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Cholinergic denervation patterns across cognitive domains in Parkinson's disease

Running head: Cholinergic pattern of cognition in Parkinson

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Abstract

Background: The cholinergic system plays a key role in cognitive impairment in Parkinson's disease (PD). Previous acetylcholinesterase PET imaging studies found memory, attention and executive function correlates of global cortical cholinergic losses. Vesicular acetylcholine transporter PET allows for more accurate topographic assessment of not only cortical but also subcortical cholinergic changes.

Objective: To investigate the topographic relationship between cognitive functioning and regional cholinergic innervation in patients with PD.

Methods: A total of 86 non-demented PD patients (age 67.8 (7.6) years, motor disease duration 5.8 (4.6) years) and 12 healthy control subjects (age 67.8 (7.8) years) underwent cholinergic [^{18}F]Fluoroethoxybenzovesamicol PET imaging. PD patients underwent neuropsychological assessment. Z-scores for each cognitive domain were determined using an age, gender and educational level-matched control group. Correlations between domain specific cognitive functioning and cholinergic innervation were examined, controlling for motor impairments and levodopa equivalent dose. Additional correlational analyses were performed using a mask limited to PD vs. normal ageing binding differences to assess for disease-specific vs normal ageing effects.

Results: Voxel-based whole brain analysis demonstrated partial overlapping topography across cognitive domains, with most robust correlations in the domains of memory, attention and executive functioning ($p < 0.01$, corrected for multiple comparisons). The shared pattern included the cingulate cortex, insula/operculum and (visual) thalamus.

Conclusion: Our results confirm and expand on previous observations of cholinergic system involvement in cognitive functioning in PD. The topographic overlap across domains may reflect a partially shared cholinergic functionality underlying cognitive functioning, representing a combination of disease-specific and aging effects.

Trial Registration: ClinicalTrials.gov Identifier: NCT01754168 & NCT02458430.

Abbreviations:

[^{18}F]FEOBV: [^{18}F]Fluoroethoxybenzovesamicol

FDR: False Discovery Rate

LED: Levodopa Equivalent Dose

MDS-UPDRS-III: Movement Disorder Society - Revised Unified Parkinson's Disease Rating Scale part III

PD: Parkinson's disease

PET: Positron Emission Tomography

VAChT: Vesicular Acetylcholine Transporter

Introduction

Cognitive impairment is a common non-motor symptom with a debilitating effect on functional capacity and quality of life in people with Parkinson's disease (PD)(1,2). Mild cognitive impairment in PD already manifests in 25-30% of newly diagnosed patients and approximately 80% of PD patients eventually develop PD dementia over the course of the disease (3–5). The profile of cognitive impairment in PD is highly heterogeneous, with multiple domains variably affected in most patients.

The pathophysiology of cognitive impairment in PD is complex and includes cumulative and interactive effects of protein depositions, neuronal and synaptic changes and alterations in various neurotransmitter systems, including the cholinergic system (6). Despite this multi-faceted pathophysiology, the cholinergic system appears to play a particularly important role. For example, *in vivo* cholinergic imaging studies show more severe cholinergic losses in PD dementia compared to PD patients without dementia (7–10). Even in the absence of dementia, cholinergic system degeneration is a major driver of cognitive impairment in PD (11).

We previously showed that deficits in attention, executive functioning and memory correlated with cholinergic losses in PD, at least at a global cortical level (10,12). Unlike traditional views of the cholinergic system as a diffuse cortical neuromodulator system (13), more recent studies emphasize the importance of regional deterministic activity of the cholinergic system (14–16). Therefore, there is a need for new studies that focus on cognitive effects of regional cholinergic alterations in PD. There are three major sources of cholinergic innervations in the brain. The basal forebrain cholinergic cell groups are the source of widespread cholinergic projections throughout the brain where specific sub-regions within the nucleus basalis of Meynert (Ch4) provide the majority of projections to the cortical mantle (17,18). The pedunculopontine nucleus-laterodorsal tegmental complex projects primarily to the thalamus, brainstem nuclei and cerebellum. The third major source is represented by cholinergic interneurons mainly found in the striatum (14). Loss of structural integrity and

connectivity of the basal forebrain subregions Ch1-2 has previously been associated with memory and visuospatial task performance in PD, whereas subregions Ch3-4 correlated with executive functions and more global cognitive performance (19).

