

Cognitive profiling accurately predicts underlying pathology in the Corticobasal Syndrome

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Introduction

The clinicopathological correlation between Corticobasal syndrome (CBS) and Corticobasal degeneration (CBD) is poor (~40-50%). CBS can often also be due to the pathologies of Alzheimer’s disease (AD) or Progressive Supranuclear Palsy (PSP)².

We tested whether initial clinical & cognitive assessments can predict pathology in CBS. This is important for:

- 1.Informing disease trajectory
- 2.Identifying eligible patients for clinical trials aimed at specific pathologies

Methods

226 patients with an initial diagnosis of CBS were assessed at the specialist Memory and Cognition & Movement Disorders clinics (1997 – 2024; Table 1).

Patients underwent **clinical assessments** with the:

- Addenbrooke’s Cognitive Exam (or revised version ACE-R)
- Cambridge Behavioural Inventory (or revised version CBI-R)
- Progressive Supranuclear Palsy Rating Scale (PSP-RS, available after 2008)

Data analysis was performed on **54/226 patients with neuropathological diagnoses at post-mortem and complete ACE-R/CBI-R results:**

STEP 1: ANCOVA used to identify differences in initial assessment across neuropathological diagnoses.

STEP 2: Principal Component Analysis (PCA) was performed to reduce the dimensionality of the data. ANCOVA was used to identify differences in principal components between neuropathological diagnoses.

STEP 3: Predictive modelling performed to assess whether clinical scores can predict neuropathology.

STEP 4: Biomarker data, including serum Aβ42:Aβ40 ratio, pTau217 and Neurofilament Light chain (NFL) were analysed across pathologically confirmed groups.

Demographics Table

Variables	Total CBS (n = 226)	AD (n = 22)	CBD (n = 20)	PSP (n = 19)	SYNUC (n=7)	Other (n = 4)	p-adj
Age at first visit	68.8 ± 8.7, [46.9 – 89.0]	63.8 ± 8.5, [48.5 – 79.3]	67.3 ± 6.5, [56.2 – 74.7]	71.0 ± 3.6† , [65.1 – 76.3]	64.5 ± 7.7 [50.7-73.1]	61.7 ± 7.8, [51.9 – 70.1]	0.047†
Sex (M:F)	101:125	7:15	9:11	11:8	3:4	3:1	ns (χ ²) ^b
Symptom Duration At first visit (years)	3.2 ± 2.2, [0.0 – 12.3]	3.4 ± 1.9, [0.5 – 7.0]	3.0 ± 1.5, [0.8 – 5.2]	2.8 ± 2.7, [0.5 – 12.2]	2.7 ± 0.8 [1.2-3.8]	3.5 ± 1.7, [2.0 – 5.7]	ns
Total (years):	7.9 ± 3.8, [0.3 – 29.8]	9.3 ± 3.3, [4.2 – 14.9]	7.6 ± 5.6, [1.9 – 29.8]	6.2 ± 2.7, [2.8 – 14.3]	6.5 ± 2.4 [4.0-11.2]	10.7 ± 4.5, [5.3 – 15.7]	ns
Proportion of Total at first visit:	0.42 ± 0.21 [0.00–1.01]	0.38 ± 0.21 [0.07–0.74]	0.43 ± 0.18 [0.12–0.75]	0.41 ± 0.22 [0.00–0.85]	0.46 ± 0.19 [0.17–0.65]	0.36 ± 0.19 [0.18–0.62]	ns
Education (years)	12.1 ± 2.7, [5.0 – 20.0]	12.1 ± 2.9, [9.0-18.0]	11.8 ± 2.3, [9.0 – 16.0]	11.2 ± 1.5, [10.0 – 15.0]	13.4 ± 3.6 [10.0–19.0]	13.0 ± 2.9 [10.0–16.0]	ns
ACE-R Total Score (max. 100)	69.2 ± 21.1, [0–98]	53.7 ± 22.2* , [13 – 98]	73.3 ± 16.7, [35 – 96]	87.3 ± 9.6, [27 – 94]	76.9 ± 16.4, [74–96]	73.8 ± 18.7 [47–90]	0.001*
CBI-R Total Score (max. 180)	42.9 ± 30.8, [0 – 142]	39.1 ± 26.1, [8 – 84]	46.0 ± 37.7, [9-142]	32.5 ±17.4, [0 – 67]	50.4 ± 25.4 [23–91]	61.7 ± 25.4 [36–77]	ns
PSP-RS Total Score (max. 100)	33.9 ± 17.0, [1 – 82]	43.3 ± 17.1, [32 – 63]	35.5 ± 30.4, [14-57]	31.0 ± 11.9, [16 – 46]	32.3 ± 2.1 [30–34]	22.5 ± 9.2 [16–29]	ns
Biomarker data available							
pTau217	0.64 ± 0.55	1.12 ± 0.62	0.67 ± 0.30	0.46 ± 0.27	0.34		ns
NFL	81.0 ± 97.0	241.3 ± 286.6	152.2 ± 192.1	128.7 ± 128.4	74.0		ns
Aβ42:Aβ40 ratio	0.056 ± 0.01	0.056 ±0.01	0.056 ± 0.01	0.060 ± 0.01	0.076		ns

