

REFINING THE BEHAVIOURAL VARIANT FRONTOTEMPORAL DEMENTIA CLASSIFICATION WITH THE SUSTAIN SUBTYPING MODEL

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INTRODUCTION

Behavioral-variant frontotemporal dementia (bvFTD) is a neurodegenerative disease with heterogeneous clinical and pathological features. **Current diagnostic criteria lack specificity**, often delaying or misclassifying bvFTD, particularly against other behavioral disorders [1,2]. **Improved methods are needed to define biologically and clinically meaningful subtypes.**

SuStaIn has been applied across dementia types, identifying biologically and clinically meaningful subtypes [3,4]. Here, we apply it to a heterogeneous bvFTD cohort to **categorize behavioral presentations and characterize the longitudinal clinical progression of each subtype.**

METHODS

Participants: 179 bvFTD diagnosed according to current consensus diagnostic criteria. Participants were then **stratified by clinician-rated diagnosis certainty** across their visits

72 certain **68 uncertain** **39 mixed**

Certain: consistently diagnosed with bvFTD with “certain” diagnostic confidence across visits; **Uncertain:** diagnosed with bvFTD but rated as “uncertain” across visits; **Mixed:** diagnosed with bvFTD at least once, with diagnostic certainty changing over time

Subtype and Staging Inference (SuStaIn) model: A machine learning model that subtypes patients by disease pattern and estimates their stage of progression at the same time.

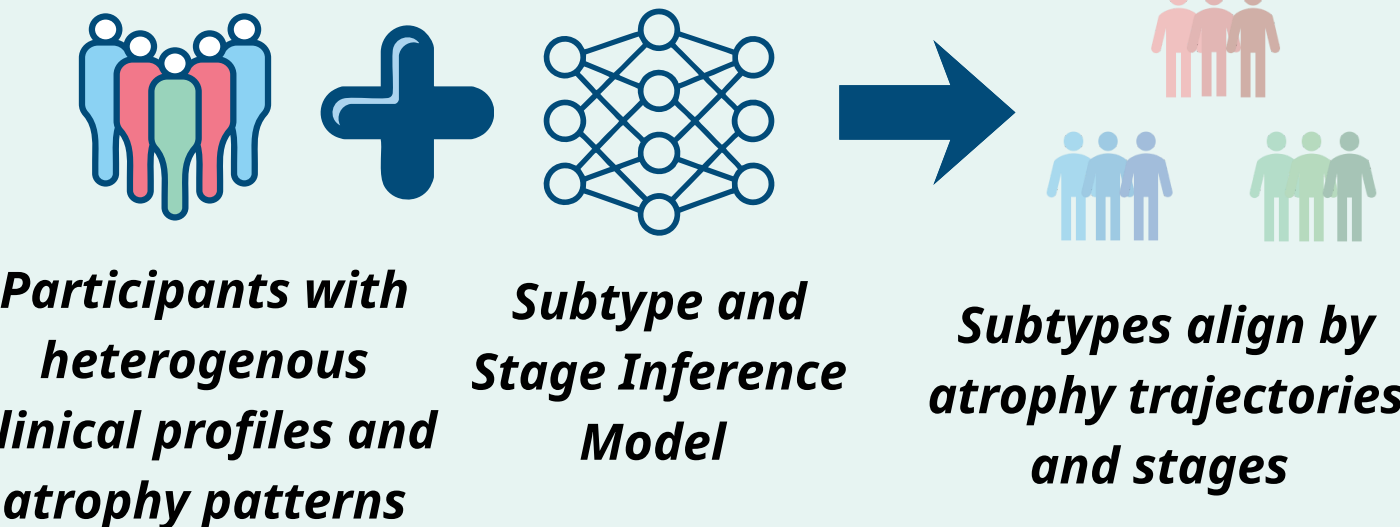
Measurement: Cortical thickness extracted from MRI scans to use as a biomarker for the SuStaIn model to estimate the subtyping and staging.

