Association of obstructive sleep apnea with brain volummetry and cognition in de novo Parkinson's disease

Josef Mana

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Methods

Neuropsychological assessment

All patients (PD) and healthy controls (HC) were administered a battery of neuropsychological tests at enrollment to the study and a subsample of participants were administered the same tests at re-test four years after the enrollment. The battery included assessment of (i) declarative memory via Rey Auditory Verbal Learing Test (RAVLT) (Bezdicek et al. 2014; Frydrychová et al. 2018); (ii) attention via Trail Making Test, part A (TMT-A) (Bezdicek et al. 2012; Bezdicek, Stepankova, et al. 2017), and dot colour naming (PST-D) as well as naming colour of neutral words (PST-W) conditions from Prague Stroop Test (Bezdicek et al. 2015); (iii) executive function via Trail Making Test, part B (Bezdicek et al. 2012; Bezdicek, Stepankova, et al. 2017), and Prague Stroop Test, interference condition (i.e., naming colour of contrasting colour words, PST-C) (Bezdicek et al. 2015); and (iv) processing speed via Grooved Pegboard Test (GPT) (Kløve 1963). The patients were further examined using tests from the standard International Parkinson and Movement Disorder Society (MDS) neuropsychological battery at Level II for mild cognitive impairment in Parkinson's disease (PD-MCI) (Litvan et al. 2012; Bezdicek, Sulc, et al. 2017). The Czech normative calculator established by Bezdicek, Sulc, et al. (2017) was used to assign PD-MCI diagnosis to each PD patient separately at enrollment and retest. Finally, all participants were administered Montreal cognitive assessment (MoCA) (Kopecek et al. 2017; Nasreddine et al. 2005) annually for cognitive screening.

Statistical analyses

All demographic (age, education, gender) and descriptive clinical (RBD, MoCA, BMI, age at first motor symptom, disease duration, MDS-UPDRS I, II and III) variables were described by their mean and standard deviation if continuous and frequency if nominal separately for HC OSA-, HC OSA+, PD OSA-, and PD OSA+ groups of participants, and compared by Gaussian (continuous variables) or logistic (binary variables) regression with group (PD vs. HC), OSA (OSA+ vs. OSA-) and their interaction as predictors if variables were measured in both PD and HC groups, and with OSA only as predictor if variables were measured in PD

group only (i.e., disease-specific variables). As we did not aim to control type I error rate in these analyses, decision threshold for claiming statistically significant difference in demographic and descriptive clinical variables was set at $p < .05$ without adjustment for multiple comparisons.

Cortical thickness

4 Fíla

Subcortical volummetry

The strength of association of subcortical structures' volume with group (PD vs HC) and OSA (OSA+ vs OSA-) was evaluated by a set of univariate linear regressions fitted to data via QR decomposition. Each subcortical structure's volume was regressed on group, OSA and their interaction as exposures of interest, and years of age, gender and TIV as additive linear covariates. All continuous variables were standardised (i.e., mean-centred and scaled by their in-sample standard deviation) before entering the analysis, and nominal variables were entered via sum coding. Each regression was tested for deviation from normality of residuals via the Shapiro-Wilk test and deviation from homoscedasticity via the Breusch-Pagan test. Within the classical Neyman-Pearson hypothesis testing framework, we selected a decision threshold for rejecting the hypothesis of zero association between subcortical structure's volume and group/OSA by adjusting for 5% false discovery rate (FDR) (Benjamini and Hochberg 1995) in tests of all main effects and interactions of interest (i.e., coefficients related to the group and OSA variables) across all subcortical structures examined in this section. The test statistics consisted of *t*-values for each relevant regression coefficient calculated by lm() function in R software for statistical computing (R Core Team 2024). The primary estimand of interest, i.e., the interaction between group and OSA, was further characterised by calculating simple main effects of OSA within each group and the difference between these simple main effects via the avg_comparisons() function in the "marginaleffects" R package (Arel-Bundock, Greifer, and Heiss Forthcoming).

Based on the results of the primary analyses outlined above, we further explored association of hippocampal fields with group and OSA in a series of post-hoc univariate regressions with identical specification as described above. The only difference between the primary analyses of the gross subcortical structures described above, and the analysis of hippocampal fields was that in the latter case, we focused on the group/OSA interaction only. The decision threshold for rejecting the hypothesis of zero group/OSA interaction was set according to adjustment for 5% FDR within this set of analyses.

