Supplementary Table 1:

Inputs to linear regression for imputing UPDRS scores from CBI, in patients with MSA. For each row, we ask which of the CBI variables in the right column best predict the single UPDRS variable on the left, using data from PSP and CBS, to establish coefficients. The coefficients are then used to estimate the UPDRS value for patients with MSA, who have known CBI but no UPDRS scores.

UPDRS variable	**CBI variables**
Psychosis	Visual hallucinations, Auditory hallucinations, Delusions
Apathy	Reduced enthusiasm, Less interest, Social motivation, Indifference, Reduced affection
Depression	Cries, Sad
Impulse control disorders / Dopamine dysregulation	Impulsivity
Sleep disturbance	Sleep disruption at night, Sleepy during day
Anxiety	Restlessness, Irritable

Supplementary Table 2: Proportion of subtypes in our dataset. PSP-RS: Richardson syndrome; PSP-C: Cortical type. PSP-SC = subcortical type including oculomotor, PSP-P (parkinsonian), and predominant gait ataxia and freezing. IDT = indeterminate. MSA-C = cerebellar subtype, MSA-P = Parkinsonian subtype. CBS-4RT = 4-repeat tau, AD+ = Alzheimer's disease (AD) biomarkers positive in cerebrospinal fluid. CBS-IDT includes 19 patients who were confirmed AD biomarker negative. Out of the 50 patients with CBS 25 patients had CSF tested for amyloid. Of those, 6 were positive for amyloid pathology.

Diagnosis	Subgroup	Count	Proportion
PSP	PSP-RS	54	50%
	PSP-C	9	8%
	PSP-SC	22	21%
	PSP-IDT	22	21%
MSA	MSA-C	22	39%
	MSA-P	30	54%
	MSA-IDT	4	7%
CBS	CBS-AD+	6	10%
	CBS-4RT	7	11%
	CBS-IDT	48	79%

Supplementary Table 3: Global cognition affected by time and motor severity.

Total adjusted MoCA was analysed using a linear model, including time since first symptom as a predictor (in years), motor severity from UPDRS part 3, and their interactions with group. Age was included as a covariate, and continuous variables were z-scored. Time since onset did not significantly affect cognition overall, however and the slope of this decline differed between the groups ($F(3,1127)=10.1$, $p<0.001$), with a relatively steeper slope seen in MSA ($t(1127)=5.18$, -0.82 MoCA points per year). MoCA declined strongly with both motor severity ($t=2.49$, 0.30 MoCA points per unit UPDRS change) and with age ($t=0.927$, 0.11 MoCA units per year). Lower table is the F statistics corresponding to ANOVA on the same linear model. Results were qualitatively unchanged when excluding any of age, motor function or time since first symptom from the model.

Time since Diagnosis	coef	t	P>|t|
Intercept [PD]	24.53	199	*** <0.001**
PSP	-1.45	-3.57	*** <0.001**
CBS	-2.66	-4.54	*** <0.001**
MSA	0.14	0.25	0.803
***time* [PD]**	0.62	4.60	*** <0.001**
PSP:time	-0.39	-1.24	0.216
CBS:time	-2.71	-6.01	*** 0.000**
MSA:time	-0.30	0.64	0.525
***motor function* [PD]**	-0.74	-5.84	*** <0.001**
PSP:motor	-0.09	-0.18	0.857
CBS:motor	-0.60	-1.12	0.264
MSA:motor	1.07	1.68	0.094
Age	-1.09	-9.31	*** <0.001**

	df	Sum sq	Mean sq	F	PR(>F)
Group	3.0	754.	252	17.8	*** <0.001**
Time since first symptom	1.0	1052	1052	74.4	0.683
Group : Time	3.0	112	37.3	2.64	*** <0.001**
Motor score	1.0	149	149.24	10.6	*** 0.001**
Group : Motor	3.0	492	164.2	11.6	0.051
Age	1.0	1225	1225	86.6	*** <0.001**
Residual	1127.0	15824	14.14		

Supplementary Table 4: Patterns of cognitive deficit in different diagnoses.

