

Key drivers of severity in Alzheimer's disease and frontotemporal dementia identified through machine learning in a Latin American cohort

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01 INTRODUCTION

The Clinical Dementia Rating (CDR) is widely used to stage disease severity in Alzheimer's disease dementia (ADD) and frontotemporal dementia (FTD). As severity progresses, ADD and FTD are characterized by increasing cognitive decline, neuropsychiatric and behavioral symptoms, and functional impairment. However, studies examining dementia severity have often considered these domains separately. Even when cognition, neuropsychiatric symptoms and functioning have been examined together, functional assessment has primarily focused on activities of daily living, with less attention to broader dimensions of everyday functioning, such as everyday cognition, mobility and social functioning.

AIM

Examine multidimensional predictors of disease severity (CDR) in ADD and FTD with machine-learning models in a Latin American cohort:

➔ To predict severity from functional, cognitive, neuropsychiatric & demographic features, and identify the most important features within each diagnostic group.

02 METHODS

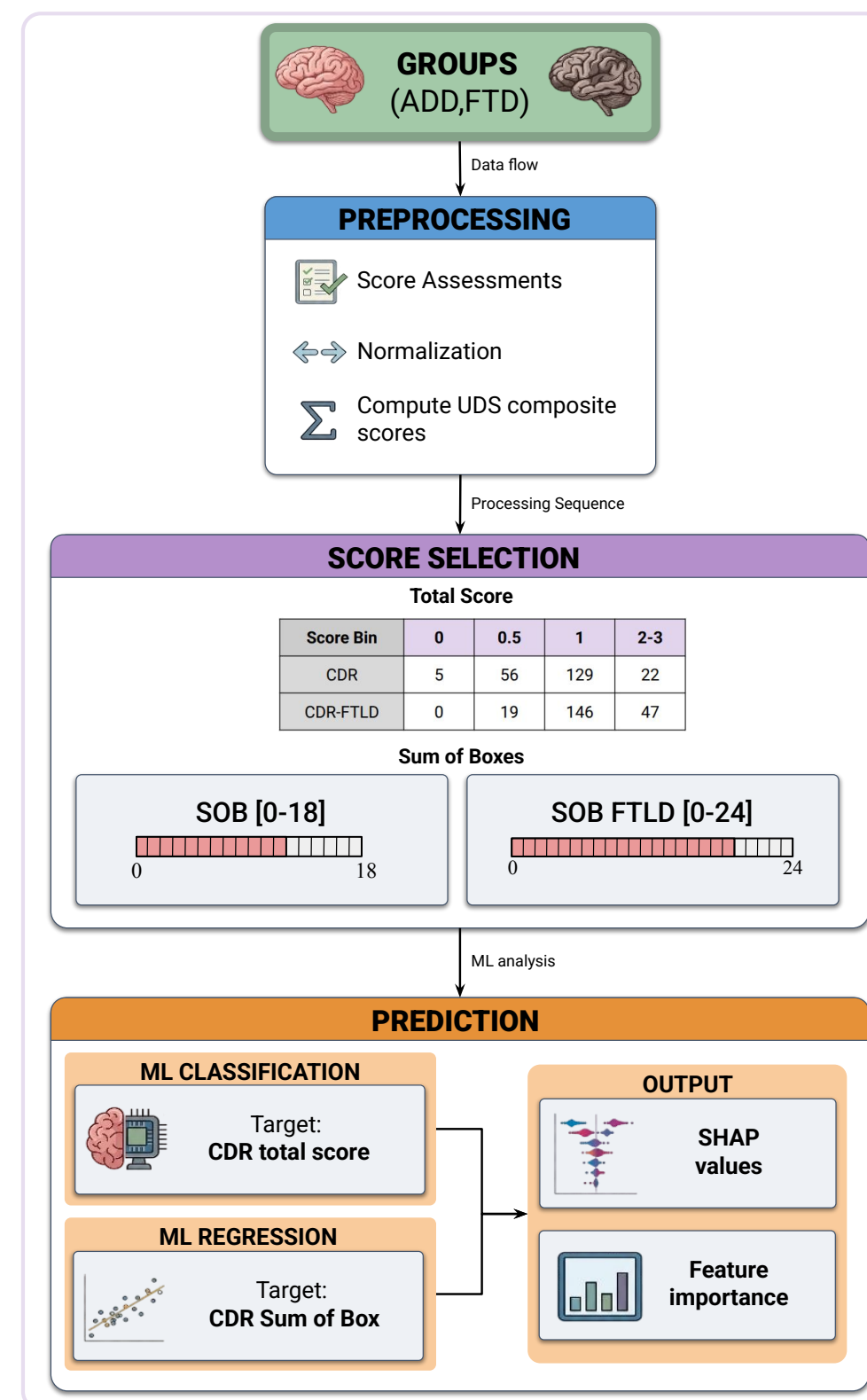