Finally, to reflect current recommendations of the American Statistical Association which advised against basing scientific conclusions on whether a *p*-value passes a specific threshold (Wasserstein and Lazar 2016), we also calculated Shannon information (i.e., s-

values) $-log_2(p)$. S-value is cognitive tool to help researchers intuitively evaluate strength of evidence against a null hypothesis contained in the results as equivalent to the number consecutive "heads" tosses that would provide the same amount of evidence against the null hypothesis that the coin is fair (Greenland 2019; Cole, Edwards, and Greenland 2021).

Cognitive variables

The distribution of cognitive performance conditional on group, OSA, and measurement occasion (enrollment vs retest) was evaluated using a set of independent Bayesian linear mixed models (LMMs) with cognitive test scores regressed on group, OSA, occasion, and their interactions as fixed effects on group-level and participant-specific random intercepts. All outcomes were standardised before entering the analysis and response time variables were log-transformed before standardising. Contrasts described by Rouder et al. (2012) as implemented in contr.equalprior() function from the "bayestestR" R package (Makowski, Ben-Shachar, and Lüdecke 2019) were specified for all group-level parameters to ensure that all pairwise prior differences are centred around zero. Weakly informative priors, i.e. *Normal(0,1)* for group-level parameters and *Exponential(1)* for participant-level and residual variances, were specified to ensure the model converges to reasonable parameter values. Employing LMMs allowed us to use all data without requiring the participants to have both enrollment and retest measurements.

To ensure the results are informed by data, prior and likelihood sensitivity of posterior estimates was evaluated via the powerscale_sensitivity() function from "priorsense" R package (Kallioinen et al. 2023). Moreover, to evaluate model fit, posterior predictive means and SDs of the model within each combination of group, OSA, and assessment were visually compared to values observed in the data. All LMMs were fitted using Stan's (version 2.21.0) build-in Hamiltonian Monte Carlo sampler accessed via R version 4.3.3 using package "brms" (Bürkner 2017; R Core Team 2024; Stan Development Team 2020). Four parallel chains were run each for 2,000 iterations for each LMM with the first 1,000 iterations serving as a warm-up. Convergence was checked numerically by inspection of the $\hat{R}s$ and visually by inspection of trace plots.

After establishing model fit, the results were summarised by computing pairwise comparisons based on main effects, two-way interactions and three-way interactions between group, OSA and occasion. These comparisons were then described by their medians, 95% equal-tailed posterior probability intervals (PPIs), and probability of direction (*pd*, i.e., the certainty associated with the most probable direction of the effect) on the original outcome scale. Since this portion of our analysis was purely exploratory and was not set-up to formally test any hypothesis, we did not set any decision threshold regarding reported posterior comparisons but instead interpreted *pd* as continous index of effect existence probability following guidelines of Makowski et al. (2019) whereby $pd \leq$

95% indicates uncertain effect, *pd* > 95% indicates possibly existing effect, *pd* > 97% indicates likely existing effect, *pd* > 99% indicates probably existing effect, and *pd* > 99.9% indicates almost certainly existing effect.

Results

Sample description

In total 45 PD patients (24 OSA- and 21 OSA+) and 41 HC subjects (21 OSA- and 20 OSA+) were included in the study. Descriptive statistics of the sample are summarised in Table 1. At the uncorrected 5% α level, we reject hypotheses of zero difference between OSA+ and OSA- groups in mean BMI and percentage of men. More precisely, the OSA+ group in our sample was characterised by higher percentage of men and higher BMI compared to the OSA- group. There were neither any statistically significant differences in descriptive variables between HC and PD groups nor any statistically significant group/OSA interactions.

Cortical thickness

4 Fíla

Subcortical volummetry

Across fitted linear regressions, models of left and right Accumbens showed deviations from homoscedasticity, and model of left Thalamus showed deviation from normality of residuals. None of the remaining models showed deviations from any assumption of linear regression (see Supplementary Table *subco_base_regression_coefficients.csv [NOTE FROM PEPA - placeholder text for a supplementary .csv or .xlsx]*). Figure 1 presents single data points organised by hemisphere, subcortical structure, diagnosis group and OSA. After adjusting decision threshold for 5% FDR, we can reject the null hypothesis of zero group/OSA interaction for age, sex and TIV adjusted hippocampal volume bilaterally (Table 2). This result stemms from the observation that whereas in PD group, OSA+ subjects had reliably smaller hippocampal adjusted volumes than OSA- subjects, in HC group, the difference between OSA+ and OSA- subjects' hippocampal adjusted volumes did not reach statistical significance (Figure 2). Similar pattern of results was observed in Pallidum, Amygdala, and Caudate without reaching significance level at the adjusted 5% FDR.

