	0.323

Linear model stats are presented as (partial) r and T value (P value). For each cognitive item score, results from single predictor linear regression models (controlled for acquisition site) are indicated in the first row, and for significant models fully covariate-controlled regression results are indicated in the second row.
Abbreviations: PD-CRS = PD-Cognitive Rating Scale.

measured by volumetric changes on MRI may only occur at a later stage of PD-related cognitive decline.

However, more subtle neuroimaging measures may increase the sensitivity to detect early neurodegenerative tissue changes in the hippocampus already at a predementia stage in PD. Thus, a previous multimodal MRI/DTI imaging study found that hippocampal diffusivity changes correlated with memory performance among non-demented PD patients, but no significant associations were observed for hippocampal volume [14]. In our DTI substudy we could confirm that hippocampal diffusivity measures were more closely associated with cognition in non-demented PD compared to volume, although this association showed a rather unexpected specificity for verbal fluency instead of memory measures.

Interestingly, in contrast to the findings for the hippocampus, DTI-based diffusivity measures of the CBF were not associated with cognition in our sample. This is partly in contrast to a previous MRI/DTI study in de novo PD patients from the PPMI cohort [11], which found both CBF volume and MD to be significant predictors of prospective cognitive decline. Similarly, another recent DTI study found significant cross-sectional correlations between diffusivity changes in CBF ROIs and cognitive performance in non-demented PD patients, but CBF volumes were not assessed in that study [26]. These different findings could at least partly relate to differences in patient characteristics, as the proportion of PD-MCI patients was notably higher (20 out of 52 patients; 38%) in this previous study compared to our current study sample (16 out of 73 patients with PD-CRS$_{total}$ ≤ 81; 22%). However, they may also reflect a generally higher variability in DTI-based diffusion measures, which are known to be more susceptible to noise compared to standard volumetric measures on structural MRI [27].

This study has several limitations. First, although the multicentric design of the study allowed us to assess CBF-cognition associations in a relatively large and clinically diverse sample of PD patients, the extracted imaging indices may have been affected by the multicentric acquisition of the imaging data, which is particularly a concern for the DTI signal measurements [27]. In addition to a generally higher susceptibility to inter-scanner related variance, DTI signal measurements may potentially also be more prone to other signal confounders, such as for example contamination by CSF signal that borders the ventral limit of the basal forebrain. Thus, besides modality-specific sensitivities for distinct neuropathological processes, the observed differences in cognition associations between these imaging modalities may also relate to technical differences in the MRI- and DTI-based measurements. However, it has to be noted that we controlled all our statistical analyses for the different acquisition sites, and the multicentric design also allowed us to demonstrate the robustness of the CBF-cognition associations across centers (see center-specific meta-analysis in the supplementary material), which is a key requirement of potential imaging markers that are to be used in wider clinical setting. Another limitation is the cross-sectional nature of our study. It remains to be determined whether the observed cognition-relevant differences in CBF volume among PD patients also translate to a higher risk for progression to dementia. Furthermore, the COPPADIS cohort represents a rather selective research cohort that may not be reflective of the general PD population, and thus our results should be replicated in less preselected cohorts from community-based studies. Another important consideration is that the employed MRI markers of CBF integrity can only serve as indirect markers of cholinergic degeneration. The analyzed CBF region corresponds to the localization of the cholinergic nuclei in the human brain as determined by cytoarchitectonic mappings from combined histology and post-mortem MRI [20], and imaging-pharmacologic [6] and imaging-neurophysiologic [28] studies provide evidence for a link between CBF integrity on MRI and cholinergic system functioning. However, one cannot exclude that the imaging indices might also reflect change in other neuronal or glial components. Finally, the correlation coefficients for the association between CBF volume and cognition are of rather moderate effect size, which, however, lies well in the range of previous studies assessing associations between regional imaging measures and cognition in PD [4,10,14]. Associations between neuroimaging measures and clinical outcomes can rarely be expected to be strictly linear and will generally depend on the functional consequences of the neurodegenerative process that is indexed by the macro- and microstructural neuroimaging alterations. A recent imaging-neuropathology association study found that CBF volume on structural MRI correlated with the extent of Lewy body pathology in the nucleus basalis of Meynert, but not with semi-quantitative assessments of cell loss in this region [29]. This indicates that the neuroimaging measures may also pick up relatively subtle tissue changes in response to neurodegenerative pathology [30].