Figure 1 · Machine Learning pipeline

222

Cognitively unimpaired

140

ADD

72

FTD

Cohort. N = 434 from Chile and Peru, recruited through ReDLat. Severity was staged using the CDR for ADD and the CDR–FTLD for FTD (FTLD: frontotemporal lobar degeneration); global score and Sum of Boxes (SoB) were analyzed.

Multidimensional assessment.

Demographics: Age · sex · education

Neuropsychiatric symptoms: NPI-Q

Cognition: cognitive battery including UDS domains (memory, executive function, language, visuospatial abilities) and MMSE (global cognition)

Everyday functioning: T-ADLQ · ECog · BDRS · WHODAS

Models. Classification (Logistic Reg., Random Forest, XGBoost) for CDR / CDR–FTLD global score; regression (Linear, Ridge, Lasso, RF, Gradient Boosting) for SoB. 10-fold CV; SHAP feature importance.

Feature subsets. F1 Cognitive battery (7) · F2 NPI (4) · F3 T-ADLQ (4) · F4 +WHODAS/BDRS/ECog (7) · **F5 all 13 features** (see table 1, all subsets contains demographics variables)

NPI-Q: Neuropsychiatric Inventory Questionnaire; UDS: Uniform data set; MMSE: Mini-Mental State Examination; T-ADLQ: Technology–Activities of Daily Living Questionnaire; ECog: Everyday Cognition scale; BDRS: Blessed Dementia Rating Scale; WHODAS: World Health Organization Disability Assessment Schedule.