Table 1. Demographic data of patients and healthy controls

	Descriptive statistics[1]				Inference statistics[2]		
	HC		PD				
	OSA-	OSA+	OSA-	OSA+	Group	OSA	Group * OSA
Sex (% male)	11 (52%)	18 (90%)	13 (54%)	14 (67%)	z = -1.35, p = .178	z = -2.47, p = .013	z = 1.48, p = .138
RBD (% present)	-	-	9 (38%)	5 (24%)	-	z = 0.98, p = .326	-
Age (years)	60.58 ± 8.69	61.12 ± 8.31	60.25 ± 8.60	62.94 ± 8.50	t = 0.40, p = .688	t = -0.87, p = .384	t = -0.58, p = .562
Education (years)	15.33 ± 3.32	14.35 ± 3.33	15.12 ± 2.80	14.95 ± 2.38	t = 0.31, p = .760	t = 0.90, p = .371	t = -0.63, p = .530
BMI	25.55 ± 3.44	28.63 ± 3.62	26.91 ± 3.03	29.72 ± 3.87	t = 1.62, p = .108	t = -3.91, p < .001	t = 0.19, p = .854
Age at first symptom (years)	-	-	59.07 ± 9.13	61.63 ± 8.54	-	t = -0.97, p = .339	-
Disease duration (years)	-	-	1.38 ± 0.66	1.29 ± 0.49	-	t = 0.52, p = .603	-
MoCA (range 0-30)	26.29 ± 1.87	24.90 ± 2.75	24.96 ± 3.08	25.14 ± 3.24	t = -0.89, p = .374	t = 0.99, p = .327	t = -1.29, p = .199
MDS-UPDRS I	-	-	4.58 ± 4.11	6.57 ± 4.71	-	t = -1.51, p = .137	-
MDS-UPDRS II	-	-	6.75 ± 4.08	7.29 ± 5.73	-	t = -0.36, p = .717	-
MDS-UPDRS III (total score)	-	-	26.58 ± 14.00	30.86 ± 14.80	-	t = -0.99, p = .325	-
MDS-UPDRS III (axial subscore)	-	-	6.25 ± 3.98	6.14 ± 3.45	-	t = 0.10, p = .924	-
MDS-UPDRS III (rigidity/akinesia subscore)	-	-	15.21 ± 8.74	18.33 ± 10.40	-	t = -1.10, p = .280	-
MDS-UPDRS III (tremor subscore)	-	-	5.12 ± 3.96	6.38 ± 4.86	-	t = -0.95, p = .345	-

[1]Presented as mean ± standard deviation for continuous and count (percentage) for binary variables.
[2]Based on Gaussian (continuous variables) or logistic (binary variables) regressions with OSA (disease-specific variables) or Group, OSA and Group * OSA interaction predictor terms with coefficients computed via QR decomposition solution to the least squares problem as implemented in R glm() function.
HC, healthy controls; PD, patients with Parkinson's disease; OSA, obstructive sleep apnea; OSA+, group with moderate to severe OSA; OSA- group without moderate to severe OSA; Group, diagnosis group (PD vs HC); RBD, Rapid eye movement sleep Behavior Disorder; BMI, Body Mass Index; MoCA, Montreal Cognitive Assessment; MDS-UPDRS, Movement Disorders Society-Unified Parkinson's Disease Rating Scale.

