

MRI Correlates of Pattern Separation: Insights from the A4 Study

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The MST’s Lure Discrimination Index selectively tracks hippocampal-subfield integrity underlying pattern separation — distinct from the broad memory signal captured by the PACC.

INTRODUCTION

Pattern separation — the ability to store highly similar experiences as distinct memories — is crucial for daily life and is among the earliest cognitive processes to decline in Alzheimer’s disease.

Inclusion of the **Mnemonic Similarity Task (MST)** in the Anti-Amyloid Treatment in Asymptomatic Alzheimer’s **(A4) Study** offers an opportunity to identify the neural correlates of pattern separation in a large, well-characterized group of older adults with amyloid biomarkers.

METHODS

- Participants:** 105 A4 trial participants with a Clinical Dementia Rating (CDR) = 0.5 (mild cognitive impairment).
- Cognitive measures:** Lure Discrimination Index (LDI) from the MST and the Preclinical Alzheimer’s Cognitive Composite (PACC).
- Imaging:** structural MRI processed with FreeSurfer 7.3.1 to derive regional and hippocampal-subfield volumes.
- Analysis:** separate linear regression models relating each cognitive measure to brain volumes, adjusting for eTIV, amyloid PET SUVR, age, sex, and education.
- Statistics:** Benjamini–Hochberg (BH) procedure controlled the False Discovery Rate; adjusted R^2 , standardized β , and FDR-adjusted p-values were extracted.

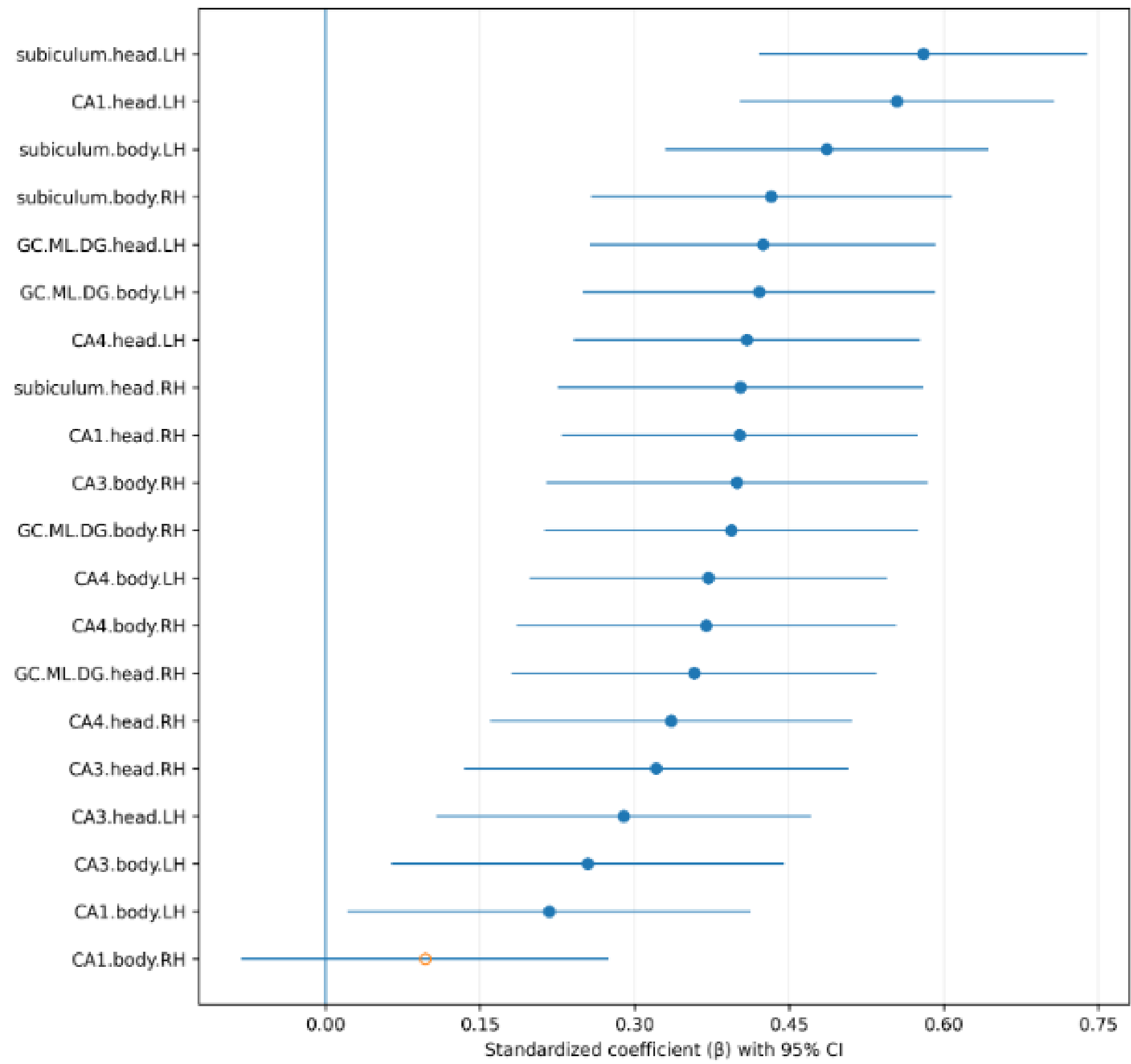
RESULTS

Table 1. Basic characteristics of the participants

Variable	Overall
n	105
Gender (%) - Male	41 (39.0%)
Gender (%) - Female	64 (61.0%)
Age (years) (mean ± SD)	72.52 ± 1.67
Education (years) (mean ± SD)	15.98 ± 2.36
SUVR (Florbetapir) (mean ± SD)	1.45 ± 0.17

Mean age was **72.52 ± 1.67** years and **61% were female** (Table 1). **PACC** was associated with bilateral whole hippocampal (L: $\beta = 0.63$; R: $\beta = 0.52$) and amygdala volumes (L: $\beta = 0.56$; R: $\beta = 0.51$), plus multiple hippocampal subfields. **LDI** showed a more selective hippocampal-subfield profile (Figure 1).