Table 1. All values are given as mean ± SD, [range] for all 226 patients, and by pathology. AD = Alzheimer’s Disease, CBD = Corticobasal degeneration, PSP = Progressive supranuclear palsy. SYNUC = Synucleinopathies. Other pathologies included TDP-43 frontotemporal dementia, Globular glial tauopathy, Pick’s disease and Argyrophilic grain disease. Mean ± SD biomarker values by pathology are then given, with the number of patients for which biomarker data was available. P-values from significance testing with ANCOVA is given in the final column. *CBS individuals with AD pathology had significantly lower ACE-R scores at first visit than other pathologies. †CBS individuals with PSP pathology were significantly older than those with AD pathology. ^bSignificance for sex was calculated with a Chi squared test.

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Results (1) CBS-AD scored poorly on initial ACE-R/CBI-R

Mean Score by Neuropathological Diagnosis

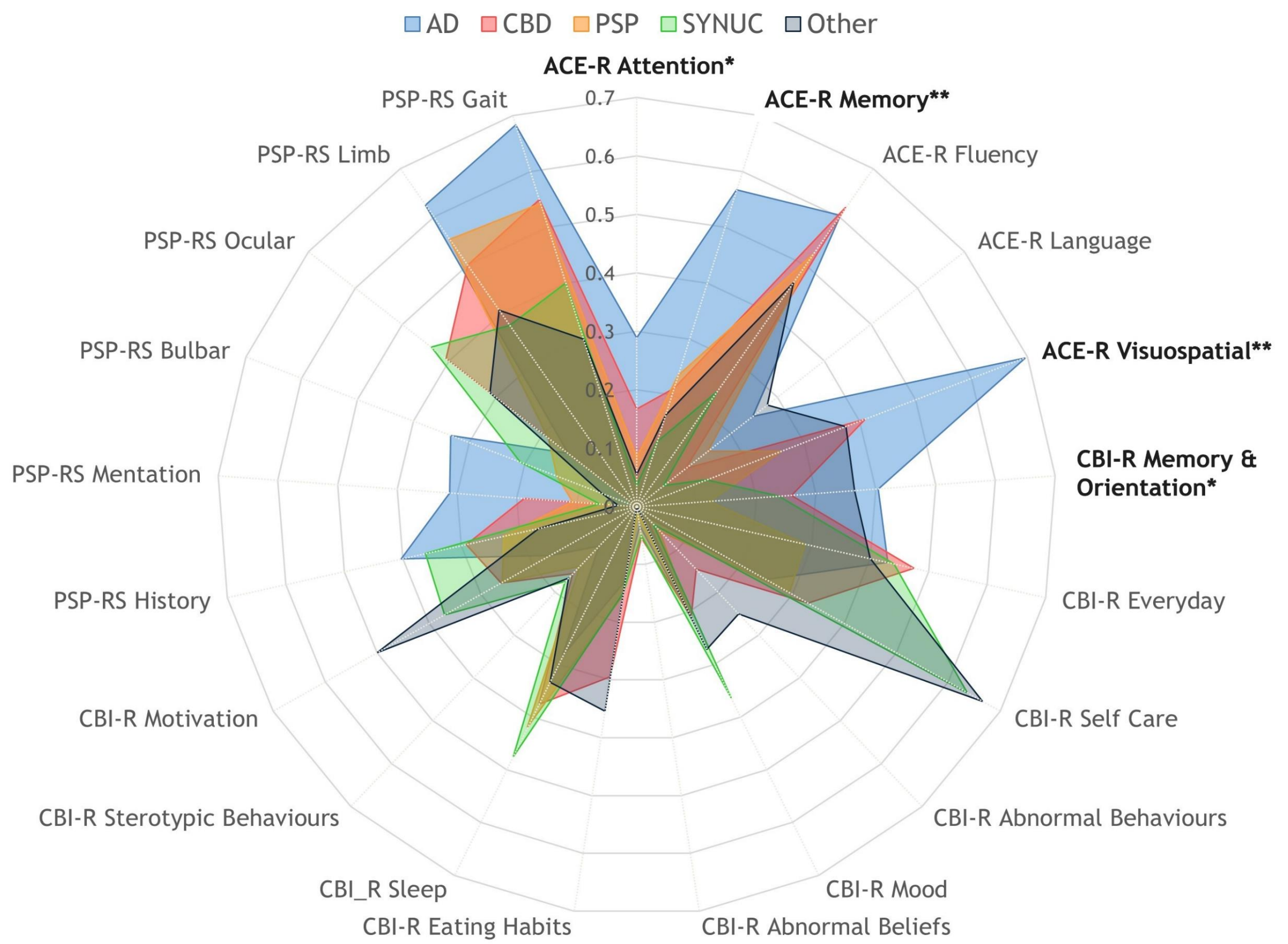


Figure 1. CBS patients with AD at postmortem, had worse ACE-R attention, memory & visuospatial scores, and worse CBI-R memory & orientation on clinical/cognitive assessment at initial presentation. Scores are standardised; higher values reflect worse severity. ANCOVA results:
• CBS-AD vs CBS-PSP: ACE-R Attention: p=0.026; ACE-R Memory: p=0.005; ACE-R Visuospatial: p=0.008; CBI-R memory & orientation, p=0.045,
• CBS-AD vs CBS-CBD: ACE-R Memory, p=0.006
• CBS-AD vs CBS-SYNUC: ACE-R Memory: p=0.050, ACE-R Visuospatial: p=0.013.

Results (2) – CBS-AD presented with worse global cognition (PC2)