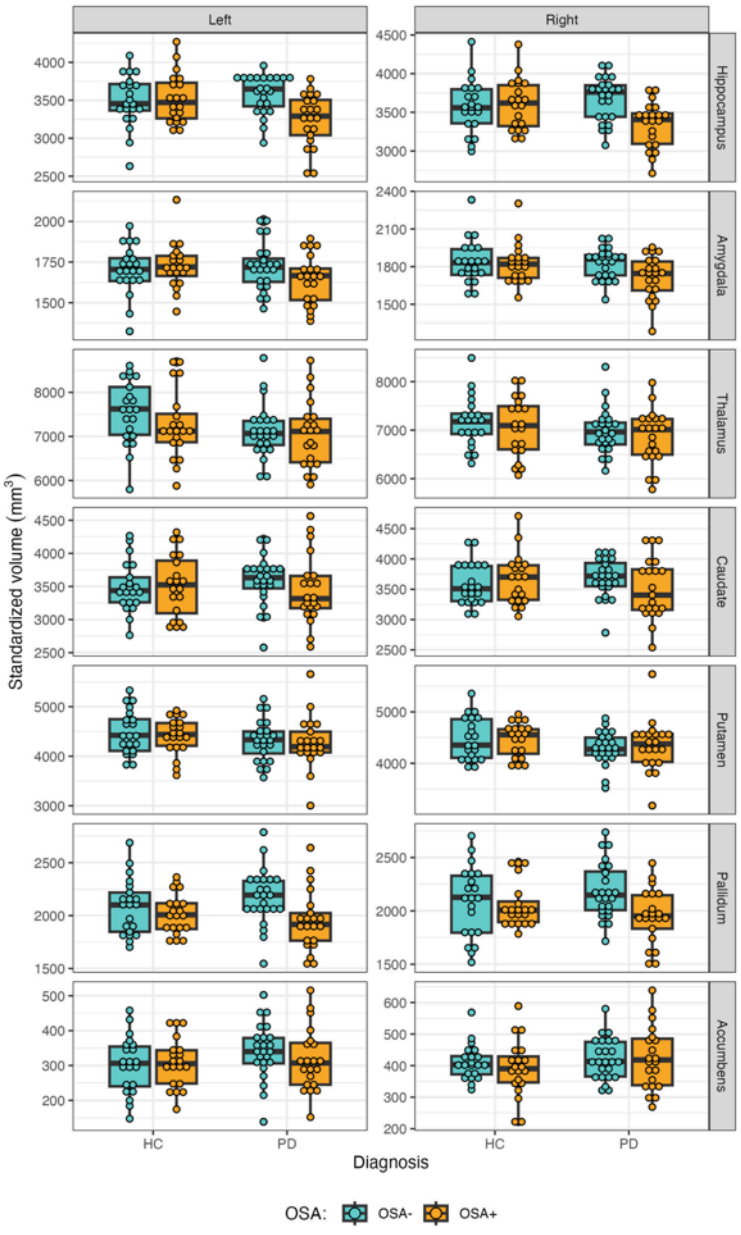

Figure 1. Raw data (points) as well as median (bar), first and third quartiles (hinges) and 1.5-times interquartile range (whiskers) of standardised volume of subcortical structures being compared between diagnostic and OSA groups. Standardisation for this figure was calculated as (raw volume/TIV) * in-sample-mean(TIV). *WILL ADD P-VALUES, PEPA.*

Table 2. Results of regression analyses estimating means of subcortical structures' volume conditional on diagnosis group and obstructive sleep apnea status

	Left hemisphere							Right hemisphere						
	β^1	SE	95% CI	t value	p-value	s-valu	sig.	β^1	SE	95% CI	t value	p-valu	s-valu	sig.
Hippocampus														
Group	-0.17	0.17	[-0.51, 0.17]	-0.990	.325	1.62		-0.20	0.18	[-0.55, 0.16]	-1.112	.270	1.89	
OSA	0.16	0.17	[-0.18, 0.49]	0.938	.351	1.51		0.18	0.17	[-0.16, 0.52]	1.057	.294	1.77	
Group * OSA	1.16	0.32	[0.52, 1.79]	3.608	< .001	10.86	*	1.09	0.33	[0.44, 1.74]	3.319	.001	9.51	*
Amygdala														
Group	-0.07	0.17	[-0.42, 0.27]	-0.430	.668	0.58		-0.24	0.18	[-0.59, 0.11]	-1.363	.177	2.50	
OSA	-0.01	0.17	[-0.34, 0.32]	-0.049	.961	0.06		0.13	0.17	[-0.21, 0.47]	0.758	.451	1.15	
Group * OSA	0.51	0.32	[-0.12, 1.15]	1.606	.112	3.16		0.55	0.33	[-0.10, 1.21]	1.679	.097	3.37	
Thalamus														
Group	-0.32	0.15	[-0.62, -0.01]	-2.061	.043	4.55		-0.13	0.16	[-0.44, 0.18]	-0.855	.395	1.34	
OSA	0.08	0.15	[-0.21, 0.38]	0.564	.574	0.80		0.08	0.15	[-0.22, 0.38]	0.546	.587	0.77	
Group * OSA	-0.24	0.28	[-0.80, 0.33]	-0.836	.406	1.30		0.00	0.29	[-0.58, 0.58]	0.002	.998	0.00	
Caudate														
Group	0.06	0.21	[-0.36, 0.48]	0.281	.780	0.36		0.01	0.21	[-0.40, 0.42]	0.041	.967	0.05	
OSA	0.05	0.20	[-0.35, 0.46]	0.265	.792	0.34		-0.02	0.20	[-0.42, 0.38]	-0.098	.922	0.12	
Group * OSA	0.35	0.39	[-0.43, 1.13]	0.899	.371	1.43		0.60	0.38	[-0.16, 1.36]	1.573	.120	3.06	