Our previous cholinergic imaging studies were performed using an acetylcholinesterase PET ligand, which does not allow for reliable estimation of cholinergic activity in high binding areas, such as striatum and cerebellum. [^{18}F]Fluoroethoxybenzovesamicol ([^{18}F]FEOBV) PET binds specifically to the vesicular acetylcholine transporter (VAChT) and allows for assessment of cholinergic nerve terminal integrity not only in the cortex but also in high binding subcortical regions, providing the opportunity of detailed assessment of regional cerebral cholinergic changes (20–22). The purpose of this study was to examine the topographic relationship between domain-specific cognitive functioning and regional cerebral VAChT binding in non-demented patients with PD.

Methods

Subjects

86 PD patients (67 males and 19 females) were included in this cross-sectional study. Patients had a mean age of 67.9 ± 7.6 years and motor disease duration of 5.8 ± 4.6 years. Inclusion criteria consisted of a clinical PD diagnosis in accordance with the UK PD Society Brain Bank clinical diagnostic criteria (23). Exclusion criteria included evidence of large vessel stroke or mass lesions on anatomic imaging, the use of anticholinergic or cholinesterase inhibitor drugs, presence of severe depression as measured using the geriatric depression scale (24), and presence of PD dementia. A healthy control (HC) group consisting of 5 males and 7 females with a mean age of 67.8 ± 7.8 years was included for normative PET imaging data. This study was approved by the Institutional Review Boards of the University of Michigan School of Medicine and Veterans Affairs Ann Arbor Healthcare System. Written informed consent was obtained

from all subjects prior to any study procedures and conducted in accordance with the Declaration of Helsinki.

All PD subjects underwent motor examination using the Movement Disorder Society Revised Unified PD Rating Scale III (MDS-UPDRS-III), with mean score of 34.3 ± 12.1 and Hoehn and Yahr score of 2.4 ± 0.6. Motor assessment was performed in the morning in the dopaminergic "off" state, i.e., after overnight withdrawal of dopaminergic medication. Mean levodopa equivalent dose (LED) (25) was 647 ± 410 mg. More details of the clinical and demographic characteristics are described in table 2.

Neuropsychological assessment

All PD subjects underwent a detailed neuropsychological assessment including at least two neuropsychological tests for each cognitive domain, in line with recommendations of the Movement Disorder Society (MDS) Task Force (26,27). The cognitive test battery consisted of California verbal learning test, Wechsler Memory Scale, Stroop Color Word test, Delis-Kaplan Executive Function System Trail Making Test, the Wechsler Adult Intelligence Scale Digit Span, matrix reasoning task and Digit-Symbol modalities test, the letter and semantic verbal fluency, Boston naming test, and Benton Judgment of Line Orientation test and the clock copy test of the PD – Cognitive Rating Scale. Conditions possibly influencing neuropsychological test performance, including visual problems, color blindness, dysarthria and dyskinesia were taken into consideration when interpreting cognitive performance, excluding (sub)tasks if needed. Patients were considered PD-MCI based on MDS PD-MCI level II criteria (26). Neuropsychological tests and subtasks represented specific cognitive domains as shown in Table 1.