Cognitive contrasts, computed from statsmodels.ols('cognitive_score ~ C(group, Treatment(reference="PD")) * C(variable, Treatment(reference="visuospatial")'). Lower table shows ANOVA F contrasts on the linear model.

		coef	std err	t	P>|t|	[0.025	0.975]
[Visuospatial]	[PD]	17.1663	0.278	61.690	0.000	16.621	17.712
[Visuospatial]	PSP	-0.7938	0.268	-2.966	*** 0.003**	-1.319	-0.269
[Visuospatial]	CBS	-2.8102	0.363	-7.752	* **0.000**	-3.521	-2.099
[Visuospatial]	MSA	0.4740	0.356	1.331	0.183	-0.224	1.172
Attention	[PD]	3.0631	0.114	26.752	* 0.000	2.839	3.288
Fluency	[PD]	-5.2037	0.114	-45.448	* 0.000	-5.428	-4.979
Language	[PD]	7.7809	0.114	67.956	* 0.000	7.556	8.005
Memory	[PD]	7.0748	0.114	61.789	* 0.000	6.850	7.299
Attention	PSP	0.1667	0.376	0.443	0.658	-0.571	0.905
Attention	CBS	0.9705	0.512	1.894	0.058	-0.034	1.975
Attention	MSA	-0.4017	0.503	-0.799	0.424	-1.387	0.584
Fluency	PSP	-1.0251	0.376	-2.723	*** 0.006**	-1.763	-0.287
Fluency	CBS	1.6867	0.512	3.292	*** 0.001**	0.682	2.691
Fluency	MSA	0.5902	0.500	1.180	0.238	-0.391	1.571
Language	PSP	1.1256	0.378	2.976	*** 0.003**	0.384	1.867
Language	CBS	0.6592	0.512	1.287	0.198	-0.345	1.664
Language	MSA	-0.3466	0.503	-0.690	0.490	-1.332	0.639
Memory	PSP	0.6757	0.376	1.795	0.073	-0.062	1.414
Memory	CBS	1.0672	0.515	2.073	*** 0.038**	0.058	2.077
Memory	MSA	-0.1461	0.503	-0.291	0.771	-1.132	0.839
Age		-0.0564	0.004	-15.125	* 0.000	-0.064	-0.049
Time since first symptom		0.0571	0.013	4.350	* 0.000	0.031	0.083
Motor severity		-0.4194	0.035	-11.949	* 0.000	-0.488	-0.351

	df	Sum sq	Mean sq	F	PR(>F)
Group	3.0	1294.548	431.516	70.632	<0.001
ACE Domain	4.0	131463...	32865.855	5379.623	<0.001
Group × Domain	12.0	350.108	29.176	4.776	<0.001
Age	1.0	2193.047	2193.047	358.967	<0.001
Time since first symptom	1.0	45.918	45.918	7.516	<0.006
Motor severity (UPDRS 3)	1.0	872.299	872.299	142.782	<0.001
Residual	5613.0	34291.632	6.109		

Supplementary Table 5: Patterns of neuropsychiatric features in different disorders.

The neuropsychiatric contrasts were computed from statsmodels.ols('C(group, Treatment(reference="PD") * C(variable, Treatment(reference="sleep"))'), on values z-scored per psychiatric label. The model has 6696 degrees of freedom in the residuals.

	df	sum_sq	mean_sq	F	PR(>F)
Group	3.0	33.709	11.236	19.022	**<0.001**
Neuropsychiatic feature	5.0	1350.445	270.089	457.225	**<0.001**
Feature × Group	15.0	189.192	12.613	21.352	**<0.001**
age	1.0	2.816	2.816	4.767	**0.029**
time_since_first_symp	1.0	17.128	17.128	28.996	**<0.001**
motor	1.0	52.375	52.375	88.665	**<0.001**
Residual	6696.0	3955.415	0.591		

Supplementary Table 6: Comparison of subgroups of patients who had neurofilament light chain (NFL) measured, with those who did not.