Table 2. Results of regression analyses estimating means of subcortical structures' volume conditional on diagnosis group and obstructive sleep apnea status

	Left hemisphere							Right hemisphere						
	β[1]	SE	95% CI	t value	p-value	s-value	sig.	β[1]	SE	95% CI	t value	p-value	s-value	sig.
Putamen														
Group	-0.19	0.17	[-0.53, 0.15]	-1.126	.263	1.92		-0.22	0.16	[-0.53, 0.10]	-1.374	.173	2.53	
OSA	0.01	0.17	[-0.32, 0.34]	0.060	.953	0.07		-0.14	0.15	[-0.44, 0.16]	-0.905	.368	1.44	
Group * OSA	-0.11	0.32	[-0.75, 0.52]	-0.355	.723	0.47		-0.18	0.29	[-0.76, 0.40]	-0.608	.545	0.88	
Pallidum														
Group	0.18	0.20	[-0.22, 0.58]	0.904	.369	1.44		0.00	0.20	[-0.40, 0.40]	0.010	.992	0.01	
OSA	0.40	0.19	[0.01, 0.78]	2.055	.043	4.53		0.28	0.19	[-0.10, 0.67]	1.452	.150	2.73	
Group * OSA	0.61	0.37	[-0.13, 1.34]	1.634	.106	3.23		0.77	0.37	[0.03, 1.51]	2.060	.043	4.55	
Accumbens														
Group	0.14	0.20	[-0.26, 0.54]	0.712	.479	1.06		0.10	0.19	[-0.29, 0.48]	0.500	.618	0.69	
OSA	0.10	0.19	[-0.28, 0.49]	0.532	.596	0.75		0.05	0.19	[-0.32, 0.43]	0.286	.775	0.37	
Group * OSA	0.22	0.37	[-0.52, 0.96]	0.594	.554	0.85		-0.24	0.36	[-0.96, 0.47]	-0.679	.499	1.00	

[1]Values based on in-sample standardised outcome predicted by Group, OSA, Group * OSA interaction, age, sex, and TIV via QR decomposition solution to the least squares problem as implemented in R lm() function. Negative values imply smaller adjusted volume of a subcortical structure in PD compared to HC (Group rows), OSA+ compared to OSA- (OSA row) or smaller OSA+ - OSA- difference in HC compared to PD (Group * OSA rows), the reverse is true for positive values.

β, regression coefficient estimate; SE, standard error; CI, confidence interval; OSA, obstructive sleep apnea; sig., coefficients statististically significantly different from 0 after adjusting the p-value threshold for 5% False Discovery Rate via Benjamini-Hochberg adjustment applied to all statistical tests presented in this table are denoted by asterisk "*".