A z-score for every subject on specific tests was calculated based on a dataset of a healthy control group of 77 older subjects. Data of these control subjects were collected in our laboratory providing normative data of a group with similar geographical and social-economic

background and reassures the use of identical assessment techniques. The healthy control group was of similar age, gender and educational level distribution as the patient population. Z-scores of the PD – Cognitive Rating Scale clock-copy test were based on normative data described previously, correcting for age, gender and educational level (28). By averaging all z-scores on the tests or subtasks, an average z-score for each cognitive domain was obtained (see Table 2). A global cognitive z-score was computed as the average of all cognitive domains. A higher z-score reflects better cognitive task performance. Neuropsychological testing of patients was performed while they were on their usual dopaminergic medications.

Imaging acquisition and analysis

All subjects underwent brain MRI and VAChT [^{18}F]FEOBV PET imaging. T1-weighted MRI was performed on a 3 Tesla Philips Achieva system (Philips, Best, The Netherlands). A 3D inversion recovery-prepared turbo-field-echo was performed in the sagittal plane using TR/TE/TI=9.8/4.6/1041ms; turbo factor=200; single average; FOV=240x200x160mm; acquired Matrix = 240x200x160 slices and reconstructed to 1mm isotropic resolution.

[^{18}F]FEOBV was prepared as described previously (29). [^{18}F]FEOBV delayed dynamic imaging was performed over 30 minutes (in six 5-minute frames) starting 3 hours after an intravenous bolus dose injection of 8 mCi [^{18}F]FEOBV(20) PET imaging was performed in 3D imaging mode using an ECAT Exact HR+ tomograph (Siemens Molecular Imaging, Inc., Knoxville, TN), which acquires 63 transaxial slices (slice thickness: 2.4 mm; intrinsic in-plane resolution: 4.1 mm full-width at half maximum over a 15.2 cm axial field-of-view). [^{18}F]FEOBV PET imaging was performed while patients were on their usual dopaminergic medication.

The PET imaging frames were spatially coregistered within subjects with a rigid-body transformation to reduce the effects of subject motion during the imaging session (30). Statistical parametric mapping (SPM) software (SPM12; Wellcome Trust Centre for Neuroimaging, London, UK) was used for PET-MRI registration using the cropped T1-weighted MR volumetric scan. Freesurfer software (Laboratory for Computational Neuroimaging, Athinoula A. Martinos Center for Biomedical Imaging, Boston, MA, USA) was used to define cortical and subcortical MR gray matter volumes-of-interest. MRI based partial volume correction of the PET data was performed (31).

Cortical volume-of-interest labels from the Mindboggle-101 dataset segmented in FreeSurfer were used to identify gray- and white-matter volumes of interest (32). A white matter reference tissue approach was used to determine VAChT binding as previously reported (21,33). Distribution volume ratios were calculated from the ratio of averaged frames for gray

matter targets and supratentorial white matter reference tissue (21). A single total neocortical volume-of-interest was created for the VOI-based statistical analysis.

Voxel-based PET analysis

Voxel-based PET analysis was performed as previously described (34). All brain images were spatially normalized to Montreal Neurological Institute template space using DARTEL normalization protocol (35) and smoothed with a Gaussian kernel of 8 mm full width half maximum to adjust the anatomical variability between the individual brains and to enhance the signal-to-noise ratio. The relevant brain areas were displayed in Montreal Neurological Institute atlas coordinates (in millimeters) in the stereotactic space using the automated anatomical labeling toolbox.

Statistics

Analyses were performed using IBM SPSS Statistics for Windows, Version 24.0 (Armonk, NY: IBM Corp). Correlations between VOI-based whole brain neocortical VAChT binding and performance on specific cognitive domains z-scores were analyzed using a partial Pearson correlation coefficient controlling for MDS-UPDRS-III scores and LED levels. The Holm-Bonferroni method was used to correct for effects of multiple testing.

Voxel-wise statistical analysis was performed using SPM12 software using the parametric [^{18}F]FEOBV distribution volume ratio images of all patients to assess both positive and negative topographic correlations between specific cognitive domain z-scores and whole-brain cholinergic binding. In addition, a voxel-wise group comparison between the PD and the HC group was performed. The result of this analysis, a topographic profile showing regions significantly different between PD and HC, was transformed into a mask. The domain specific voxel-wise analyses were then repeated using this mask, in order to identify PD-specific vs. aging-related regions. Both domain-specific voxel-based analyses were controlled for MDS-

UPDRS-III scores and LED levels. The false discovery rate (FDR) approach was used for correction for multiple testing effects in the voxel-based analysis.

