

LATE-NC is associated with both hippocampal atrophy and asymmetry



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Introduction

- Limbic-predominant age-related TDP-43 encephalopathy neuropathologic change (LATE-NC) is a major, under-recognized contributor to dementia in late life.
- There are currently no in vivo markers for LATE-NC, which often clinically resembles, and co-occurs with, Alzheimer’s disease NC (ADNC).
- Some forms of frontotemporal dementia (FTD) with TDP-43 show asymmetric medial temporal atrophy, suggesting asymmetry may signal TDP-43 pathology.
- **Goal:** Test whether hippocampal volume and hemispheric asymmetry predict LATE-NC and/or ADNC at autopsy.

Methods

- **Datasets:**
 - Participants with MRI and pathology from:
 - *The 90+ Study* (N=126)
 - National Alzheimer’s Coordinating Center (NACC, N=270, from 12 ADRCs)
 - Excluding e.g., FTLD-TDP
- **MRI processing:**
 - Harmonized atlas-based diffeomorphic registration pipeline (IDeA Lab, UC Davis)
 - Extracted left and right hippocampal volumes
- **Hippocampus metrics:**
 - Total volume (L+R)
 - Asymmetry - absolute difference: |L – R|
 - Asymmetry - ratio: max(L,R)/min(L,R) – 1
- **Outcomes:**
 - LATE-NC stage 2+ (binary)
 - Ordinal LATE-NC stage
 - Ordinal ADNC likelihood
- **Models:**
 - Bayesian logistic (binary) and ordinal regressions
 - Adjusted for age at MRI, sex, education, intracranial volume
 - Multilevel varying intercepts for center
 - Weakly-informative priors
- **Performance:**
 - ROC AUC
 - PSIS-LOO cross-validation

Results Part I

- **Sample (Table-1):**
 - Total N=396
 - 30% LATE-NC presence (stage 1+)
- **Associations (Figure-1 & Figure-2):**
 - ↑ LATE-NC → hippocampal volume ↓
 - ↑ ADNC → hippocampal volume ↓
 - ↑ LATE-NC → hippocampal asymmetry ↑
- **Prediction of LATE-NC stage 2+ (Figure-1):**
 - Hippocampal volume AUC = 0.70
 - Asymmetry ratio AUC = 0.71
 - Optimal asymmetry ratio threshold ≈ 9%

Table 1. Participant characteristics	The 90+ Study (N=126)	NACC (N=270)	Overall (N=396)
Age at MRI (years)	94.3 (3.12)	76.3 (10.5)	82.0 (12.2)
Age at death (years)	97.2 (3.54)	82.7 (10.8)	87.3 (11.4)
Years MRI to death	2.91 (1.81)	6.46 (3.34)	5.33 (3.37)
Education (College+)	68 (54.0%)	156 (58.0%)	224 (56.7%)
Women	76 (60.3%)	138 (51.1%)	214 (54.0%)
LATE-NC			
None	82 (65.1%)	196 (72.6%)	278 (70.2%)
Stage 1	6 (4.8%)	20 (7.4%)	26 (6.6%)
Stage 2	34 (27.0%)	46 (17.0%)	80 (20.2%)
Stage 3	4 (3.2%)	8 (3.0%)	12 (3.0%)
HS-A			
Absent	110 (87.3%)	247 (91.5%)	357 (90.2%)
Present	16 (12.7%)	23 (8.5%)	39 (9.8%)
ADNC			
None	7 (5.6%)	31 (11.5%)	38 (9.6%)
Low	30 (23.8%)	43 (15.9%)	73 (18.4%)
Intermediate	51 (40.5%)	53 (19.6%)	104 (26.3%)
High	38 (30.2%)	143 (53.0%)	181 (45.7%)
MRI Hippocampus			
Total Hipp. Vol. (mL)	5.51 (0.68)	5.78 (0.96)	5.70 (0.89)
Asym: Abs. Diff. (mL)	0.20 (0.19)	0.22 (0.19)	0.21 (0.19)
Asym: Ratio (%)	8.4% (8.7%)	8.4% (8.4%)	8.4% (8.5%)