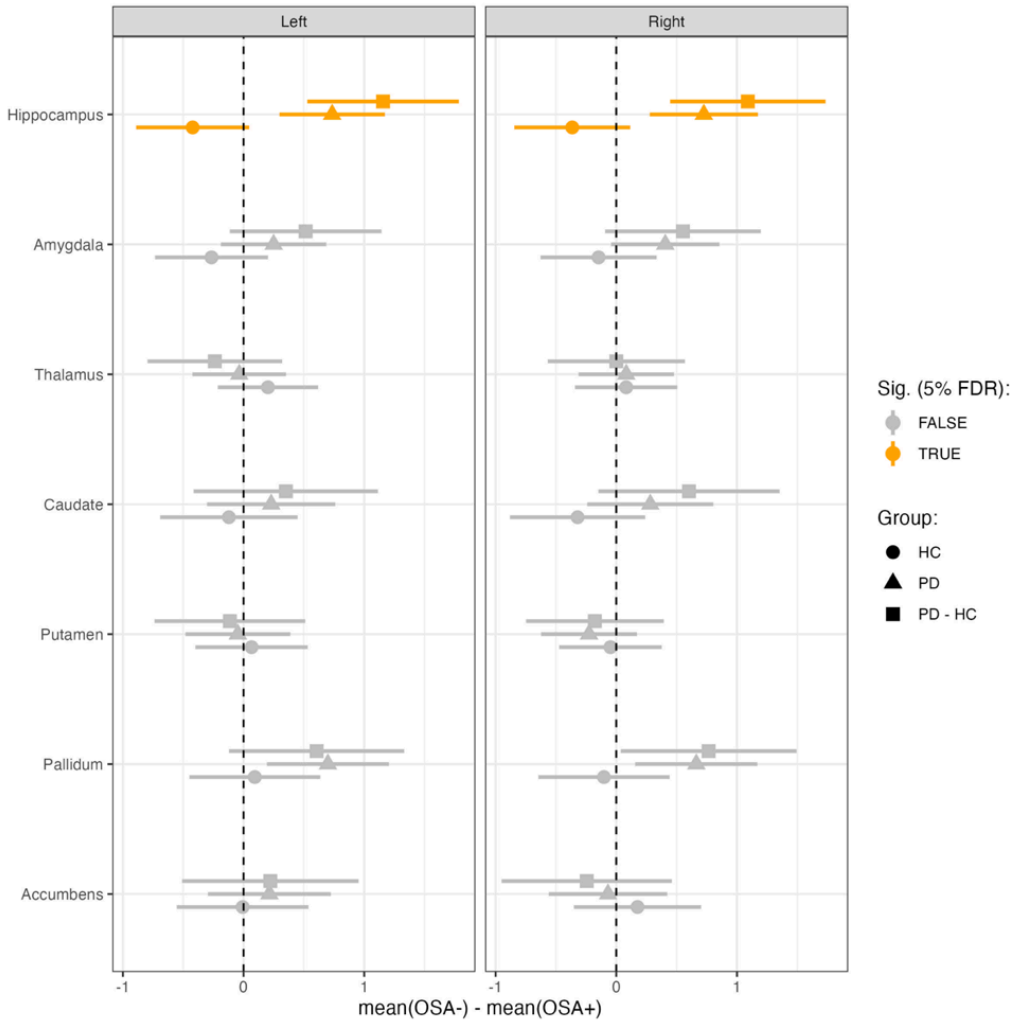

Figure 2. Forest plot showing comparisons of estimated mean age, sex, and TIV adjusted volumes of subcortical structures conditional on group diagnosis and OSA. X-axis represents in-sample standardised difference between mean of OSA- and OSA+ groups estimated from linear regression separately in HC group (circles), PD group (triangles), and difference-in-differences (i.e., interaction) between PD and HC groups (square). Horizontal bars represent non-adjusted 95% confidence intervals. Cases with interaction statistically significantly different from zero after adjusting for 5% false discovery rate via the Benjamini-Hochberg procedure are printed in orange. The figure is based on Supplementary table *subco_base_marginal_effects.csv (NOTE FROM PEPA - placeholder text for a supplementary .csv or .xlsx)*

Hippocampal fields

Across fitted linear regressions, only the model of left Presubiculum body showed deviation from normality of residuals, none of the remaining models showed any deviations from any assumption of linear regression (see Supplementary Table *hippo_base_regression_coefficients.csv [NOTE FROM PEPA - placeholder text for a supplementary .csv or .xlsx]*). The group/OSA interaction was detected using the 5% FDR adjusted threshold in all but right hippocampal tail adjusted volume in the longitudinal axis, in bilateral Presubiculum (both head and body), Subiculum body, and CA1 head as well as in right Parasubiculum, left Subiculum head, right CA4DG head and right HATA (Figure 3).

Cognitive variables

Number of subjects available for the analysis of cognitive variables is presented in Table A1. More retests were available in the PD compared to HC group. All LMMs converged to a stable posterior distribution according to convergence diagnostics ($\hat{Rs} \leq 1.01$). According to posterior predictive checks, all models represent data means well in each combination of measurement occasion (enrollment vs. retest), group (HC vs. PD) and OSA (OSA+ vs. OSA-) cells, and we did not detect prior sensitivity in any parameter of any model implying that posterior model parameters are likely primarily informed by the data. The raw data are presented in Figure A1 and modelling results are presented in Table A2. Across analyses, we observed a likely existing occasion * group interaction in index of episodic memory and learning RAVLT immediate recall (IR), and attention indexes TMT-A, PST-D, and PST-W, as well as probably existing main effect of group in case of both parts of TMT as well as almost certainly existing group main effect in GPT bilaterally. Regarding the main effect of group, PD patients showed smaller completion times of both parts of TMT and GPT indicating processing speed, attention, visuo-spatial scanning or fine motor skill with upper extremity deficit in de novo PD. In RAVLT-IR, patients with PD recalled less words in the retest compared to enrollment whereas number of words recalled by HC subjects did not noticeably change implying early verbal memory and learning decline in de novo PD (similar pattern of results was observed in delayed recall of RAVLT, however, it was of uncertain level of effect existence probability, see Table A2). On the other hand, in the attention indexes TMT-A, PST-D and PST-W, patients with PD showed slowing in retest compared to enrollment whereas HC subjects showed relatively faster completion times in retest compared to enrollment implying that de novo PD patient may show not only slowing of their performance in sustained attention task but also a lack of practice effect that would be otherwise present. Model means of cognitive effect indexes conditional on OSA and its interaction with group or occasion were of uncertain probability of effect existence across outcome variables.