Results

Cognitive functioning

Based on MDS PD-MCI level II criteria, 39 subjects (45.3%) of the PD group classified as PD-MCI (table 2). Only 3 of the 39 PD-MCI patients presented with single domain PD-MCI, all other PD-MCI patients showed multidomain impairments. Attention was the most commonly affected domain (n=30), followed by executive functions (n=28) and memory (n=27) in the 39 PD-MCI patients. The language and visual domain was affected in resp. 18 and 14 of the 39 PD-MCI patients.

Domain-specific cognitive correlates of global neocortical [^{18}F]FEOBV distribution volume ratios

Significant correlations were present between volume-of-interest-based global cortical VAChT binding and memory ($r = .423$, $p < 0.001$), executive function ($r = .352$, $p < 0.001$) and attention ($r = .321$, $p = 0.003$) domains (table 3).

Voxel-based regional cerebral [^{18}F]FEOBV binding correlates of different cognitive domains

Whole-brain voxel-based analyses were performed to explore the correlation between regional brain VAChT binding and the different cognitive domains, controlling for LED levels and parkinsonian motor impairment as measured by the MDS-UPDRS-III. Only positive correlations were found across domains with no negative correlations observed. Positive correlations indicate that a higher cholinergic binding is associated with better cognitive performance.

For the memory domain z-score, regional cerebral cholinergic correlations ($p < 0.01$ FDR corrected) were seen in widespread cortical and subcortical brain regions (figure 1A). The topographic profile included cingulate cortex (anterior, mid, posterior and retrosplenial

regions), prefrontal cortex (dorsolateral prefrontal cortex, orbitofrontal cortex and gyrus rectus regions), insula and operculum, thalamus and visual thalamus with the pulvinar and lateral geniculate nucleus (LGN), caudate nucleus, hippocampus and parahippocampal regions, temporal lobe (superior, middle and inferior temporal gyrus, temporal pole) bilaterally, and left lingual gyrus.

Results found for the executive function (figure 1B) and attention domains (figure 1C) showed partially overlapping topography with the memory domain. Overlapping regions across all three domains included the cingulate cortex, the insula/operculum the visual thalamus (esp. the LGN) and the hippocampal region ($p < 0.01$ FDR corrected). Compared to the memory domain, involvement of the temporal lobe and prefrontal cortex was more limited for executive functions. The spatial extent of overlap was less for the attention domain but included cingulate cortex, the insula/operculum, the temporal pole, the right LGN and the LGN-fimbria transitional area ($p < 0.01$ FDR corrected).

The topographic profile for the language domain showed limited regional VAChT binding correlates, mainly including the right LGN, the hippocampal fimbria and the LGN-fimbria transitional region ($p < 0.01$ FDR corrected, figure 1D).

Whole brain voxel-based analysis for the visuospatial domain did not show significant voxels after correction for multiple comparisons.

Sensitivity analysis of voxel-based regional cerebral [^{18}F]FEOBV binding correlates of different cognitive domains superimposed on PD vs. HC related cholinergic innervation changes.

Whole-brain voxel-based group comparison between the PD and the HC group was first performed to identify disease-specific VAChT binding differences ($p < 0.05$ FDR corrected, supplementary figure 1). Widespread predominant posterior cortical and subcortical differences were found. Subcortical regions included the thalamus and pallidum. Analyses in the opposite direction showed no significant higher cholinergic binding in the PD group.