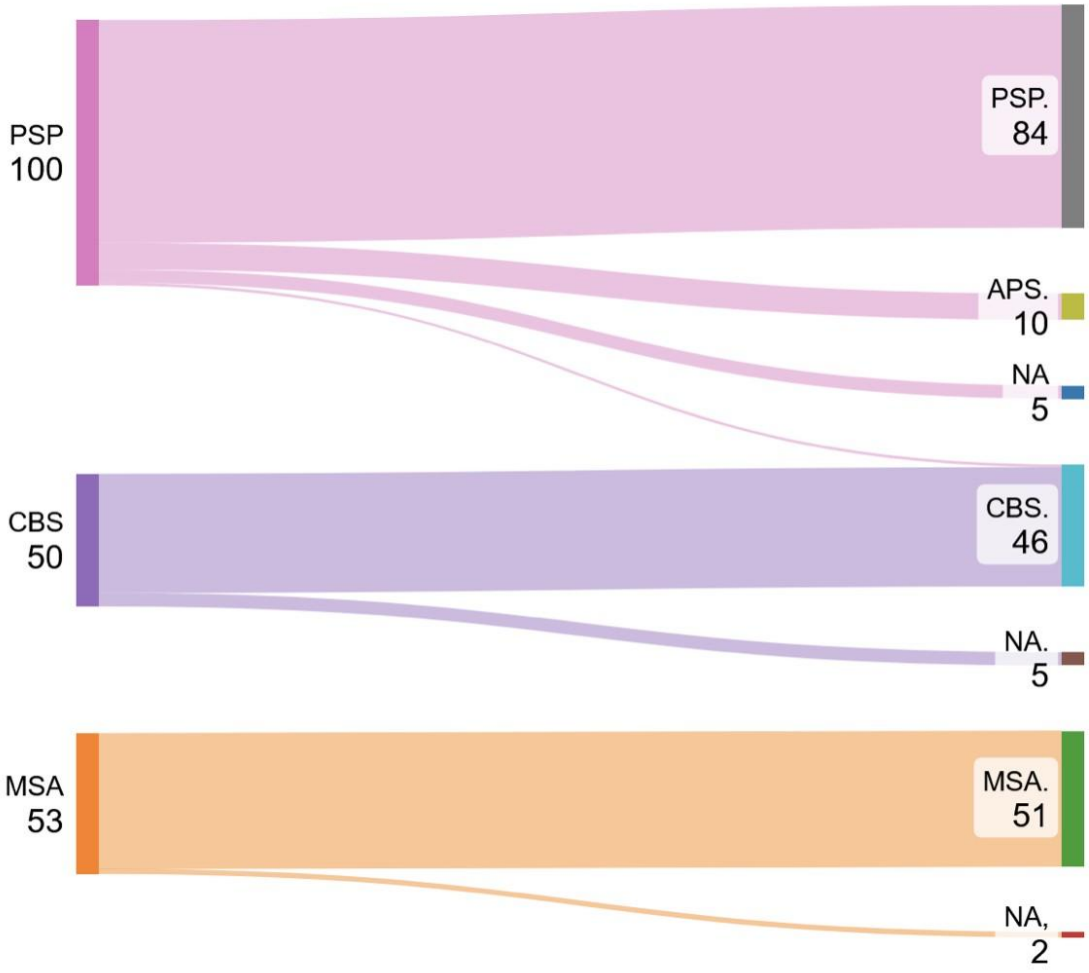
	Non-NFL mean (std)	NFL	*t* stat	p-value
Number	104	107		
Age (y)	68.6 (7.61)	65.3 (9.18)	0.36	0.72
Time since first symptom (y)	5.12 (3.24)	5.39 (3.30)	0.92	0.36
Motor score (Z)	0.126 (1.01)	-0.169 (0.88)	0.25	0.80
Schwab & England (%)	54.7 (21.5)	59.2 (22.7)	1.25	0.22

Supplementary Table 7:

NFL might also relate to rate of decline. To test this, A linear model was fitted to predict the rate of decline in cognition or motor features. As a proxy for the rate of decline, the severity (31 minus MoCA, or motor symptom score) was divided by time since symptom onset. Neither MoCA decline rate nor motor decline rate were predicted by NFL.