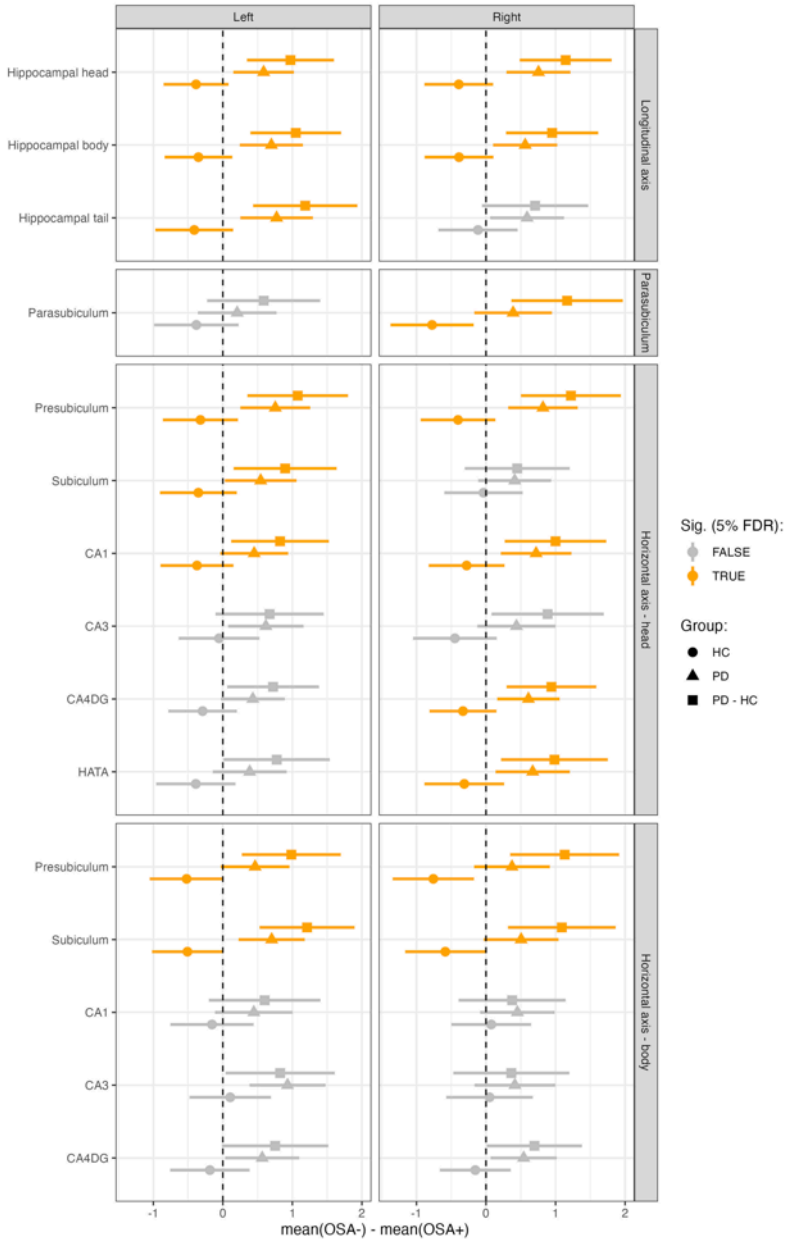

Figure 3. Forest plot showing comparisons of estimated mean age, sex, and TIV adjusted volumes of hippocampal fields conditional on group diagnosis and OSA. X-axis represents in-sample standardised difference between mean of OSA- and OSA+ groups estimated from linear regression separately in HC group (circles), PD group (triangles), and difference-in-differences (i.e., interaction) between PD and HC groups (square). Horizontal bars represent non-adjusted 95% confidence intervals. Cases with interaction statistically significantly different from zero after adjusting for 5% false discovery rate via the Benjamini-Hochberg procedure are printed in orange. The figure is based on Supplementary table *hippo_base_marginal_effects.csv (NOTE FROM PEPA - placeholder text for a supplementary .csv or .xlsx)*

THIS PART ABOUT COGNITION MAY BE BETTER PUT IN A MORE DETAIL TO SUPPLEMENTARY MATERIALS (TOGETHER WITH ITS METHODS SECTION) AND REPORTED IN THE MAIN TEXT ONLY IN SMALLER POINTS, PEPA.