The regional topography was then used as a mask to repeat the voxel-based cognitive domain-specific analyses. After correcting for multiple comparisons, the memory and executive function domain showed significant regional correlates with overlapping topography across both domains (figure 2, $p < 0.05$ FDR corrected). The significant regions for the memory domain (figure 2A) were less extensive but topographically comparable to the correlates in the non-PD specific analysis (figure 1). The most prominent regions included the superior and medial temporal lobe, hippocampus and parahippocampal region, thalamus (including the left visual thalamus), insula, operculum, superior frontal region, postcentral gyrus, the anterior and posterior cingulum and the precuneus. The cholinergic correlates of the executive functions domain (figure 2B) show overlapping regions with the memory domain, including the temporal lobe, the parahippocampal regions and left hippocampus, the thalamus and left visual thalamus, the insula and operculum, the cingulum and the postcentral gyrus. The significant regions for the attention domain (figure 2C) included the insula, operculum, (para)hippocampal region and the middle and anterior cingulate cortex. The language domain (figure 2D) showed significant regions in the (para)hippocampal region and LGN, left more than right.

Discussion

Findings of this study confirm and expand on our previous studies. First, analyses of volume of interest based global neocortical VAChT binding confirmed our previous observations of

significant correlations between attention, memory and executive function domains and global cortical acetylcholinesterase hydrolysis rates (10,12). Second, the voxel-based analysis demonstrated novel findings of a shared topographic pattern of vulnerability of brain anatomic cholinergic projections underlying multiple cognitive domains, while controlling for the severity of PD specific motor impairment and LED levels. Third, this cholinergic pattern represents a combination of disease-specific and aging effects. PD-specific regional brain changes included the cingulum, bilateral insula and operculum, hippocampal region and the visual thalamus.

These overlapping anatomic regions have previously been associated with cognitive functions. For example, the insula plays a key role in task set and control (36,37), and as part of the saliency network together with the anterior cingulate cortex, is of importance for stimuli detection, facilitating attention shifting and memory function (38,39). In addition, both the posterior cingulate cortex and hippocampus are involved in memory, showing co-activation during an episodic memory encoding tasks in Alzheimer's disease patients (40). Furthermore, reduced blood flow in the posterior cingulate cortex is predictive of more global cognitive decline rather than being limited to impaired memory functions in Alzheimer's disease (41). Our findings suggest that cholinergic changes within these anatomic regions are of relevance for the cognitive impairment syndrome in PD. Furthermore, the overlapping cholinergic topography across different cognitive domains also suggests that these regions may serve a shared cognitive processing function underlying and serving multiple cognitive domains. Furthermore, cholinergic losses in these regions suggest vulnerability of not only the basal forebrain (both (para)limbic and neocortical projections) but also brainstem cholinergic projections and striatal cholinergic interneurons underlying the cognitive impairment syndrome in PD.

Our sensitivity analysis using a mask based on PD vs. HC VAChT binding differences indicated both disease-specific as well as normal aging components contributing to the cholinergic topographic correlated of cognitive changes in the patients. Although less extensive, comparable cholinergic topography was observed for the domains of memory and executive

functions, including the temporal lobe, (para)hippocampal region, thalamus, insula and operculum, and the cingulate cortex. Topography was more limited when applying the PD mask likely suggesting a component of normal ageing contributing to cognitive impairment in PD. This is not unexpected as cholinergic changes, as measured with [^{18}F]FEOBV, also occur with normal aging as previously reported (42). This is similar to nigrostrial dopaminergic losses in PD that effectively are a composite of normal aging and PD-specific dopaminergic losses (43). Given the reported symptomatic motor denervation threshold of about 50% loss of dopamine transporters in the putamen (44), findings explain the increasing incident of PD with older age. Similarly to the dopaminergic system, we postulate that aging plays an important role in cholinergic denervation and its relationship with cognitive functioning, including the demonstrated topography. These regions could also be of particular interest in other age-related neurodegenerative disorders, including Alzheimer's disease.