Brain regions: Identified based on data-driven methods and previous literature

Input: Cortical thickness and subcortical volume from all participants

Notes: 63 participants were removed due to low probability classification from SuStaIn model

SuStaIn pipeline: Cortical thickness across brain regions was used as input to the SuStaIn model to derive distinct subtypes



RESULTS

SUBTYPES IDENTIFIED BASED ON CORTICAL THICKNESS DERIVED FROM SUSTAIN MODEL

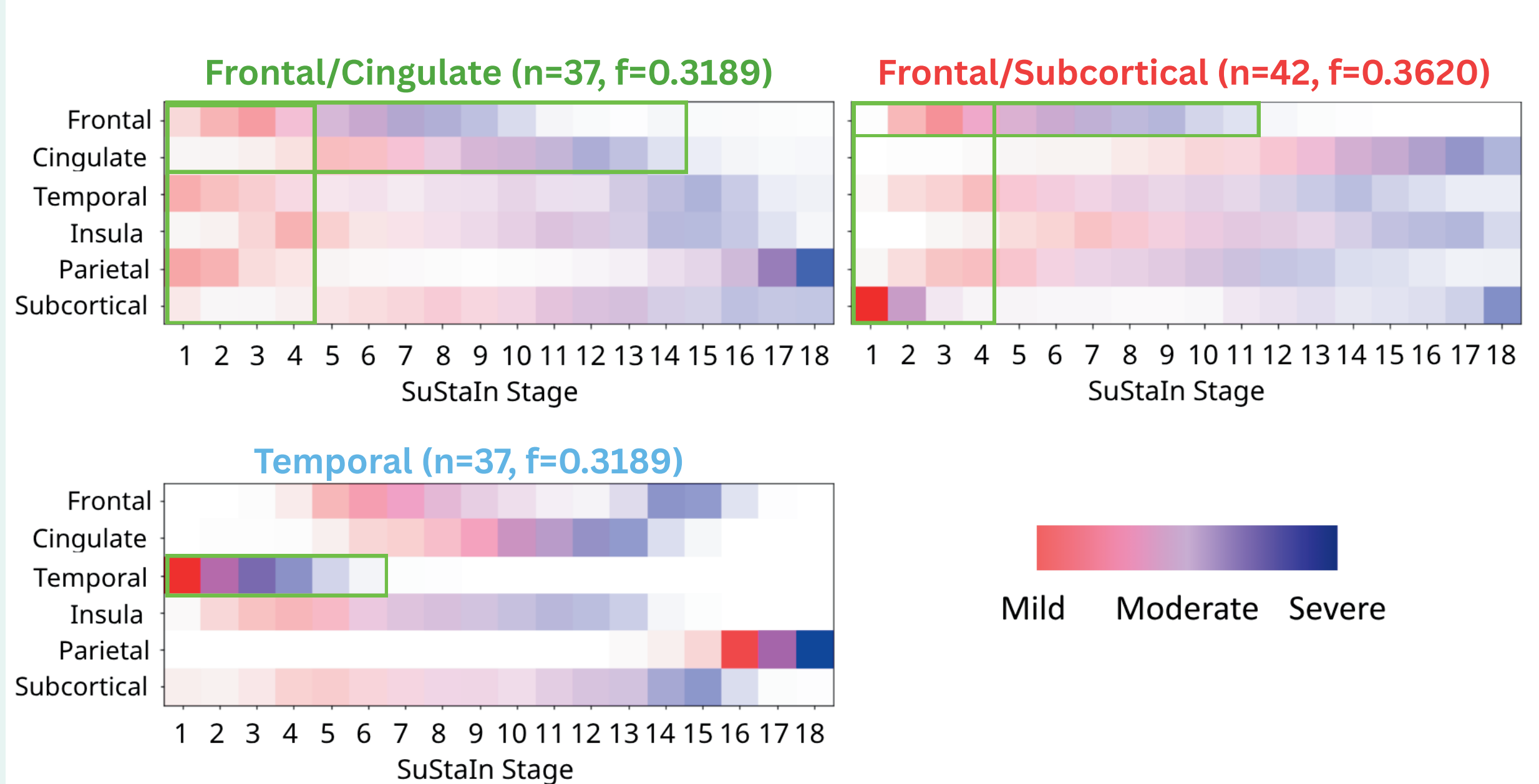
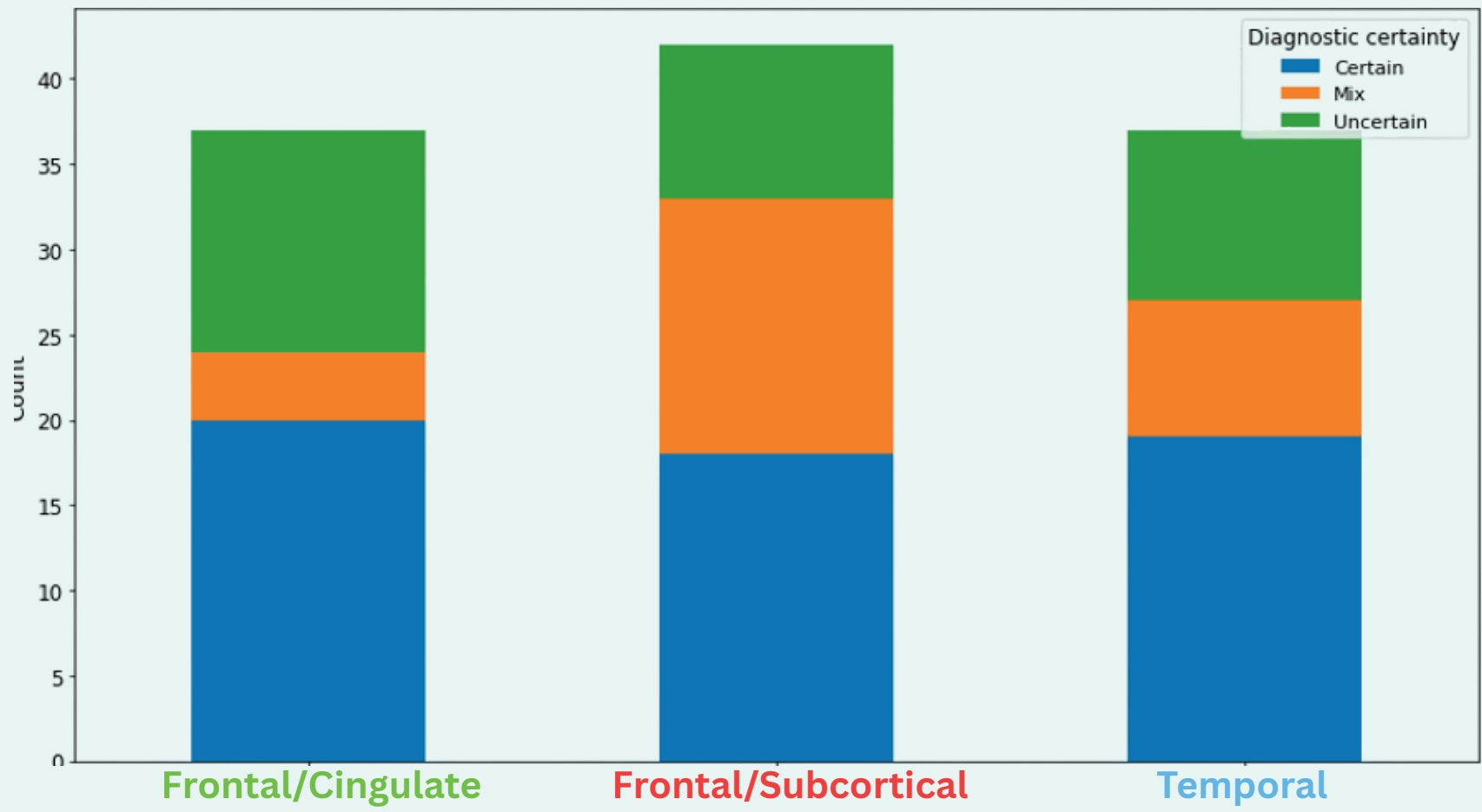