Appendix

Table A1. Number of participants included in the exploratory analysis of cognition

	Enrollment				Retest			
	HC		PD		HC		PD	
	OSA-	OSA+	OSA-	OSA+	OSA-	OSA+	OSA-	OSA+
Memory								
RAVLT-IR	21	20	23	20	10	5	17	13
RAVLT-B	21	20	23	20	10	5	17	13
RAVLT-DR	21	20	23	20	10	5	17	13
RAVLT-Rec-FP	20	20	23	20	10	5	17	13
RAVLT-Rec-FN	21	20	23	20	10	5	17	13
Attention								
TMT-A	21	20	23	20	10	5	17	13
PST-D	21	20	21	19	10	5	17	11
PST-W	21	20	21	19	10	5	17	11
Executive function								
TMT-B	21	20	23	20	10	5	15	13
PST-C	21	20	21	19	10	5	17	11
Processing speed								
GPT right	21	20	23	19	10	5	16	11
GPT left	21	20	23	19	10	5	16	11

The table shows number of participants available for each analysis of cognitive functions conditional on measurement occasion (Enrollment vs. Retest after four years), diagnosis group (HC vs PD), and OSA condition. WILL ADD ALL ACRONYMS, PEPA.

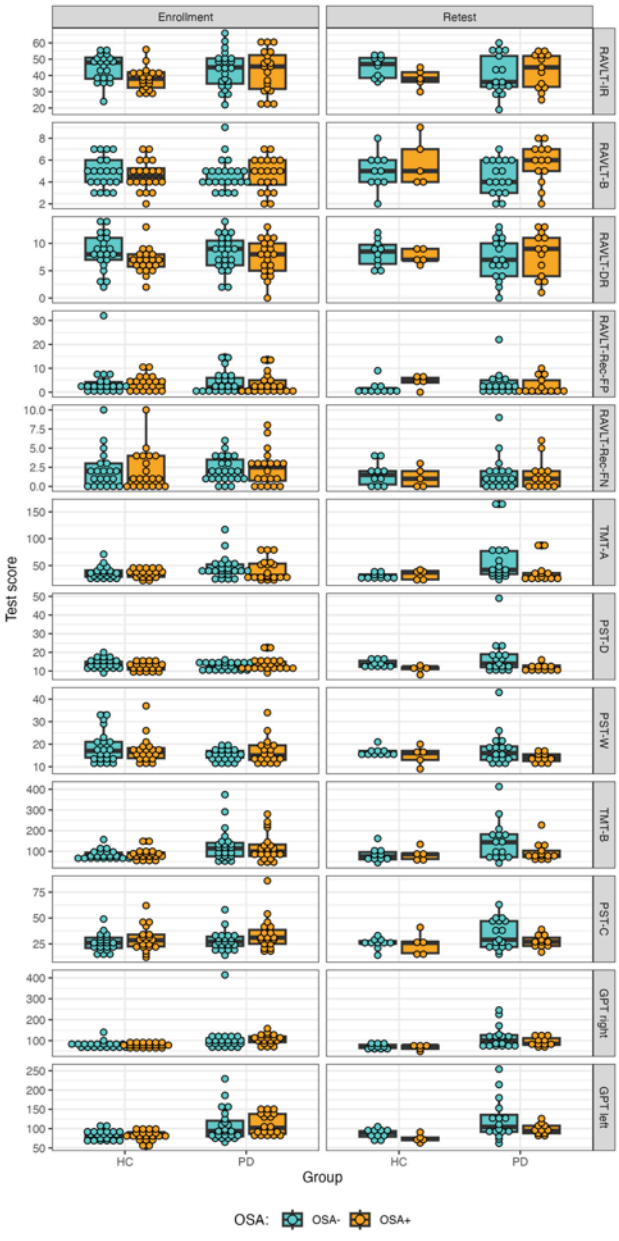

Figure A1. Raw data (points) as well as median (bar), first and third quartiles (hinges) and 1.5-times interquartile range (whiskers) of indexes of cognitive functions being compared between measurement occasion, diagnostic and OSA groups.

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