The overlapping topography across domains also suggests a role for attention and overall awareness. Attention is a prerequisite for cognitive functions, such as memory and executive functions. Therefore, attention may explain some element of the observed cholinergic communality underlying these cognitive domains. However, the more limited spatial extent of the shared topographic pattern found for the attention domain suggests that other mechanisms may also play a role. Cholinergic losses in the visual thalamus, including the LGN, are consistent with vulnerability of the pedunculopontine nucleus-thalamic projections (18,45). Although typically viewed as a visual relay station, more recent literature describes the LGN as an active filtering centre with an important role in modulating attention and cognitive control of visual information (46).

Interestingly, when comparing cholinergic binding differences between PD and HC, most prominent cholinergic denervation is found in the posterior cortical (parieto-occipital) regions, while cholinergic correlates of cognitive functioning are more prominent in more centrally located frontal and temporal regions. The predominant posterior cortical binding differences between PD and HC is in line with previous cholinergic imaging studies(7–9,22). Despite these prior observations, we did not find robust relationships between cognitive functioning and VAChT uptake in posterior cortical regions with the exception of the posterior cingulum and precuneus. However, these findings are mainly based on comparisons between patients and control groups, rather than looking at regional cerebral correlates of cognition in PD or within control subjects. It is possible that relatively isolated posterior cortical cholinergic losses in PD may not be sufficient to cause clinically manifest cognitive changes. This may be because of preservation of more anterior cholinergic projections. In other words, the symptomatic threshold for cognitive impairment due to cholinergic changes in PD may be more related to expanded network rather than local cortical changes.

Another explanation may be that the assumed but not proven posterior-to-anterior cortical cholinergic denervation gradient may result in a statistical 'floor' effect of cholinergic bindings measures related to cognitive performance in posterior brain regions when performing correlation analyses. This explanation is less likely as the thalamic complex and posterior cingulum are both part of the posterior (subcortical and limbocortical) brain that have strong functional and structural connectivity with the occipital cortex (47).

A major strength of this study is the use of whole brain voxel-based analyses to allow a more granular assessment of regional cerebral cholinergic correlates of cognitive functions in PD while controlling for PD-specific motor impairment and LED levels. This approach is particularly important to allow the identification of smaller regions that may be otherwise lost if only global cortical or large lobar cholinergic binding measures were used. For that reason, we did not

apply a minimum large voxel cluster size to avoid missing small sized regions that are of potential importance for cognitive functions for the same reason. For example, our novel observation of the cholinergic LGN correlating with cognitive domains of memory, language and executive function would have been easily missed otherwise. There are also several limitations of this study. This study included only a small control group for which no detailed neuropsychological assessment was available. However, we were able to perform a sensitivity analyses to determine PD-specific vs. aging related changes. Another limitation is that patients were studied on their usual dopaminergic medication during the [^{18}F]FEOBV PET scan and cognitive assessment for reasons of patient comfort. However, our analyses were adjusted for LED levels.

Our findings may augur further research into a personalized medicine approach for use of cholinesterase inhibitors in patients with PD with cognitive complaints. In particular, PD-MCI patients with more prominent memory, executive function or attentional deficits may be preferential candidates for such cholinergic augmentation studies.

To conclude, our findings confirm and expand on previous observations of robust cholinergic correlates of memory, attention and executive functions in PD. Novel observations include evidence of a common cholinergic pattern with overlapping bilateral cholinergic topographic profiles associated with changes in these specific cognitive domains function in PD, including the insula, cingulate cortex, hippocampus and thalamus, including the LGN.

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Conflict of interest:

Dr. Kanel and Ms. Van der Zee have nothing to disclose. Dr. Van Laar has received research support from the Weston Brain Institute, speaker fees from Britannia, AbbVie and Medtronic, and is on the advisory board of LTI and Neuroderm. Dr. Muller has research support from the NIH, Michael J. Fox Foundation, and the Department of Veteran Affairs. Dr. Bohnen has received research funding from the NIH, Department of Veterans Affairs and the Michael J. Fox Foundation, Eisai, and EIP Pharma. He has participated in an Eisai advisory board and received in kind research support from Expansion Therapeutics and Innovative Health Solutions.