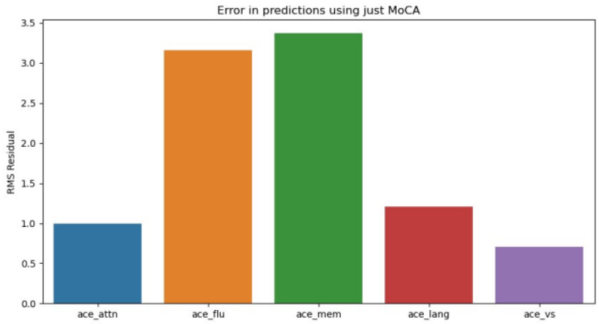
Group	**Rate of decline in:**	***t***	***p***
PSP	MoCA	$t(68)=0.49$	0.626
CBS	MoCA	$t(29)=0.58$	0.568
PSP	Motor	$t(68)=0.52$	0.607
CBS	Motor	$t(29)=0.77$	0.448

Supplementary Figure 1: Sankey diagram of Diagnosis at 12 month clinician review. Patients were re-assessed at 12 months, and clinician review diagnosis was assigned at this second timepoint. A total of 10 patients were re-labelled, where 10 were PSP patients were later labelled atypical and 1 was relabelled as CBS. NA: not assessed.

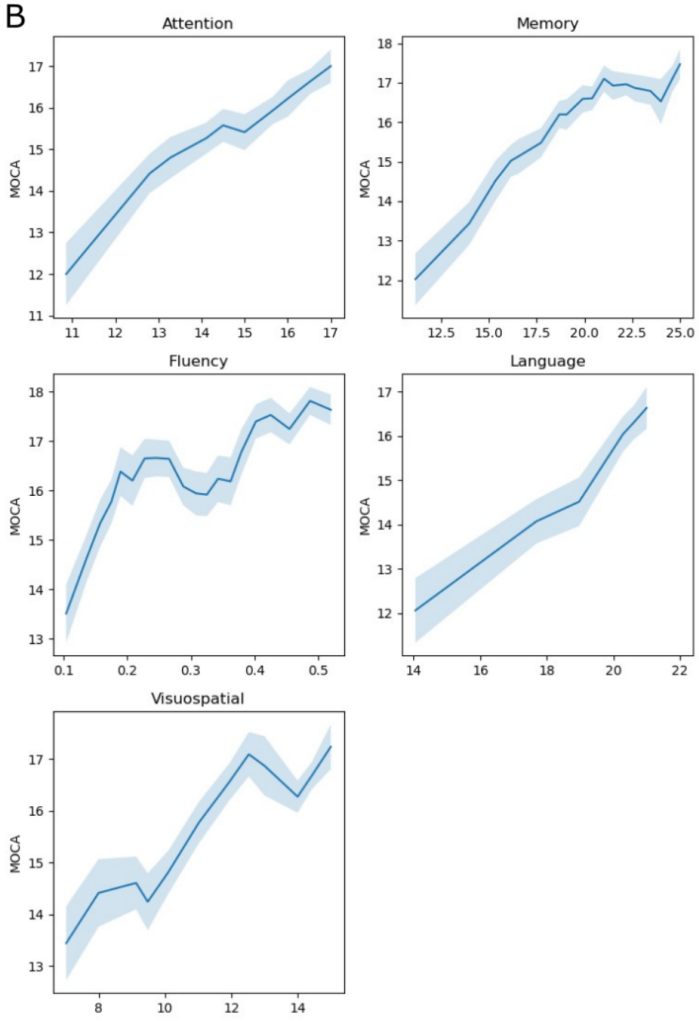


Supplementary Figure 2: Imputing cognitive domains from MoCA using the ACE. **A.** Error in estimating the ACE (root mean squared deviation) for each domain, across PROSPECT. B) Correlations between total MoCA and each of the ACE cognitive domains, illustrated using **C**. Weights for mapping Montreal Cognitive Assessment (MoCA) components onto the Addenbrooke's Cognitive Examination (ACE) domains. Computed using regularised linear regression on the N=177 individuals with both scores in PROSPECT.

