



Structural Neuroimaging Signatures Discriminate Neuropathologies in Agrammatic Primary Progressive Aphasia

Jane Stocks¹, Rachel Keszycki¹, Daniel Gutstein¹, Tamar Gefen¹, Elena Barbieri¹, M.-Marsel Mesulam¹

¹Mesulam Institute for Cognitive Neurology and Alzheimer’s Disease, Northwestern University Feinberg School of Medicine

BACKGROUND

- Agrammatic/non-fluent PPA (agPPA) is a clinical dementia syndrome defined by morpho-syntactic impairment that may or may not co-occur with motor speech abnormalities
- Despite a shared clinical phenotype, agPPA arises from distinct neuropathologies:
 - FTLD-tau 3-repeat (3R)
 - FTLD-tau 4-repeat (4R):
 - Progressive Supranuclear Palsy (PSP), Corticobasal Degeneration (CBD)
 - Alzheimer’s Disease (AD)
- Distinguishing these substrates in vivo remains a clinical challenge
- Machine learning offers a framework for identifying pathology-specific atrophy signatures

SUBJECTS

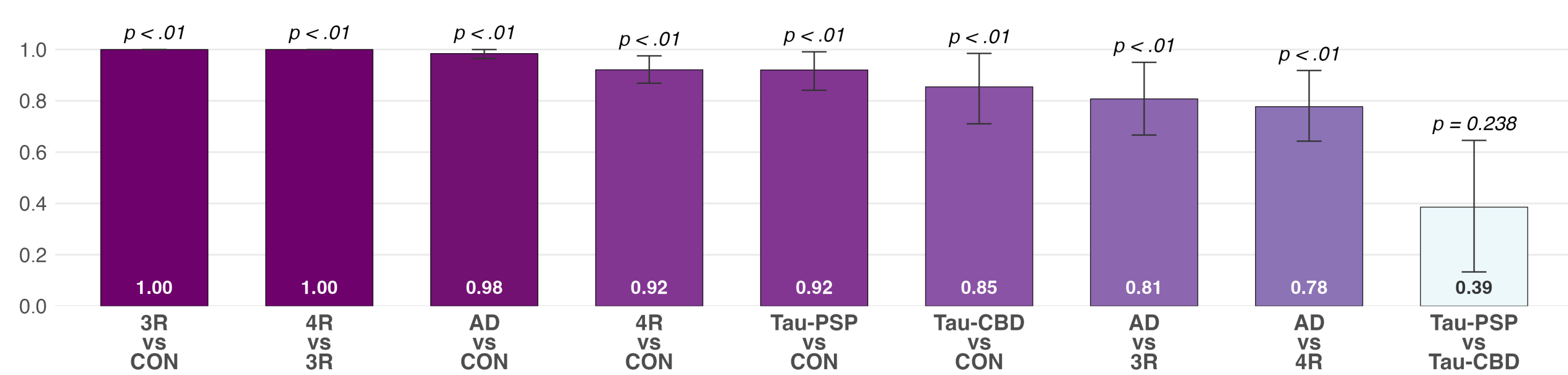
	3R N = 10 ¹	4R N = 19 ¹	AD N = 13 ¹	CON N = 54 ¹
N Scans (Visit 1/2/3)	10/6/2	19/11/6	13/8/3	54/4
CBD/PSP/CBD-PSP	-	7/10/2	-	-
Age Visit A	64.70 (6.2)	69.58 (7.6)	64.62 (6.8)	63.04 (6.6)
Age Onset	58.00 (5.6)	66.26 (8.3)	59.92 (6.8)	-
Age Death	68.80 (4.3)	75.68 (7.9)	70.54 (7.3)	-
Sex (F)	40%	58%	38%	54%
Education	14.80 (2.4)	15.37 (2.3)	16.69 (2.9)	16.78 (2.3)
Race (White)	100%	100%	100%	87%
WAB AQ	79.92 (9.6)	85.74 (7.7)	77.89 (7.4)	99.67 (0.7)
CDR Global	0.45 (0.2)	0.24 (0.3)	0.35 (0.2)	0.00 (0.0)