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Figure legends

Figure 1: Statistical parametric voxel-based analysis (FDR corrected $p < 0.01$) of the correlation between VAChT binding and (1A) memory domain z-scores, (1B) executive function domain z-scores (1C) attention domain z-scores and (1D) language domain z-scores, controlled for parkinsonian motor impairment and levodopa equivalent dose.

Figure 2: Statistical parametric voxel-based analysis (FDR corrected $p < 0.05$) of the correlation between VAChT binding and (2A) memory domain z-scores, (2B) executive function domain z-scores, (2C) attention domain z-scores and (2D) language domain z-scores controlled for parkinsonian motor impairment and levodopa equivalent dose, superimposed on a PD impairment related mask.

Supplementary material

Supplementary Figure 1: Statistical parametric voxel-based analysis (FDR corrected $p < 0.05$) showing the significant lower VAChT binding in PD patients compared to HC.

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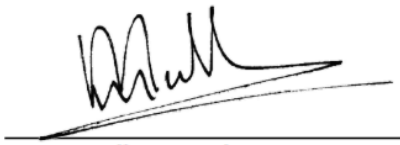

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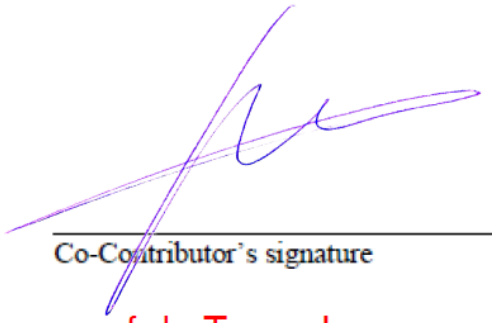

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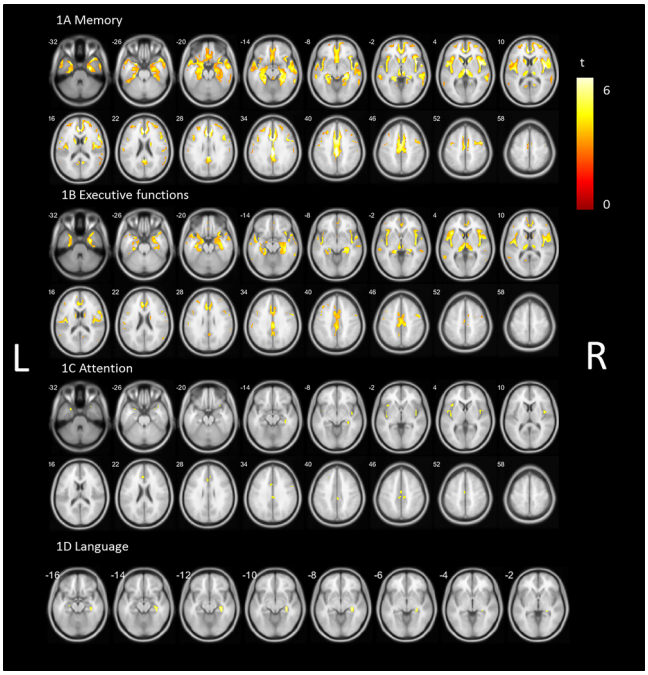