In conclusion, we demonstrate in a well-characterized multicentric sample of PD patients without dementia that cognitive differences in this non-demented spectrum are more closely related to structural MRI measures of CBF degeneration than hippocampal degeneration. DTI-based diffusion measures could increase the sensitivity to detect

cognition-relevant tissue changes in the hippocampus, but at least in the context of unharmonized multicentric imaging acquisitions appear to be inferior to standard volumetric measures for capturing cognition-relevant CBF changes. These findings may have important implications for the development of clinically useful imaging biomarkers aiding in the early detection of PD patients at increased risk for cognitive decline.

Authors' contribution

Michel J. Grothe: conception of the manuscript, study design, analysis, writing of the first draft of the manuscript, review and critique. Miguel A. Labrador-Espinosa: conception of the manuscript, study design, analysis, review and critique. Silvia Jesús: review and critique; recruitment and/or assessment of participants. Daniel Macías-García: review and critique; recruitment and/or assessment of participants. Astrid Adarmes-Gómez: review and critique; recruitment and/or assessment of participants. Elena Iglesias Camacho: review and critique. Pablo Franco-Rosado: review and critique. Florinda Roldán Lora: review and critique; acquisition of neuroimaging data. Juan Francisco Martín-Rodríguez: review and critique. Miquel Aguilar Barberá: review and critique; recruitment and/or assessment of participants. Pau Pastor: review and critique; recruitment and/or assessment of participants. Sonia Escalante Arroyo: review and critique; recruitment and/or assessment of participants. Berta Solano Vila: review and critique; recruitment and/or assessment of participants. Anna Cots Foraster: review and critique; recruitment and/or assessment of participants. Javier Ruiz Martínez: review and critique; recruitment and/or assessment of participants. Francisco Carrillo Padilla: review and critique; recruitment and/or assessment of participants. Mercedes Pueyo Morlans: review and critique; recruitment and/or assessment of participants. Isabel González Aramburu: review and critique; recruitment and/or assessment of participants. Jon Infante Ceberio: review and critique; recruitment and/or assessment of participants. Jorge Hernández Vara: review and critique; recruitment and/or assessment of participants. Oriol de Fábregues-Boixar: review and critique; recruitment and/or assessment of participants. Teresa de Deus Fonticoba: review and critique; recruitment and/or assessment of participants. Berta Pascual-Sedano: review and critique; recruitment and/or assessment of participants. Jaime Kulisevsky: review and critique. Overall supervision. Pablo Martínez-Martín: review and critique. Overall supervision. Diego Santos-García: conception, organization, and execution of the project; recruitment and/or assessment of participants; review and critique. Pablo Mir: conception of the manuscript, study design, review and critique.

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Declaration of competing interest

None.

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Appendix A. Supplementary data

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References

[1] P. Svenningsson, E. Westman, C. Ballard, D. Aarsland, Cognitive impairment in patients with Parkinson's disease: diagnosis, biomarkers, and treatment, the Lancet, Neurology 11 (8) (2012) 697–707.