METHODS

- Neuroimaging features: cortical volumes (Schaefer-400), subcortical volumes (Tian S3), brainstem parcels (FreeSurfer)
- Model: elastic-net logistic regression with feature selection by univariate AUC (top-15 per fold)
- Validation: stratified group k-fold CV (3-fold, 10 repeats), permutation testing (1,000), bootstrap CIs (1,000)
- Interpretability: feature stability frequency across CV folds + regularized ridge coefficients
- Correction: Benjamini–Hochberg FDR across all 9 comparisons

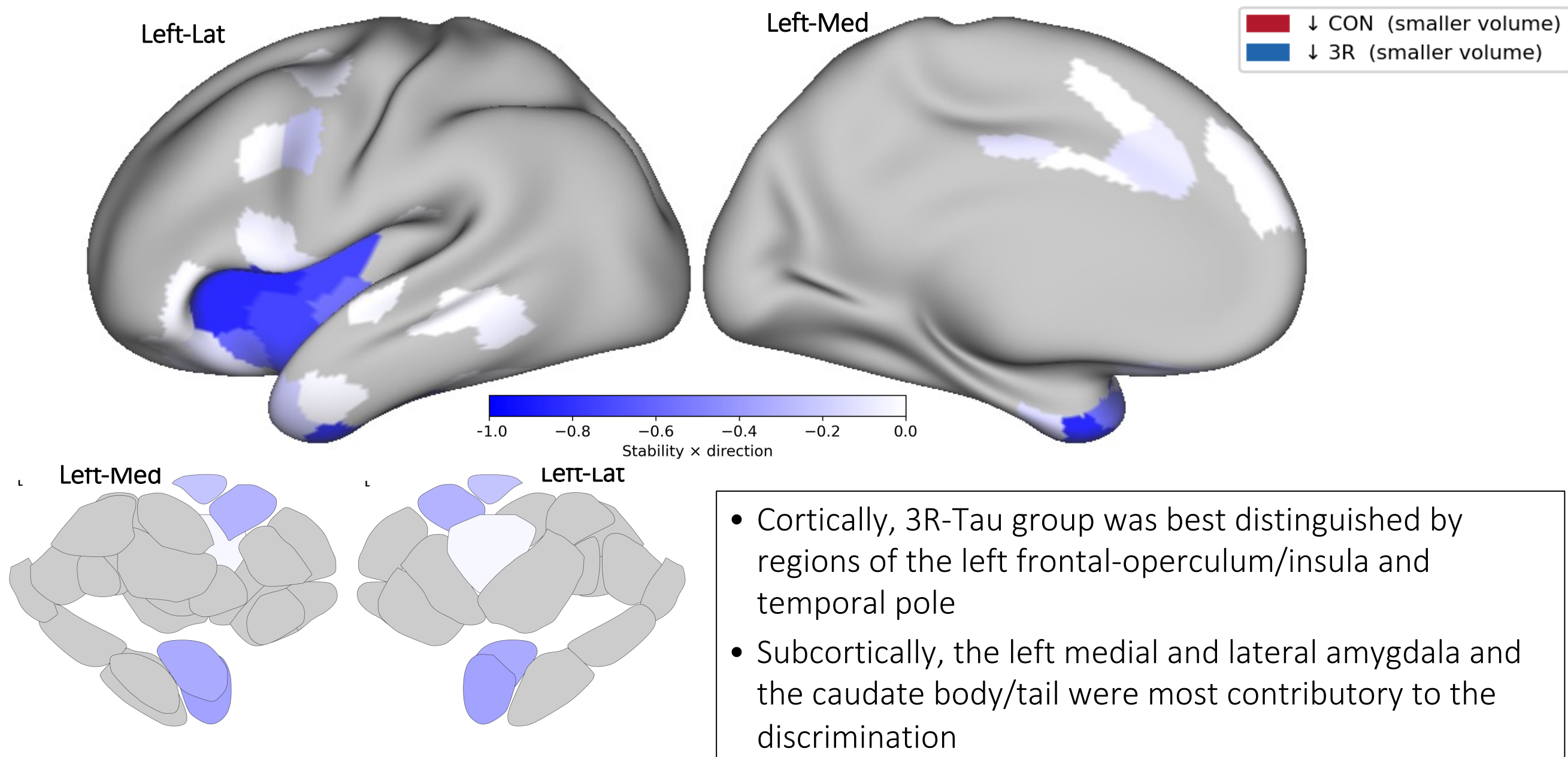
CLASSIFICATION PERFORMANCE (AUC)