Results Part II

- **Model improvement with asymmetry:**
 - AUC improved from 0.70 → 0.76 when adding asymmetry to volume-only models
 - PSIS-LOO improvements:
 - LATE-NC stage: elpd $\Delta \mu = -10.7$ (sd 4.9)
 - LATE-NC 2+: elpd $\Delta \mu = -12.6$ (sd 5.5)

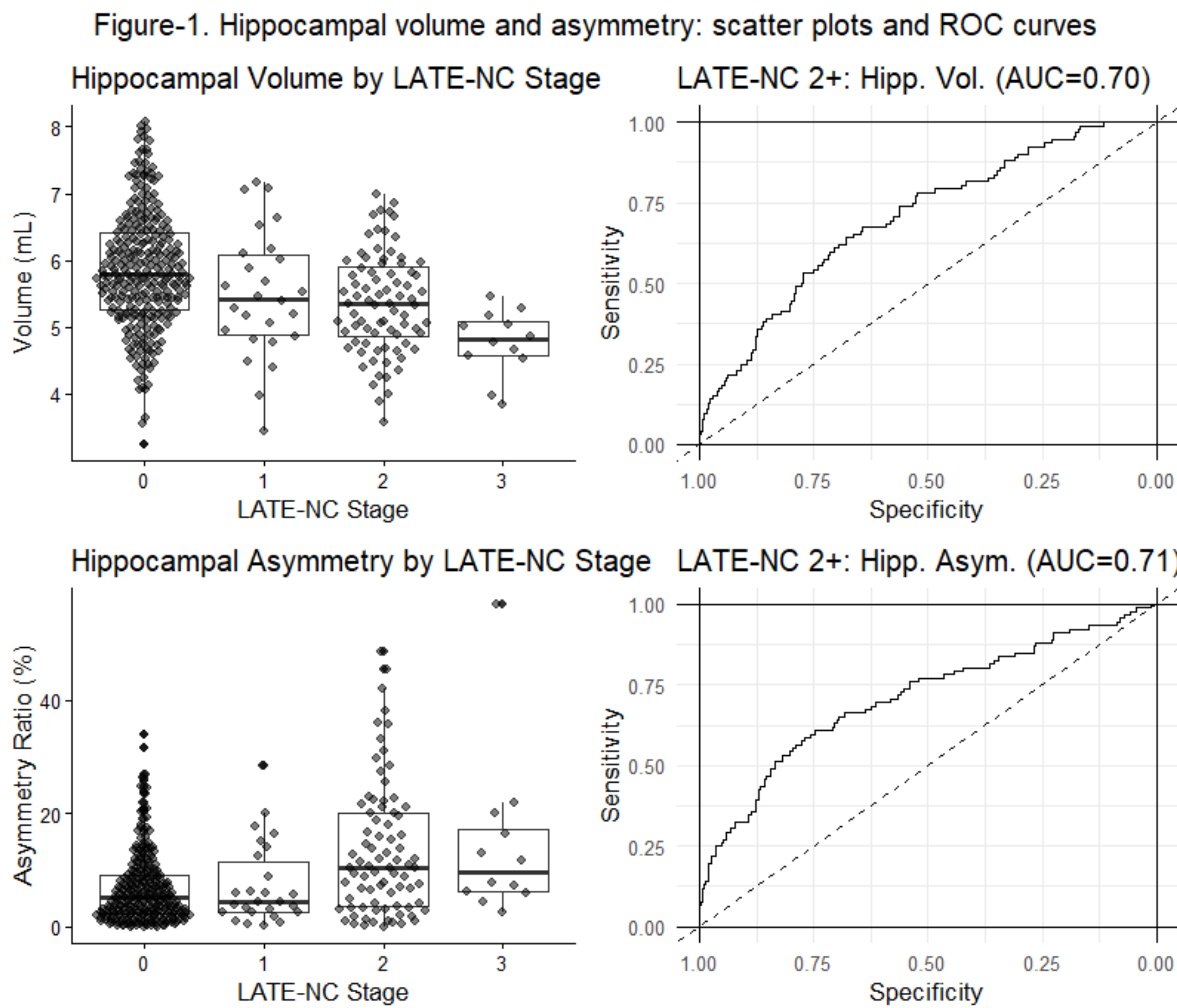
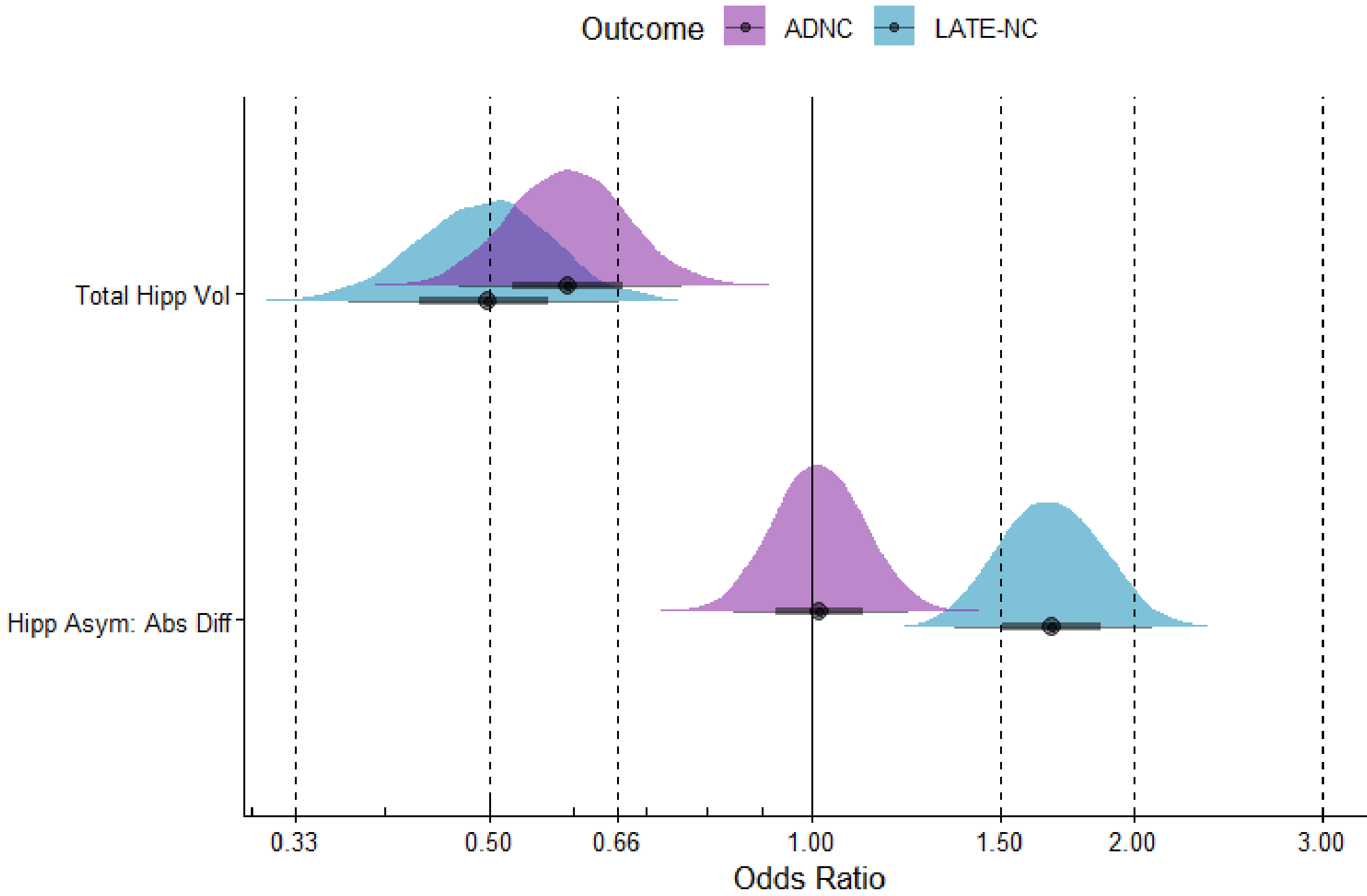


Figure-2 Coefficients of hippocampal volume and asymmetry for outcome of ADNC or LATE-NC



Summary

- LATE-NC is characterized by both hippocampal atrophy and hemispheric asymmetry, while ADNC is associated with volume but not asymmetry.
- Combining hippocampal volume with asymmetry yields better prediction of LATE-NC than either measure alone.
 - **Conclusion:** Hippocampal asymmetry, alongside hippocampal atrophy, is a promising imaging marker for identifying LATE-NC *in vivo*.

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