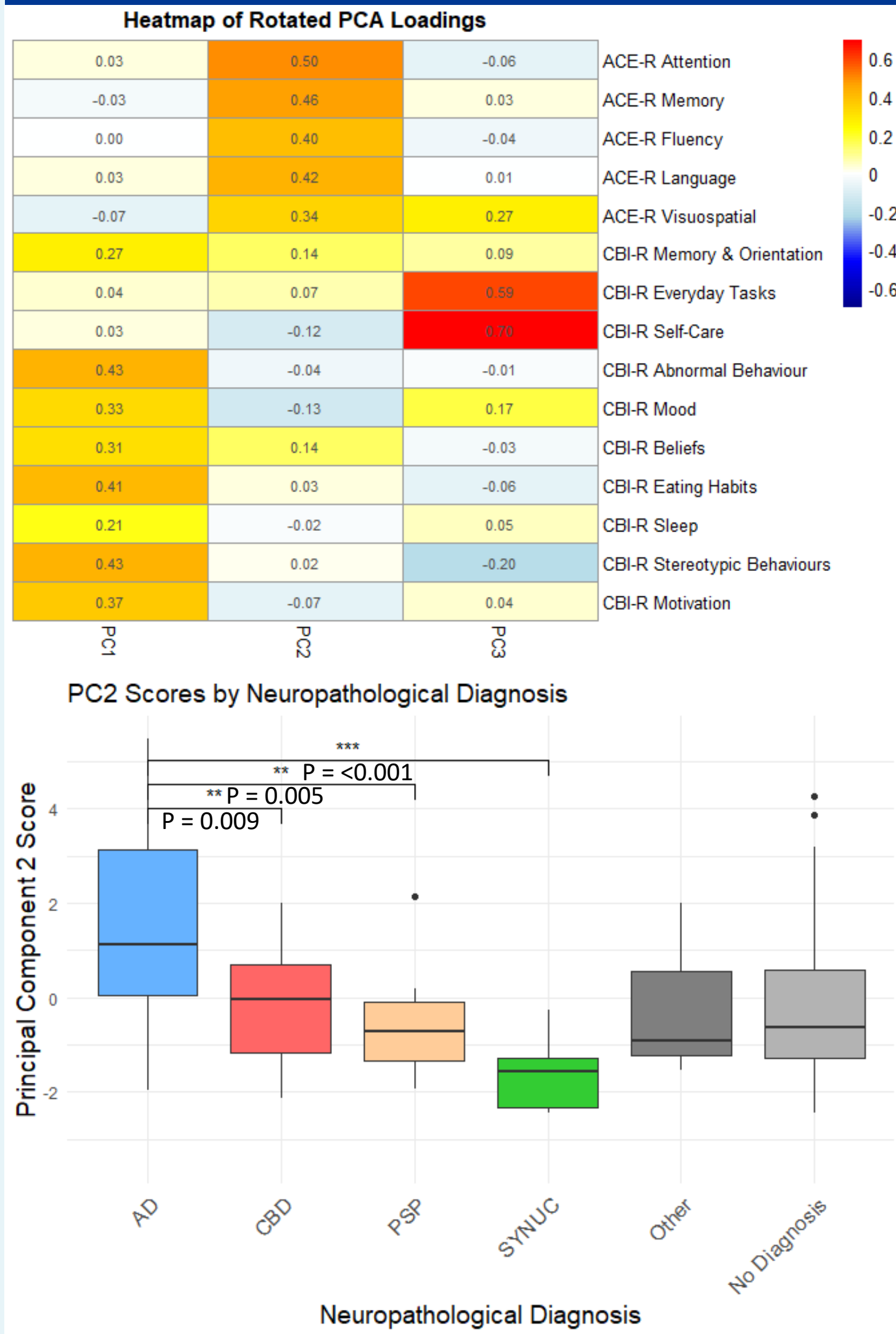


Figure 2. (A) PCA loadings heatmap of retained, varimax rotated components. **PC1: Behavioural component. PC2: Cognitive component. PC3: Functional component.** **(B)** Boxplots for PC2. **CBS-AD patients have higher PC2 scores = Worse global cognition**

Result (3) Predictive modelling can predict AD pathology at initial assessment with 85.6% accuracy