AUC Classification Performance

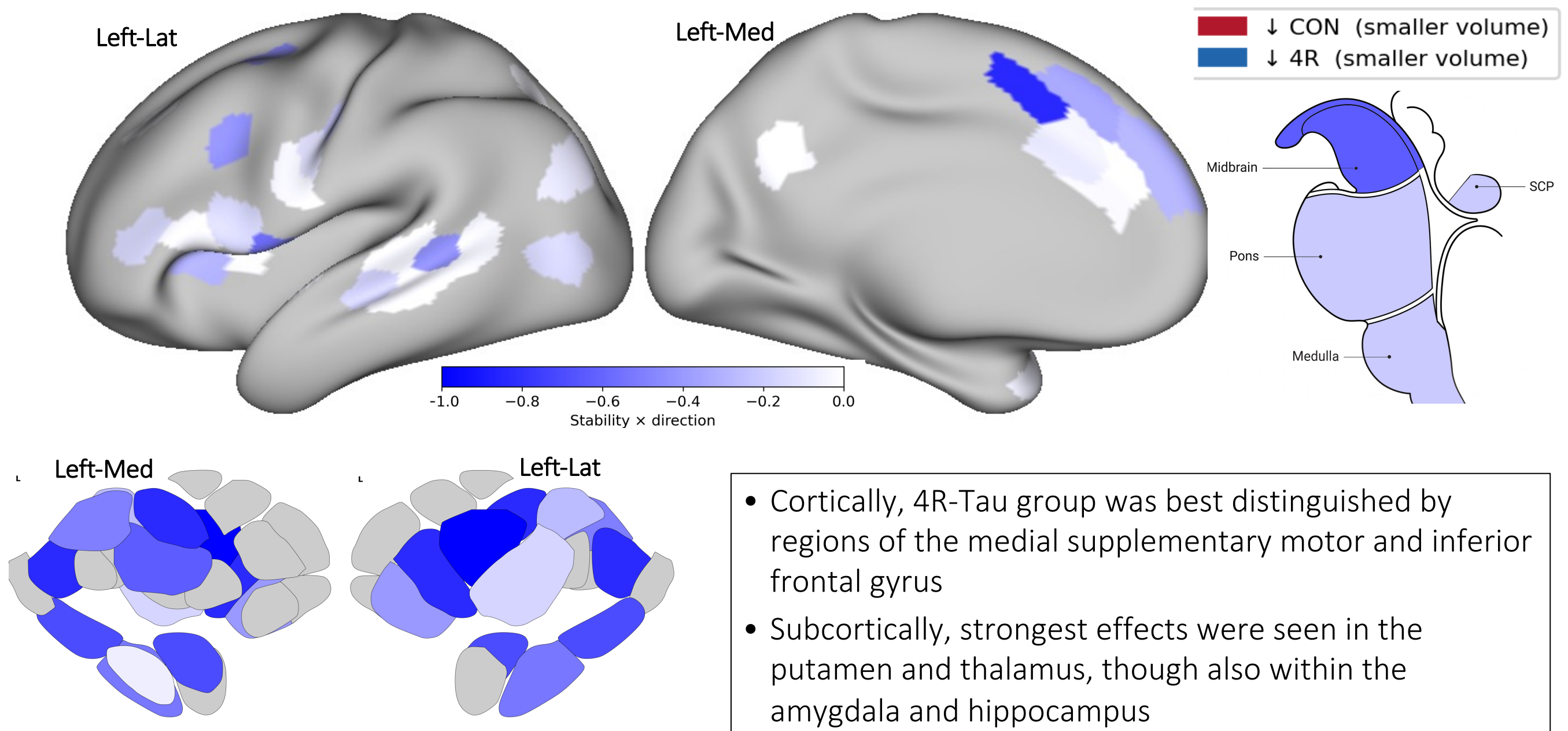


PATHOLOGY-SPECIFIC NEUROIMAGING SIGNATURES

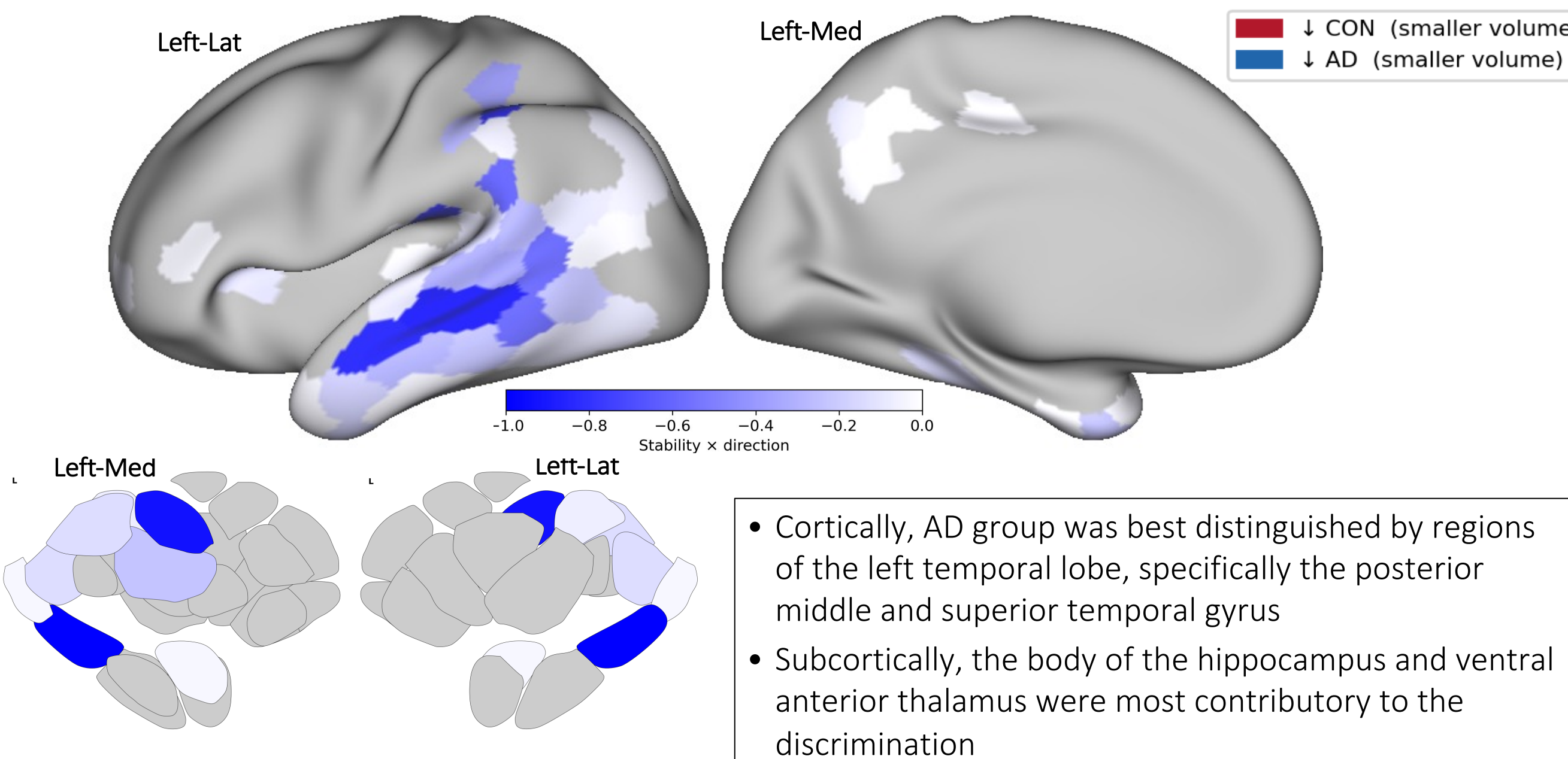
3R-TAU (PICK’S DISEASE) vs. CON



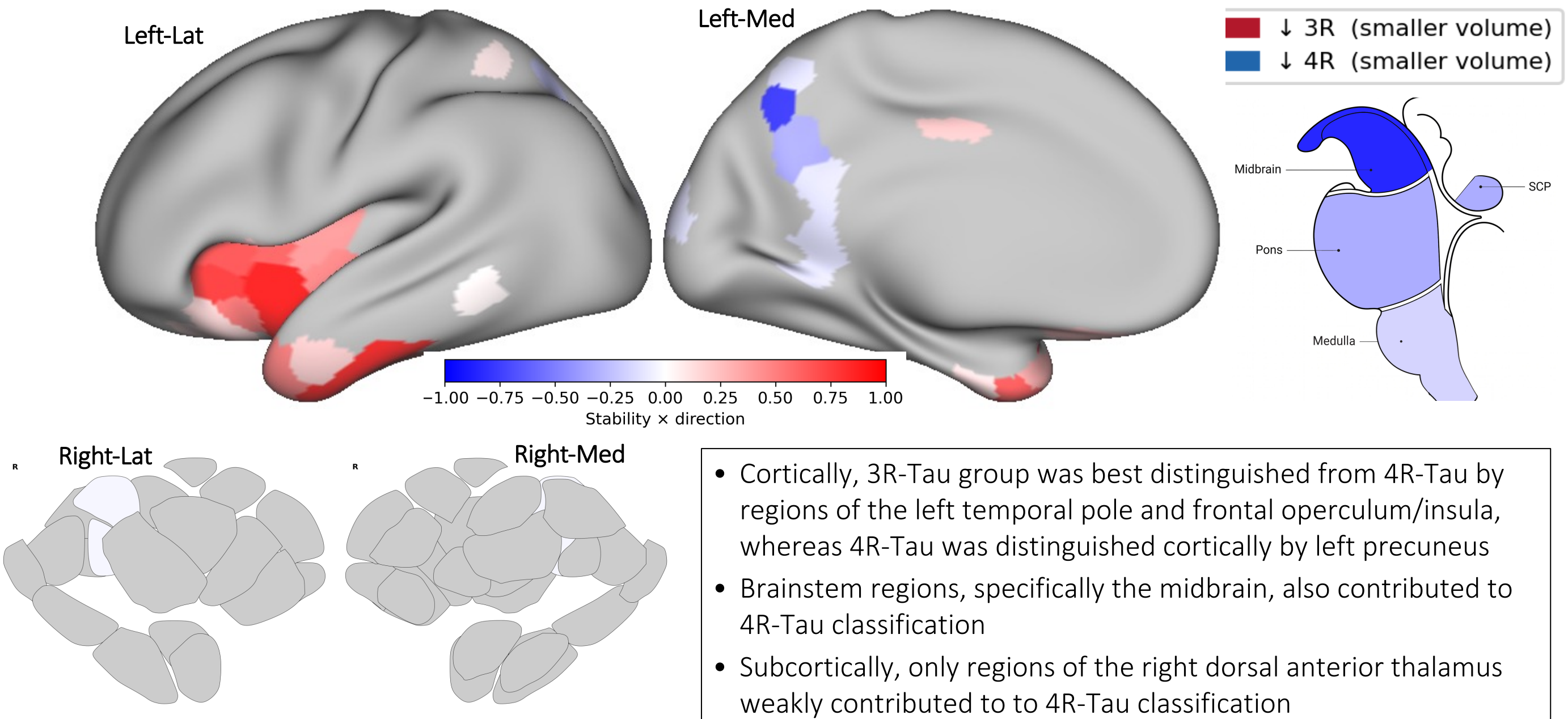
4R-TAU (CBD, PSP) vs. CON



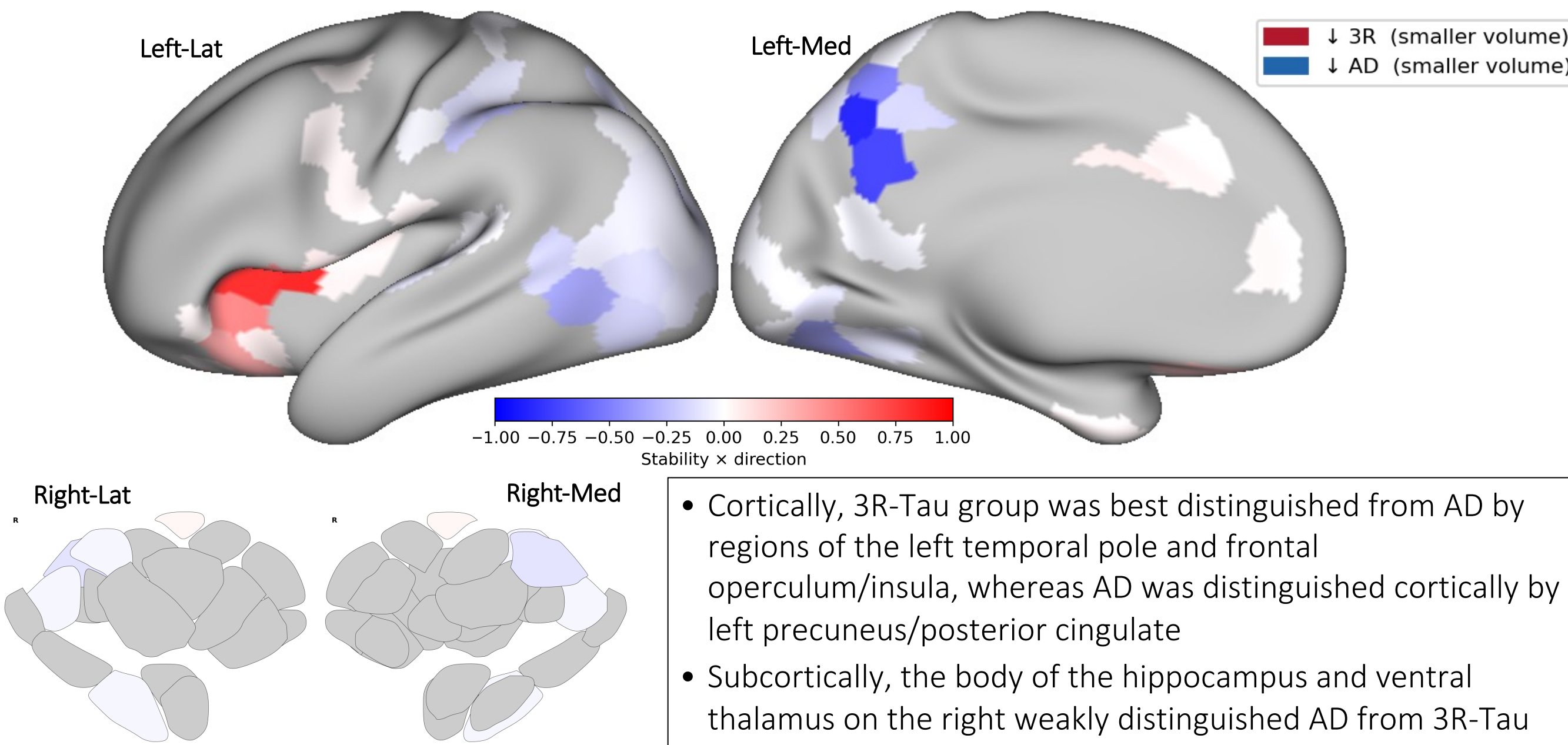
AD vs. CON