[2] N.I. Bohnen, M.J. Grothe, N.J. Ray, M. Muller, S.J. Teipel, Recent advances in cholinergic imaging and cognitive decline-Revisiting the cholinergic hypothesis of dementia, Current geriatrics reports 7 (1) (2018) 1–11.
[3] H. Hanyu, Y. Tanaka, S. Shimizu, H. Sakurai, T. Iwamoto, K. Abe, Differences in MR features of the substantia innominata between dementia with Lewy bodies and Alzheimer's disease, J. Neurol. 252 (4) (2005) 482–484.
[4] S.H. Choi, T.M. Jung, J.E. Lee, S.K. Lee, Y.H. Sohn, P.H. Lee, Volumetric analysis of the substantia innominata in patients with Parkinson's disease according to cognitive status, Neurobiol. Aging 33 (7) (2012) 1265–1272.
[5] M.J. Grothe, C. Schuster, F. Bauer, H. Heinsen, J. Prudlo, S.J. Teipel, Atrophy of the cholinergic basal forebrain in dementia with Lewy bodies and Alzheimer's disease dementia, J. Neurol. 261 (10) (2014) 1939–1948.
[6] H. Hanyu, S. Shimizu, Y. Tanaka, K. Hirao, T. Iwamoto, K. Abe, MR features of the substantia innominata and therapeutic implications in dementias, Neurobiol. Aging 28 (4) (2007) 548–554.
[7] J.E. Lee, K.H. Cho, S.K. Song, H.J. Kim, H.S. Lee, Y.H. Sohn, P.H. Lee, Exploratory analysis of neuropsychological and neuroanatomical correlates of progressive mild cognitive impairment in Parkinson's disease, J. Neurol. Neurosurg. Psychiatr. 85 (1) (2014) 7–16.
[8] M. Grothe, H. Heinsen, S.J. Teipel, Atrophy of the cholinergic Basal forebrain over the adult age range and in early stages of Alzheimer's disease, Biol. Psychiatr. 71 (9) (2012) 805–813.
[9] N.J. Ray, S. Bradburn, C. Murgatroyd, U. Toseeb, P. Mir, G.K. Kountouriotis, S. J. Teipel, M.J. Grothe, In vivo cholinergic basal forebrain atrophy predicts cognitive decline in de novo Parkinson's disease, Brain : J. Neurol. 141 (1) (2018) 165–176.
[10] M.J. Barrett, S.A. Sperling, J.C. Blair, C.S. Freeman, J.L. Flanigan, M.E. Smolkin, C. A. Manning, T.J. Druzgal, Lower volume, more impairment: reduced cholinergic basal forebrain grey matter density is associated with impaired cognition in Parkinson disease, J. Neurol. Neurosurg. Psychiatr. 90 (11) (2019) 1251–1256.
[11] J. Schulz, G. Pagano, J.A. Fernández Bonfante, H. Wilson, M. Politis, Nucleus basalis of Meynert degeneration precedes and predicts cognitive impairment in Parkinson's disease, Brain : J. Neurol. 141 (5) (2018) 1501–1516.
[12] E.J. Burton, I.G. McKeith, D.J. Burn, E.D. Williams, J.T. O'Brien, Cerebral atrophy in Parkinson's disease with and without dementia: a comparison with Alzheimer's disease, dementia with Lewy bodies and controls, Brain : J. Neurol. 127 (Pt 4) (2004) 791–800.
[13] T.R. Melzer, R. Watts, M.R. MacAskill, T.L. Pitcher, L. Livingston, R.J. Keenan, J. C. Dalrymple-Alford, T.J. Anderson, Grey matter atrophy in cognitively impaired Parkinson's disease, J. Neurol. Neurosurg. Psychiatr. 83 (2) (2012) 188–194.
[14] G.A. Carlesimo, F. Piras, F. Assogna, F.E. Pontieri, C. Caltagirone, G. Spalletta, Hippocampal abnormalities and memory deficits in Parkinson disease: a multimodal imaging study, Neurology 78 (24) (2012) 1939–1945.
[15] F. Sampedro, S. Martínez-Horta, J. Marín-Lahoz, J. Pagonabarraga, J. Kulisevsky, Longitudinal intracortical diffusivity changes in de-novo Parkinson's disease: a promising imaging biomarker, Park. Relat. Disord. 68 (2019) 22–25.
[16] D. Santos-Garcia, P. Mir, E. Cubo, L. Vela, M.C. Rodriguez-Oroz, M.J. Marti, J. M. Arbelo, J. Infante, J. Kulisevsky, P. Martinez-Martin, COPPADIS-2015 (COhort of Patients with Parkinson's DIsease in Spain, 2015), a global–clinical evaluations, serum biomarkers, genetic studies and neuroimaging–prospective, multicenter, non-interventional, long-term study on Parkinson's disease progression, BMC Neurol. 16 (2016) 26.