Figure 1. Subtypes identified from cortical thickness and subcortical volume patterns using SuStaIn. Data-driven subtypes show distinct sequences of regional degeneration. Positional variance diagrams show atrophy by SuStaIn stage (x-axis) for cortical and subcortical regions (y-axis). Colours indicate severity of each stage; Red: Mild atrophy ($z > 1$), Magenta: Moderate atrophy ($z > 2$), Blue: Severe atrophy ($z > 3$).



CAMBRIDGE BEHAVIORAL INVENTORY SCORE LONGITUDINAL CHANGES ACROSS SUBTYPES

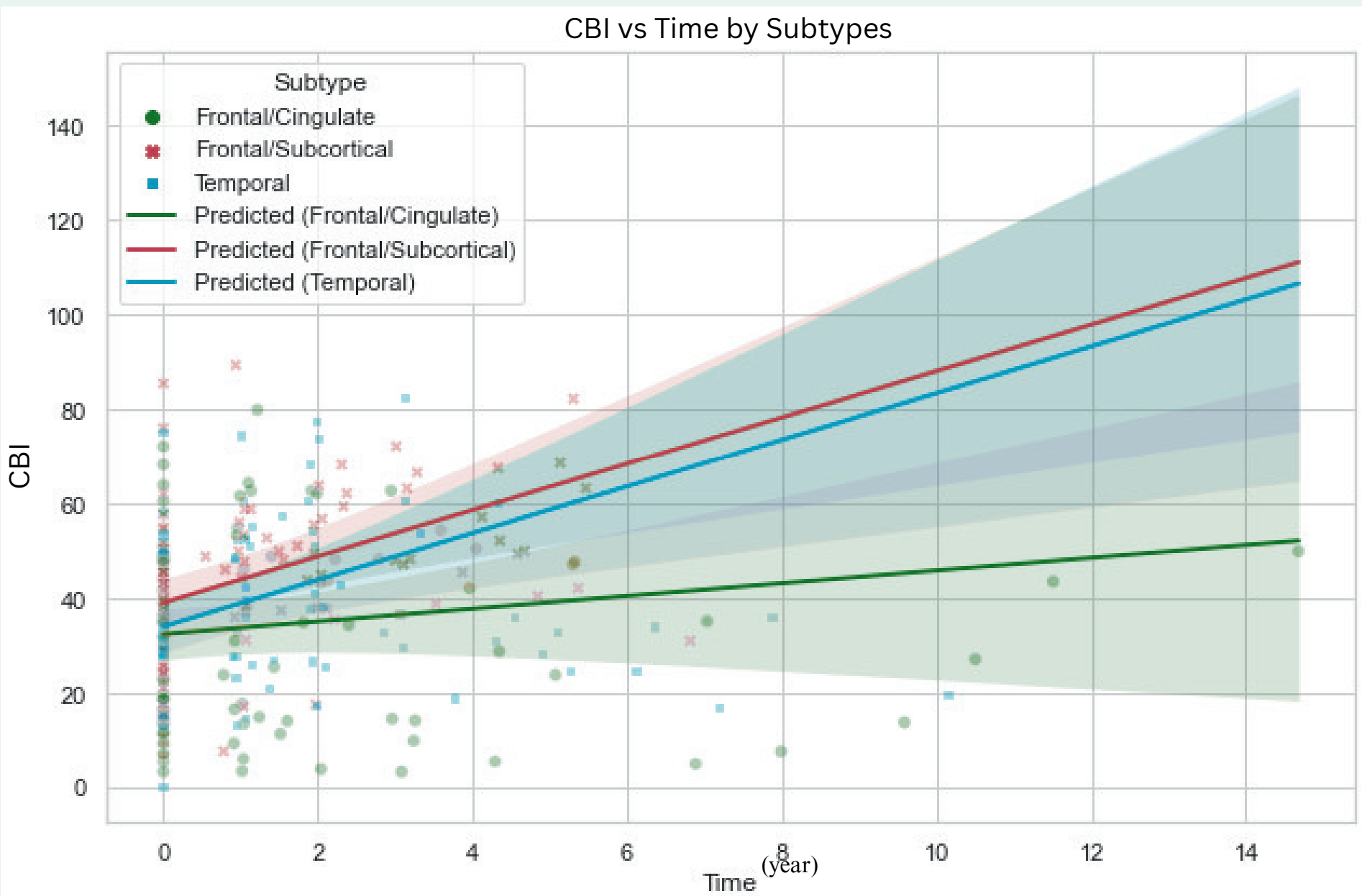


Figure 4: Longitudinal changes of the Cambridge Behavioral Inventory across 3 subtypes. Y-axis indicates CBI score, X-axis indicates the time in year