03 SAMPLE CHARACTERISTICS

Table 1 · Demographic & neuropsychological profile (mean ± SD (min-max))				
Variable	CU	ADD	FTD	χ ² global p
Demographics				
N (% Chile)	222 (52)	140 (41)	72 (27)	-
Female	77%	72%	47%	<.001 ^{1,3}
Age (years)	66.53 ± 8.23 (48–80)	71.00 ± 7.22 (48–80)	66.26 ± 8.33 (47–80)	<.001 ^{1,3}
Education (years)	13.47 ± 4.81 (4–26)	13.37 ± 4.03 (4–26)	13.47 ± 3.50 (4–21)	-
Dementia Severity				
CDR-FTLD total score	0.00 ± 0.00 (0–0)	1.16 ± 0.44 (0.5–2)	1.24 ± 0.57 (0.5–3)	<.001 ^{1,2}
CDR-FTLD SoB	0.00 ± 0.00 (0–0)	5.66 ± 2.34 (2–12)	6.83 ± 3.49 (0.5–19)	<.001 ^{1,3}
CDR total score	0.00 ± 0.00 (0–0)	0.99 ± 0.41 (0.5–2)	0.89 ± 0.53 (0–3)	<.001 ^{1,2}
CDR SoB	0.00 ± 0.00 (0–0)	5.45 ± 2.30 (2–12)	5.15 ± 2.84 (0–15)	<.001 ^{1,2}
Functional measures				
T-ADLQ	1.24 ± 2.35 (0–14.44)	33.58 ± 19.74 (1.15–82.80)	35.71 ± 25.07 (0–88.89)	<.001 ^{1,2}
WHODAS	1.06 ± 2.23 (0–14)	2.60 ± 3.23 (0–13)	4.86 ± 4.96 (0–18)	<.001 ^{1,3}
BLESSED	21.49 ± 1.28 (13–22)	18.72 ± 2.84 (12–22)	17.83 ± 3.56 (11–22)	<.001 ^{1,2}
ECog	1.09 ± 0.17 (1–2.03)	2.54 ± 0.74 (1–4)	2.38 ± 0.90 (1–4)	<.001 ^{1,2}
Global cognitive functioning				
MMSE	28.22 ± 1.60 (24–30)	20.70 ± 4.63 (9–30)	21.29 ± 5.37 (5–30)	<.001 ^{1,2}
Memory				
Craft story	13.25 ± 5.58 (1–27)	2.56 ± 4.04 (0–18)	5.43 ± 5.14 (0–16)	<.001 ^{1,3}
Benson delay	0.72 ± 0.19 (0.06–1.07)	0.16 ± 0.26 (0–1)	0.38 ± 0.36 (0–2.00)	<.001 ^{1,3}
Executive function				
Verbal fluency	27.06 ± 9.21 (5–50)	16.32 ± 8.37 (1–53)	13.28 ± 7.78 (2–34)	<.001 ^{1,2}
Digitis backward	4.82 ± 1.83 (1–11)	3.14 ± 1.58 (0–8)	2.76 ± 1.50 (0–6)	<.05 [*]
TMT-B	13.60 ± 6.56 (1.40–41.14)	5.41 ± 4.98 (0–27.17)	5.86 ± 4.19 (0.20–16.63)	<.001 ^{1,2}
Language				
MINT	28.84 ± 2.82 (9–32)	22.74 ± 7.20 (0–32)	23.18 ± 8.18 (0–32)	<.001 ^{1,2}
Visuospatial abilities				
Benson copy	15.60 ± 1.47 (9–17)	12.32 ± 4.93 (0–17)	12.65 ± 4.60 (0–17)	<.001 ^{1,2}
Neuropsychiatric symptoms				
NPI total	0.92 ± 1.95 (0–16)	7.12 ± 5.24 (0–24)	8.24 ± 5.86 (0–33)	<.001 ^{1,2}

Pairwise differences (Dunn, Bonferroni): 1 = CU vs ADD, 2 = CU vs FTD, 3 = ADD vs FTD. CU = cognitively unimpaired; ADD = Alzheimer's; FTD = frontotemporal dementia.