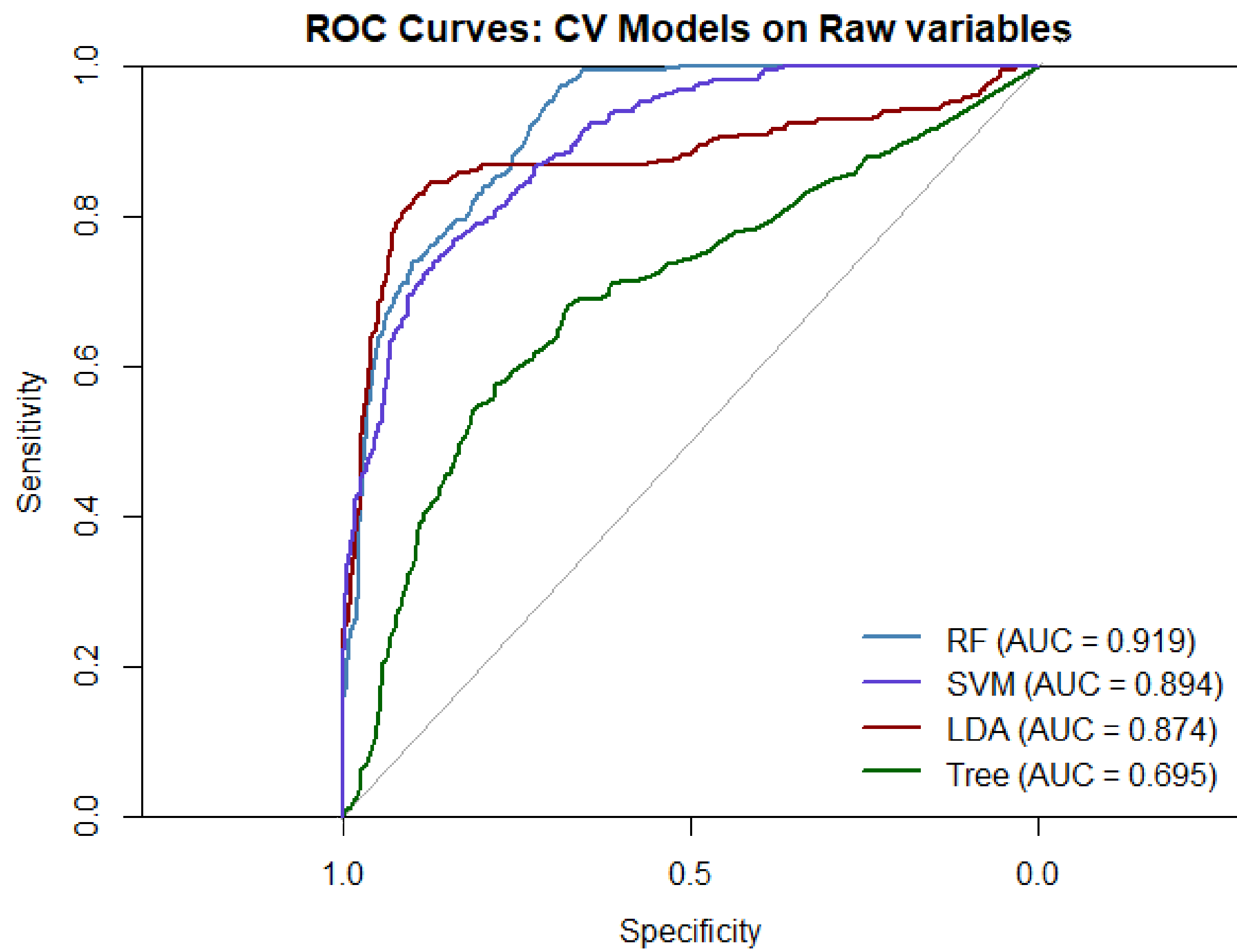


Figure 3. Random Forest (RF), Support Vector Machine (SVM), and Linear Discriminant Analysis (LDA) models were able to accurately predict AD pathology from ACE-R/CBI-R scores.

The best model was **Random Forest** with: **AUC 0.919, Accuracy 85.6%, Sensitivity 59.3%, Specificity 95.7%.**
The **most important variables** were: **ACE-R Visuospatial, ACE-R Memory, and CBI-R Memory & Orientation.**