GROUP-LEVEL NEUROIMAGING COMPARISON

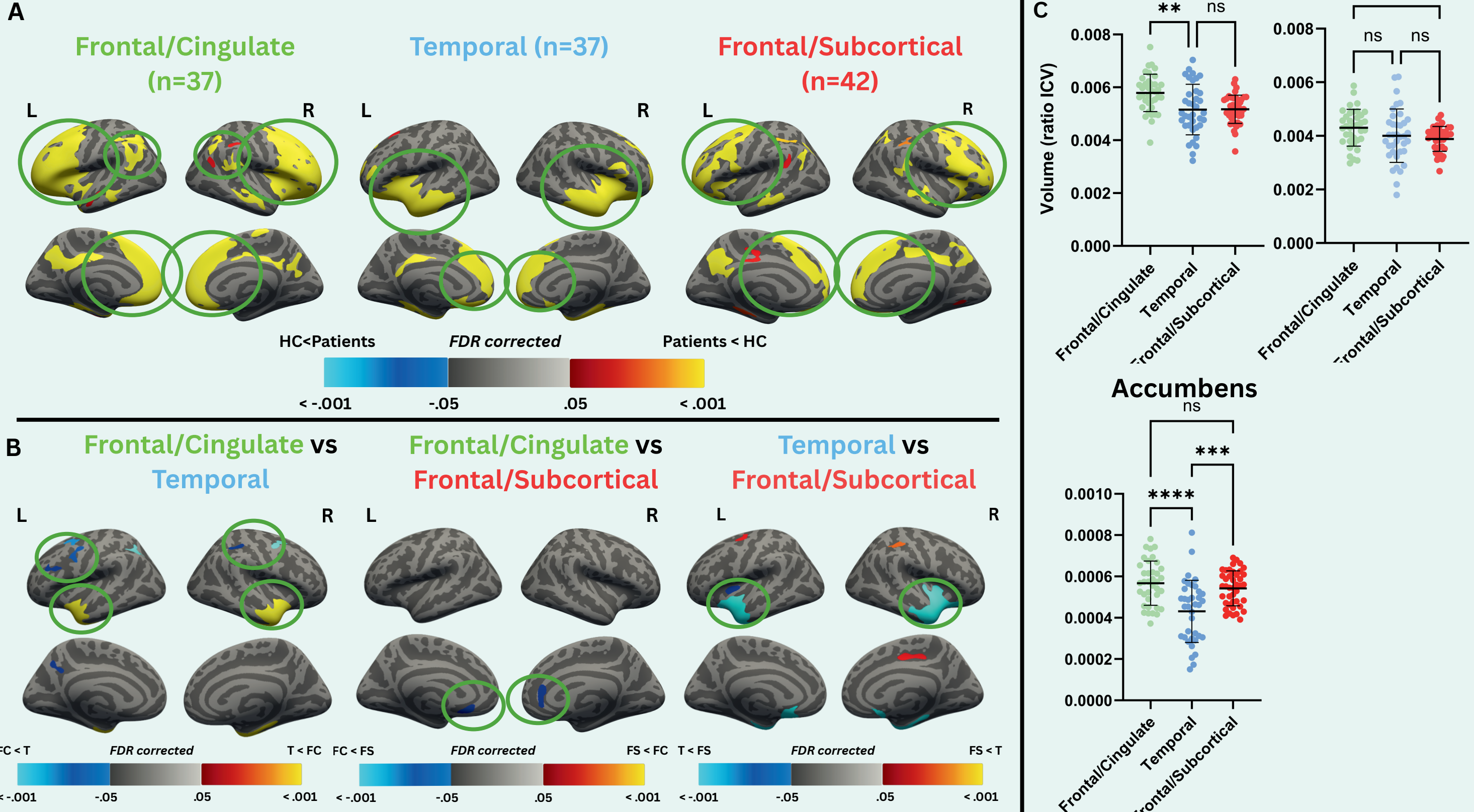


Figure 2. Group-level neuroimaging findings in SuStaIn-identified subtypes. (A) Cortical thickness in each subtype relative to controls. (B) The differences in cortical thickness in each subtype relative to other subtypes. (C) Subcortical volume differences between subtypes. FC = Frontal/Cingulate; FS = Frontal/Subcortical; T = Temporal; ** $p < .01$; *** $p < .001$.