04 RESULTS

— severity prediction across feature subsets & SHAP importance

+11–13%

CDR–FTLD recall gain vs. CDR

F5

full multidimensional set predicts best

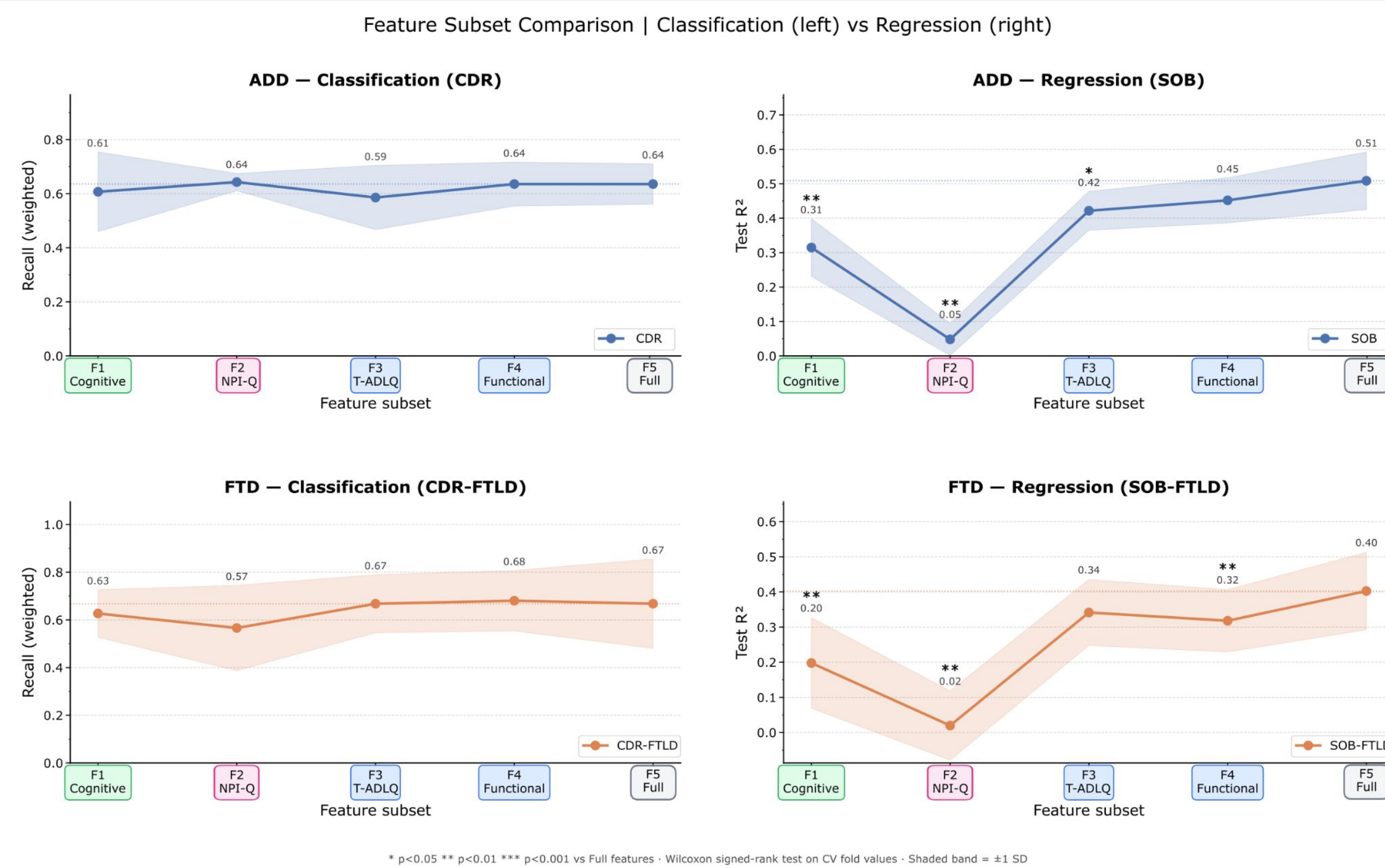
➔ **Adding function helps.** Recall (classification) and R² (regression) rise consistently as activities of daily living and broader functional dimensions are added peaking at the full feature set F5.

➔ **ADD is more predictable.** Severity is predicted more consistently in ADD than FTD, regardless of instrument (CDR / CDR-FTLD) or score (total / SoB).

➔ **Function leads importance.** T-ADLQ and ECog rank as the top SHAP predictors in both groups; ADL weighs even more heavily in FTD.