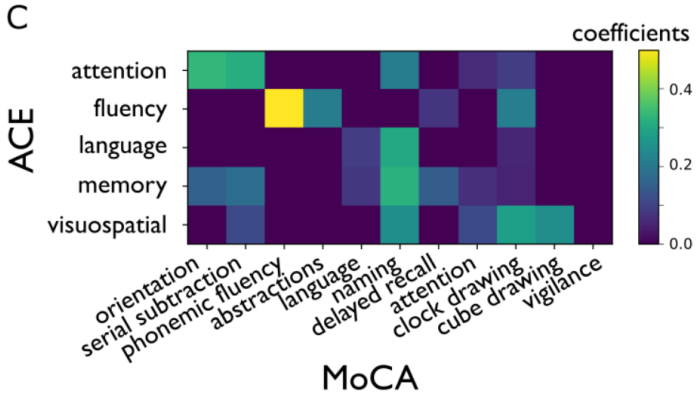
A


Error in predictions using just MoCA
RMS Residual
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ace_attn
ace_flu
ace_mem
ace_lang
ace_vs

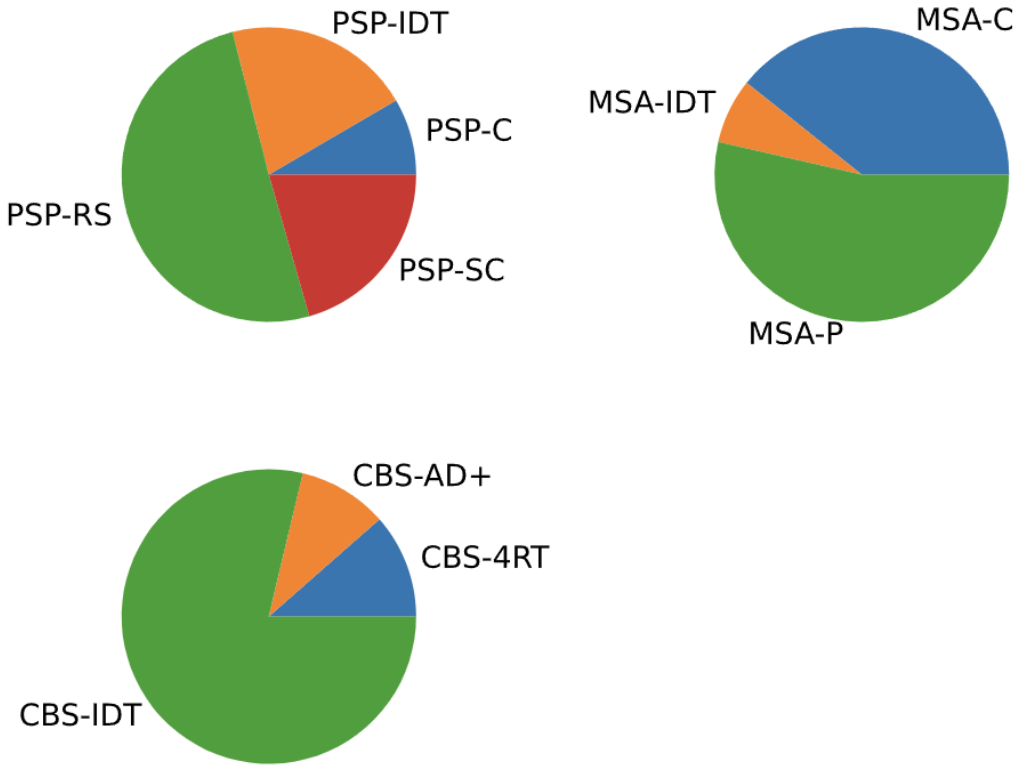
B


Attention
Memory
Fluency
Language
Visuospatial