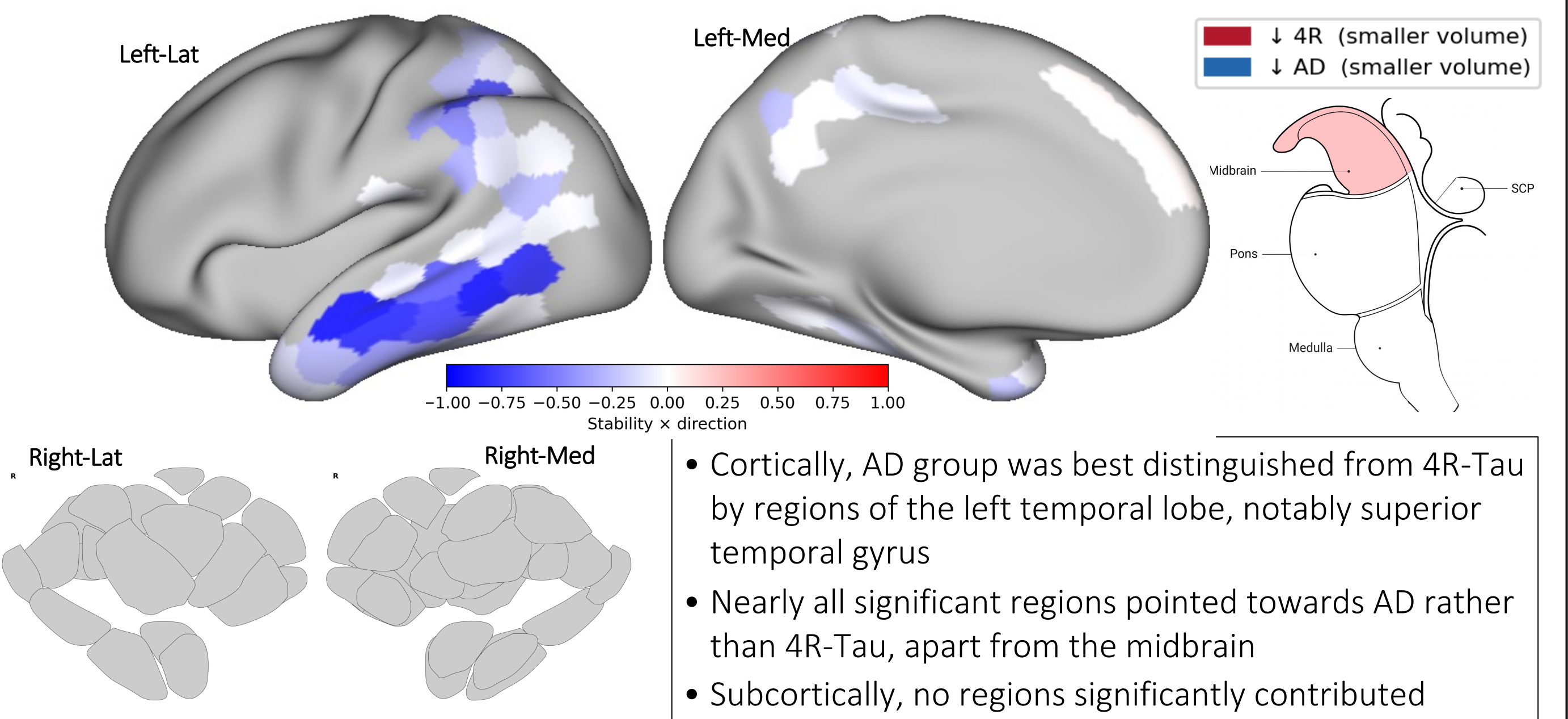
3R-Tau vs. 4R-Tau



3R-Tau vs. AD



AD vs. 4R-Tau



DISCUSSION

- In the current machine learning models, rather than asking whether individual regions differ between groups, the model learns which weighted combination of regional volumes best distinguishes one pathology from another.
- Repeated cross-validation provides stable performance estimates despite small sample sizes. Feature stability frequency measures how consistently a region was selected across CV folds
- All pathology-versus-control comparisons achieved high classification accuracy (AUC > 0.90), and direct pathology-to-pathology discrimination remained strong (AUC > 0.86), demonstrating that structural MRI can reliably distinguish the underlying cause of agPPA.
- Each pathology showed a distinct anatomical signature: 3R-tau was characterized by frontal-opercular and temporal atrophy, 4R-tau by subcortical involvement of the putamen and thalamus, and AD by posterior temporal regions, despite all three presenting with the same clinical syndrome.
- These imaging signatures could serve as in vivo biomarkers to support pathologic prediction during life, with potential applications in clinical trial enrollment and targeted therapeutic selection as disease-modifying treatments emerge for specific tauopathies.