[17] J. Pagonabarraga, J. Kulisevsky, G. Llebaria, C. Garcia-Sanchez, B. Pascual-Sedano, A. Gironell, Parkinson's disease-cognitive rating scale: a new cognitive scale specific for Parkinson's disease, Mov. Disord. : official journal of the Movement Disorder Society 23 (7) (2008) 998–1005.
[18] D. Wolf, M. Bocchetta, G.M. Preboske, M. Boccardi, M.J. Grothe, Reference Standard Space hippocampus Labels According to the EADC-ADNI Harmonized Protocol: Utility in Automated Volumetry, Alzheimers Dement, 2017.
[19] M.J. Grothe, I. Kilimann, L. Grinberg, H. Heinsen, S. Teipel, In vivo volumetry of the cholinergic basal forebrain, in: R. Perneczky (Ed.), Biomarkers for Preclinical Alzheimer's Disease, Springer Science+Business Media, LLC, 2018, pp. 213–232.
[20] H.J. Fritz, N. Ray, M. Dyrba, C. Sorg, S. Teipel, M.J. Grothe, The Corticotopic Organization of the Human Basal Forebrain as Revealed by Regionally Selective Functional Connectivity Profiles, Hum. Brain Mapp. 40 (3) (2019 Feb 15) 868–878, https://doi.org/10.1002/hbm.24417. Epub 2018 Oct 11. PMID: 30311315.
[21] R.A. Armstrong, When to use the Bonferroni correction, Ophthalmic Physiol. Opt. : the journal of the British College of Ophthalmic Opticians (Optometrists) 34 (5) (2014) 502–508.
[22] A.K. Liu, R.C. Chang, R.K. Pearce, S.M. Gentleman, Nucleus basalis of Meynert revisited: anatomy, history and differential involvement in Alzheimer's and Parkinson's disease, Acta Neuropathol. 129 (4) (2015) 527–540.
[23] N.I. Bohnen, M.L. Müller, V. Kotagal, R.A. Koeppe, M.A. Kilbourn, R.L. Albin, K. A. Frey, Olfactory dysfunction, central cholinergic integrity and cognitive impairment in Parkinson's disease, Brain : J. Neurol. 133 (Pt 6) (2010) 1747–1754.
[24] S. van der Zee, M.L.T.M. Müller, P. Kanel, T. van Laar, N.I. Bohnen, Cholinergic denervation patterns across cognitive domains in Parkinson's disease, Mov. Disord. : official journal of the Movement Disorder Society 36 (3) (2021 Mar) 642–650, https://doi.org/10.1002/mds.28360. Epub 2020 Nov 2. PMID: 33137238.
[25] A.S. Mihaescu, M. Masellis, A. Graff-Guerrero, J. Kim, M. Criaud, S.S. Cho, C. Ghadery, M. Valli, A.P. Strafella, Brain degeneration in Parkinson's disease patients with cognitive decline: a coordinate-based meta-analysis, Brain imaging and behavior 13 (4) (2019) 1021–1034.
[26] F. Gargouri, C. Gallea, M. Mongin, N. Pyatigorskaya, R. Valabregue, C. Ewenczyk, M. Sarazin, L. Yahia-Cherif, M. Vidailhet, S. Lehéricy, Multimodal magnetic resonance imaging investigation of basal forebrain damage and cognitive deficits in Parkinson's disease, Mov. Disord. : official journal of the Movement Disorder Society 34 (4) (2019) 516–525.
[27] S.J. Teipel, S. Reuter, B. Stieltjes, J. Acosta-Cabronero, U. Ernemann, A. Fellgiebel, M. Filippi, G. Frisoni, F. Hentschel, F. Jessen, S. Klöppel, T. Meindl, P.J. W. Pouwels, K.H. Hauenstein, H. Hampel, Multicenter stability of diffusion tensor imaging measures: a European clinical and physical phantom study, Psychiatr. Res. 194 (3) (2011) 363–371.
[28] J. Peter, J. Lahr, L. Minkova, E. Lauer, M.J. Grothe, S. Teipel, L. Köstering, C. P. Kaller, B. Heimbach, M. Hüll, C. Normann, C. Nissen, J. Reis, S. Klöppel, Contribution of the cholinergic system to verbal memory performance in mild cognitive impairment, J. Alzheim. Dis. : JAD 53 (3) (2016) 991–1001.
[29] S.J. Teipel, H.C. Fritz, M.J. Grothe, Neuropathologic features associated with basal forebrain atrophy in Alzheimer disease, Neurology 95 (10) (2020) e1301–e1311.
[30] S. Teipel, A. Drzezga, M.J. Grothe, H. Barthel, G. Chetelat, N. Schuff, P. Skudlarski, E. Cavedo, G.B. Frisoni, W. Hoffmann, J.R. Thyrian, C. Fox, S. Minoshima, O. Sabri, A. Fellgiebel, Multimodal imaging in Alzheimer's disease: validity and usefulness for early detection, the Lancet, Neurology 14 (10) (2015) 1037–1053.