MOCA

C

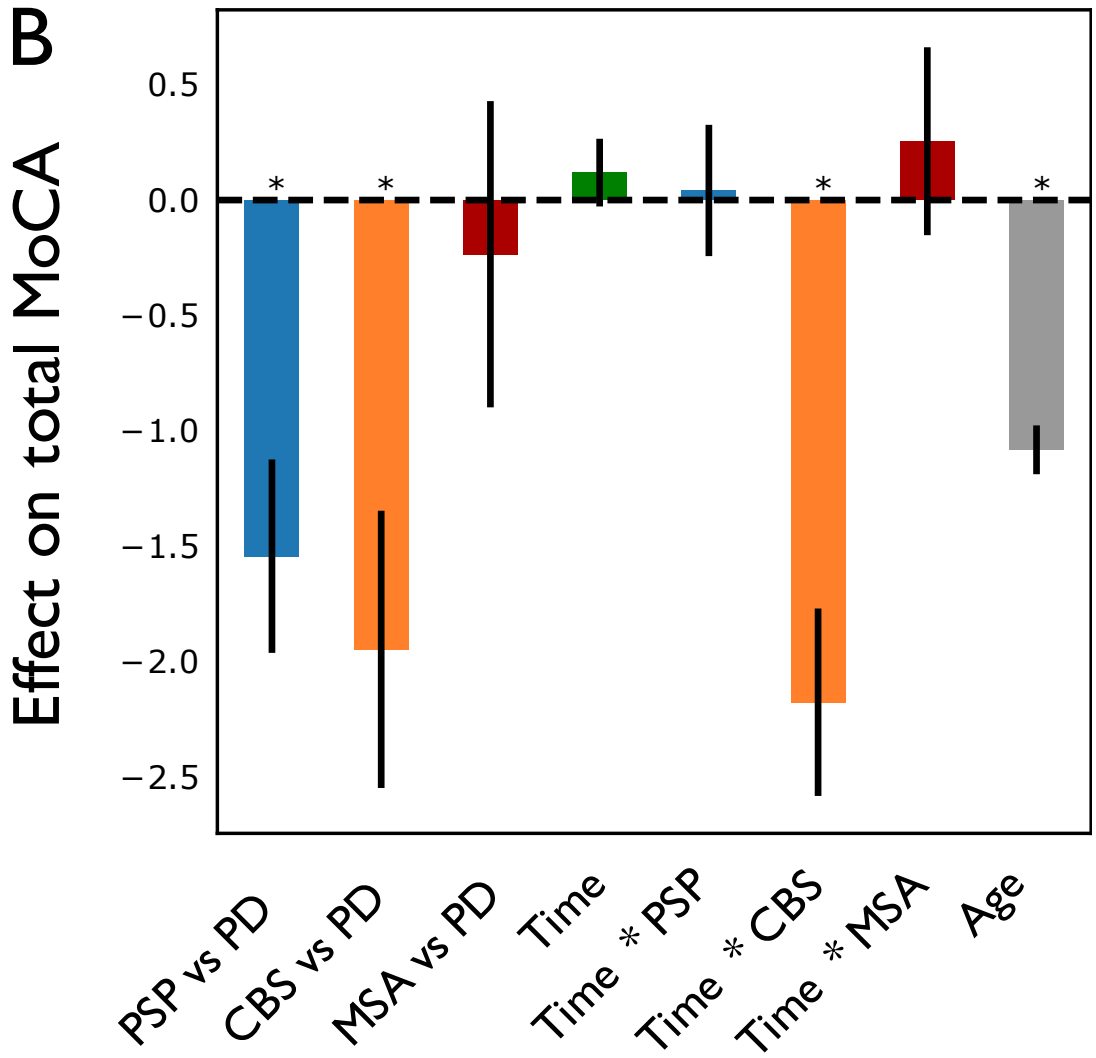

coefficients
0.4
0.2
0.0
ACE
attention
fluency
language
memory
visuospatial
orientation
serial subtraction
phonemic fluency
abstractions
language
naming
delayed recall
attention
clock drawing
cube drawing
vigilance
MoCA