Results (4) – Plasma biomarkers did not reliably differentiate pathology

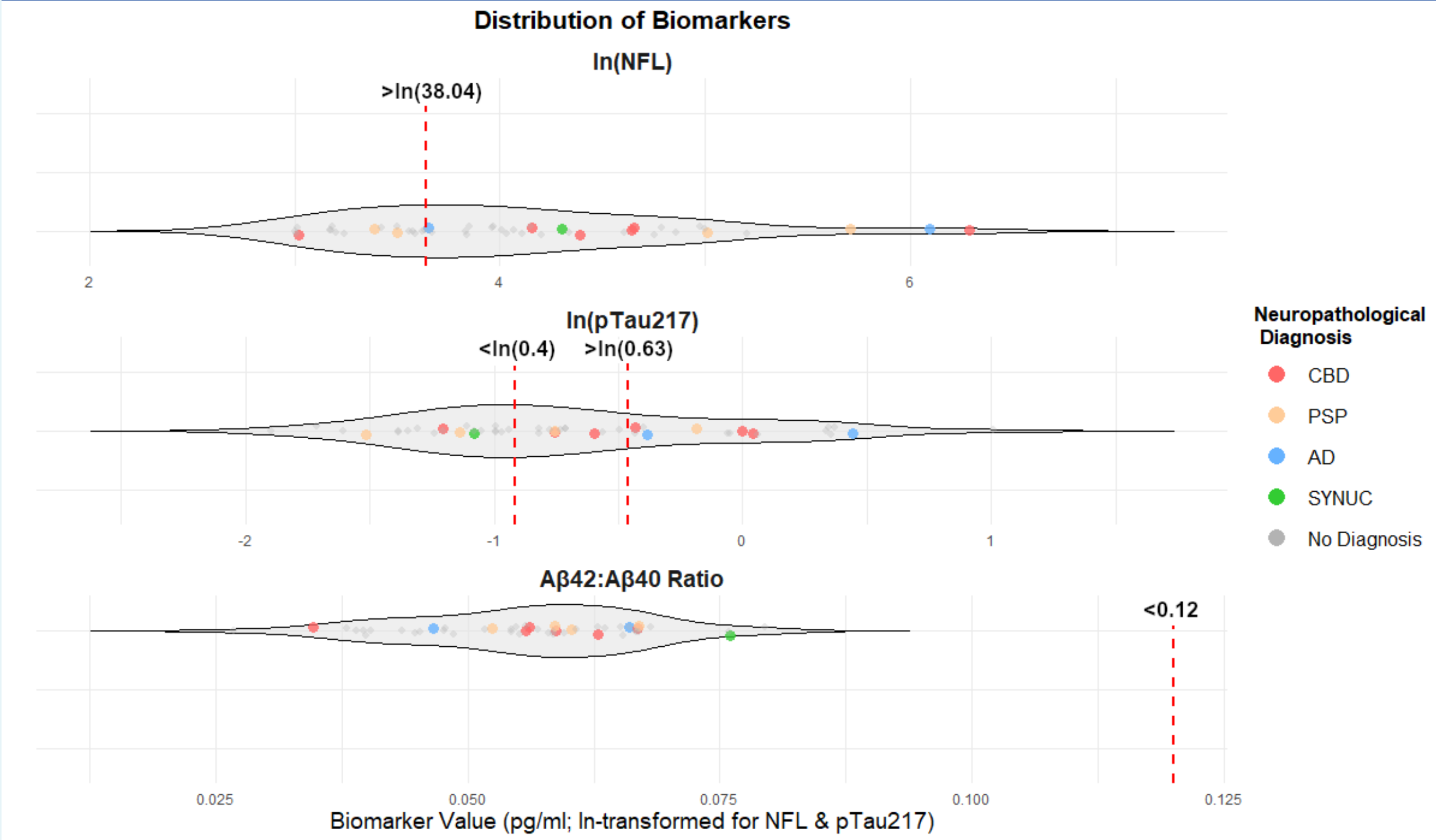


Figure 4. Violin plots showing the distribution of biomarkers, with patient datapoints colour coded by pathological diagnosis.

Cut-offs for predicting AD pathology are shown with dashed lines (Aβ42:Aβ40: <0.15²; NFL: >38.04³; NFL:pTau217: >102, <23.89⁴; pTau217: >0.63, <0.4⁴).

All patients were under the cut-off for Aβ42:Aβ40, despite many being confirmed as not having AD primary pathology.

Conclusions

1. Patients with CBS-AD had a cognitive profile with worse attention, memory & visuospatial function at 1st clinic presentation
2. Patients with CBS-AD had worse global cognition at 1st clinic presentation, but behavioural/functional components were the same.
3. Initial ACE-R/CBI-R scores differentiate CBS-AD from CBS-CBD/PSP with 85.6% accuracy in predictive models.
4. There is a high % of ‘AD’ biomarker positivity even in patients with CBS-PSP/CBD.
5. Quick/cost-effective cognitive assessments can be used to predict CBS pathology but larger sample size with biomarkers are needed in the future

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