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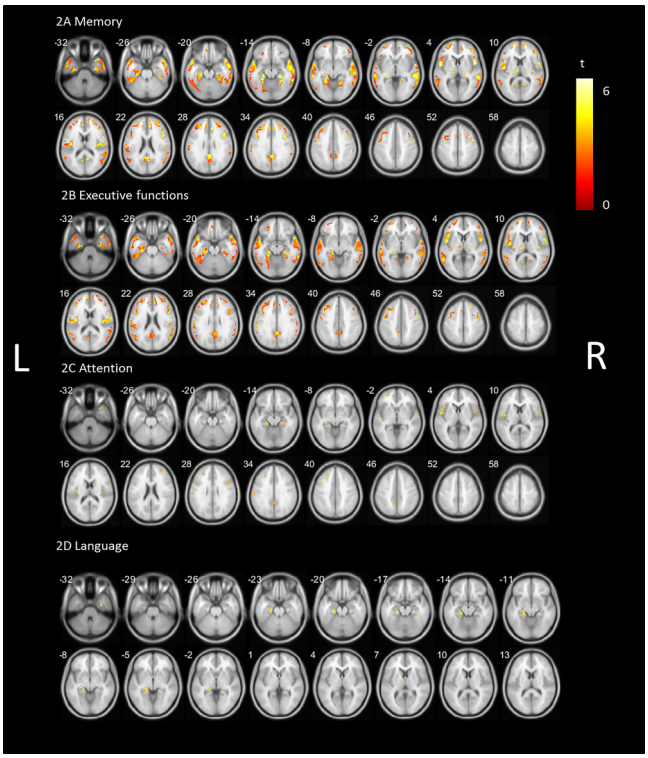

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Table 1: Neuropsychological tests per cognitive domain

Domain	Neuropsychological (sub)test
Memory	California verbal learning test: immediate recall
	California verbal learning test: delayed free recall
	Wechsler Memory Scale
Attention	Stroop 2: Color test
	Delis–Kaplan Executive Function System, Trail Making Test 2: Number sequencing
	Symbol digit modalities test
	Wechsler Adult Intelligence Scale: Digit Span backward
Executive function	Stroop 4: Adjusted Color-Word test
	Delis–Kaplan Executive Function System, Trail Making Test 4: Letter - number sequencing
	Wechsler Adult Intelligence Scale: Matrix Reasoning
	Letter fluency
Language	Boston Naming Test
	Verbal fluency: animals
Visuospatial function	Judgment of line orientation
	Parkinson's disease – cognitive rating scale: Clock copy

Table 2: Demographic and clinical characteristics of included PD subjects. Mean and SD are presented for numerical variables.

	n = 86
Age	67.8 (7.6)
Gender (m:f)	67:19
Education (years)	15.6 (2.7)
Motor disease duration (years)	5.8 (4.6)
Hoehn & Yahr	2.4 (0.6)
MDS-UPDRS-III	34.3 (12.1)
LED (mg)	647.2 (410)
PD-MCI	39 (45.3%)
MoCA	26.2 (3.0)
Z-score memory	-0.44 (1.03)
Z-score attention	-0.41 (0.87)
Z-score executive function	-0.55 (1.27)
Z-score language	-0.48 (1.11)
Z-score visuospatial function	-0.12 (0.84)

MDS-UPDRS: Movement Disorder Society – Unified Parkinson's Disease Rating Scale; LED: Levodopa Equivalent Dose; PD-MCI: Parkinson's disease mild cognitive impairment; MoCA: Montreal Cognitive Assessment

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MDS-UPDRS: Movement Disorder Society – Unified Parkinson's Disease Rating Scale; LED: Levodopa Equivalent Dose; PD-MCI: Parkinson's disease mild cognitive impairment; MoCA: Montreal Cognitive Assessment

Table 3: Correlations between global cortical VAChT binding and performance on different cognitive domains, controlled for LED and MDS-UPDRS-III

Cognitive domain	R	*P*
Memory	.423	**<.001***
Executive functioning	.352	**<.001***
Attention	.321	**.003***
Language	.128	.247
Visuospatial	.192	.080
Global cognition	.364	**.001***

** significant after Holm-Bonferroni correction.*

VAChT: Vesicular acetylcholine transporter; MDS-UPDRS-III: Movement Disorders Society – Unified Parkinson's Disease Rating Scale part III; LED: Levodopa Equivalent Dose; Global cognition: average z-score of all cognitive domains