Supplementary Figure 3: Proportions of subgroups within each atypical diagnosis. Proportion of subtypes in our dataset. PSP-RS: Richardson syndrome; PSP-C: Cortical type. PSP-SC = subcortical type including oculomotor, PSP-P (parkinsonian), and predominant gait ataxia and freezing. IDT = intederminate. MSA-C = cerebellar subtype, MSA-P = Parkinsonian subtype. CBS-4RT = 4-repeat tau, AD+ = Alzheimer's disease (AD) biomarkers positive in cerebrospinal fluid. CBS-IDT includes 19 patients who were confirmed AD biomarker negative.



Supplementary Figure 4: **Coefficients of linear model predicting cognitive performance.**

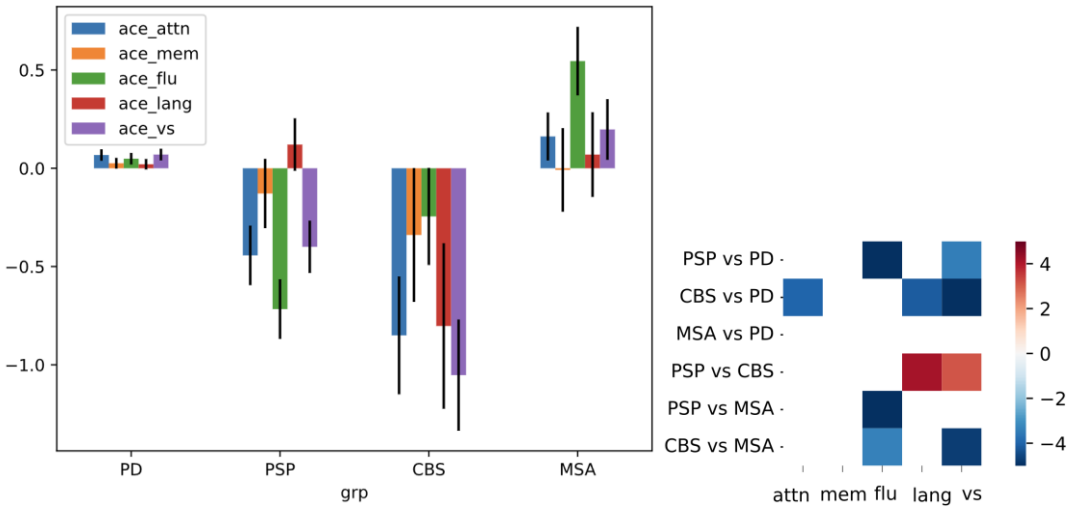
Predicting MoCA based on group, and group-specific slopes over time since symptom, with age as a covariate. CBS showed a steeper slope with increasing time, than other groups.



Supplementary Figure 5

Left: Same as figure 2A when all patients with symptoms for longer than 7.5 years were excluded.

Right: Significant contrasts after multiple comparisons correction, but excluding all patients who had symptoms for longer than 7.5 years.



Supplementary Figure 6 : Linear classifiers trained to discriminate between pairs of conditions. **A)**: Classifier using attention, memory, fluency, language and visuospatial function from the ACE. This classifier performed reasonably for PSP vs PD, but performed poorly on other groups. B) Classifier using psychosis, apathy, depression and dopamine dysregulation. The classifier performed well on PSP vs PD and MSA vs PD, with moderate scores on PSP vs CBS and MSA, and on CBS vs PD.