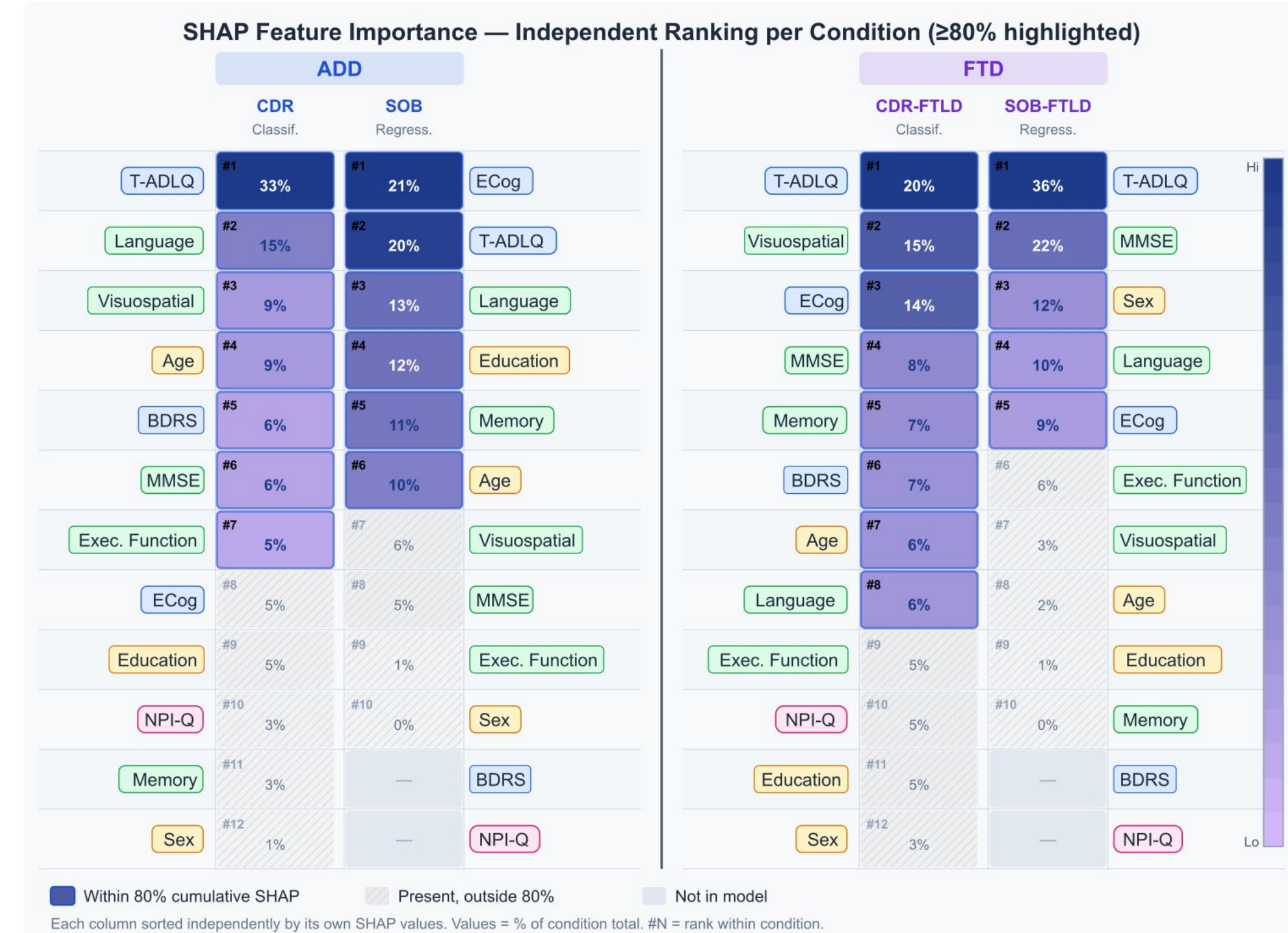
➔ **NPI-Q Relevance.** While the NPI-Q is effective at differentiating between healthy individuals and those with mild or severe dementia, it exhibits unstable behaviour when applied to precise predictions (SOB), thereby limiting its predictive accuracy.

Figure 2 · Severity prediction by feature subset (F1–F5)



* p<0.05 ** p<0.01 *** p<0.001 vs Full features · Wilcoxon signed-rank test on CV fold values · Shaded band = ±1 SD

Figure 3 · SHAP feature-importance ranking (ADD & FTD)



05 CONCLUSIONS

1 Everyday **functioning** — activities of daily living and everyday cognition — is the major predictor of CDR severity in both ADD and FTD.

2 Severity is not driven by cognition alone; **functional impact** is central to disease progression.

3 Implementing a **multidimensional approach** captures a more precise profile of **dementia subtypes**. This is vital for clinical characterization and research within Latin American cohorts.

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