DIAGNOSTIC CERTAINTY DISTRIBUTED ACROSS SUBTYPES

Figure 3: Diagnostic certainty distribution across SuStaIn-identified subtypes. Stacked bars show case counts for three certainty groups – Certain (blue), Mixed (orange), and Uncertain (green) – across the frontal/cingulate, temporal, and frontal/parietal subtypes.

CLINICAL DIFFERENCES BETWEEN SUBTYPES

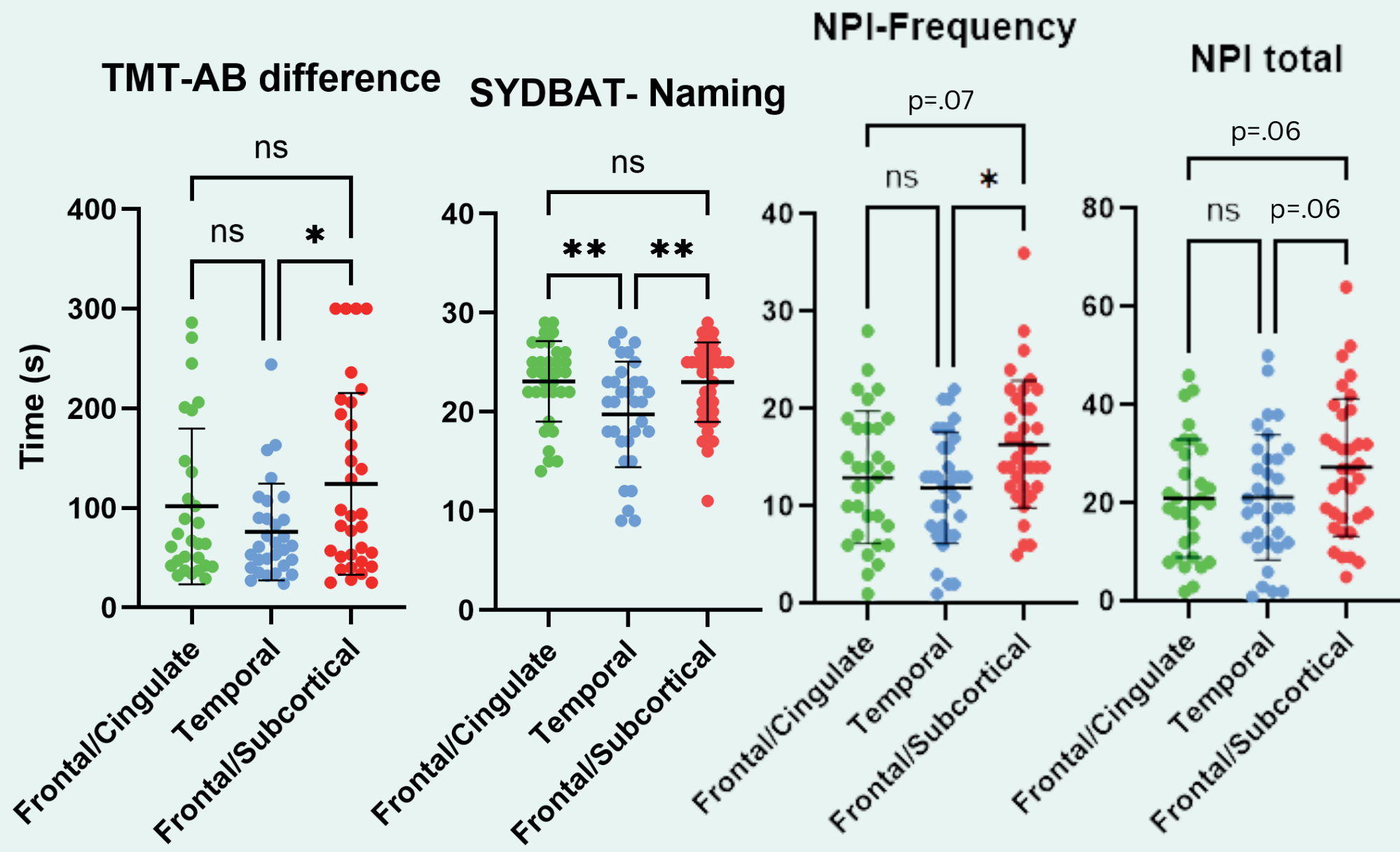


Figure 5: Severity of executive function, language, and psychiatric impairment across three subtypes. TMT-AB = Trails Making Test-AB time difference, SYDBAT = Sydney Language Battery, NPI = Neuropsychiatry Inventory

TABLE 1: DEMOGRAPHIC AND CLINICAL DATA

	Frontal/Cingulate	Temporal	Frontal/Subcortical	Post hoc
	Mean (SD) [Min-Max]	Mean (SD) [Min-Max]	Mean (SD) [Min-Max]	
N	37	37	42	
Sex (F:M)	14:23	14:23	10:32	$\chi^2 = 2.39$, $p = .3$
Age at Assessment (years) ^a	63 (6) [48.17 - 72.32]	62.57 (9.68) [34.15-80.77]	61.69 (6.45) [51.04-77.82]	$p = .76$
Education (years) ^b	12.46 (3.49) [9-25]	12.26 (2.75) [6-19]	12.59 (3) [8-22.5]	$p = .89$
Disease duration (years)	4.30 (2.68) [0.66 - 11.93]	4.33 (2.28) [0.5-9.48]	4.67 (3.24) [0.71-14.16]	$p = .8$
FRS (Rasch score) ^c	-0.16 (1.4) [-3.09 - 2.19]	-0.15 (1.2) [-2.58 - 2.49]	-0.34 (1.23) [-2.18 - 2.86]	$p = .78$
ACE total ^d	79.03 (10.84) [58 - 99]	76.97 (10.72) [50 - 96]	80 (11.28) [52 - 97]	$p = .48$
CBI total ^e	31.66 (19.00) [3.3 - 72.2]	32.65 (16.41) [0 - 75]	37.84 (16.73) [14.44 - 85.56]	$p = .25$
Trails AB time difference (second) ^f	101.7 (78.3) [29 - 286]	76.03 (48.58) [24 - 244]	124.3 (91.27) [25 - 300]	$p = .03$ FS > T
NPI total ^g	21.03 (12) [2 - 46]	21.21 (12.66) [1 - 50]	28.89 (16.76) [5 - 84]	$p = .03$ FS > FC & T
SYDBAT - Naming ^h	23.09 (4.05) [21.67 - 24.5]	19.75 (5.32) [17.83 - 21.67]	23 (4.01) [21.7 - 24.3]	$p = .003$ T < FC & FS

DISCUSSION

- SuStaIn identified three distinct disease trajectories. Each subtype contained a mix of diagnostic certainty levels, underscoring the complexity of bvFTD.
- Each subtype demonstrates a distinctive clinical symptom and atrophy pattern at baseline
- Behavioral symptoms appear similar across the three subtypes at baseline but progress differently, suggesting distinct clinical trajectories within bvFTD.
- Current diagnostic criteria cannot capture these subtype differences, highlighting the need for new diagnostic approaches.

TAKE HOME MESSAGE

- Three bvFTD subtypes were identified, each with distinct atrophy patterns and clinical symptoms.
- At baseline, cognitive and behavioral profiles show little difference across subtypes, underscoring the need for more sensitive biomarkers to improve diagnosis.
- Longitudinally, clinical progression rates differ across subtypes

References

1. De Boer et al. (2025). Differentiating sporadic frontotemporal dementia from late-onset primary psychiatric disorders. Brain Communications, 7(3).
2. Harris, J. M., et al. (2011). Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain, 134(9), 2456.
3. Young, A. L., et al. (2020). Subtype and stage inference identifies distinct atrophy patterns in genetic frontotemporal dementia that MAP onto specific MAPT mutations. Alzheimer's & Dementia, 16(S1), e042996.
4. Young, A. L., et al. (2018). Uncovering the heterogeneity and temporal complexity of neurodegenerative diseases with Subtype and Stage Inference. Nature Communications, 9(1).

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