(a) PACC associations



(b) LDI associations

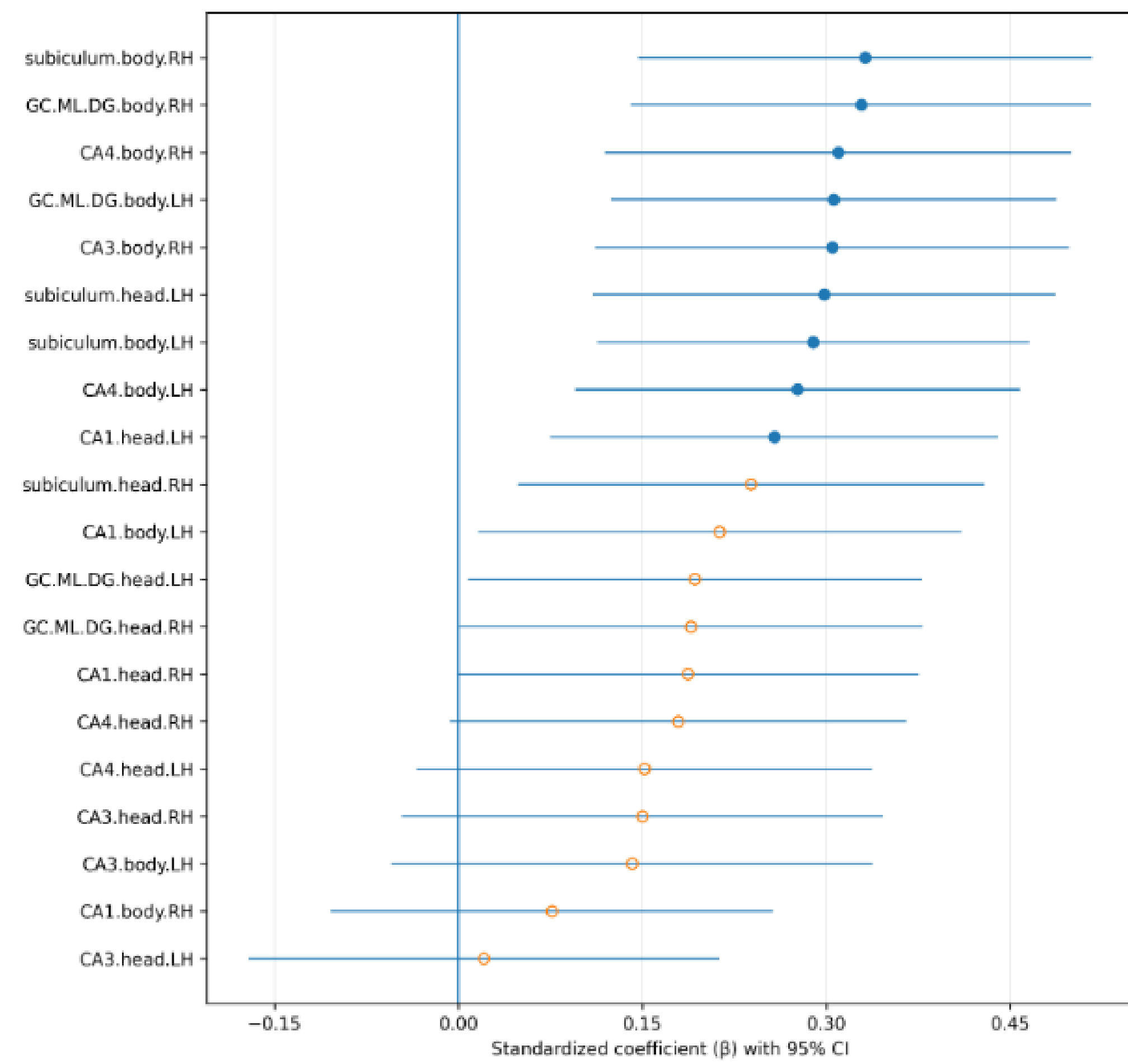


Figure 1. Standardized regression coefficients (β) with 95% CIs for associations between (a) PACC and (b) LDI and volumetric regions. Solid circles denote regions surviving BH-FDR correction (FDR-p < 0.05). Abbreviations: PACC, Preclinical Alzheimer’s Cognitive Composite; LDI, Lure Discrimination Index; CA1/CA3/CA4, cornu ammonis subfields 1, 3, and 4; GC-ML-DG, granule cell and molecular layer of the dentate gyrus; LH/RH, left/right hemisphere;

CONCLUSIONS

PACC performance associated with broad medial-temporal and limbic atrophy — consistent with global episodic-memory decline.

LDI showed a selective profile, correlating with CA4, dentate gyrus, and subiculum subfields, but **not** with whole hippocampal or amygdala volumes — indicating sensitivity to hippocampal-circuit integrity.

The MST may therefore provide a sensitive, **circuit-specific marker** of early hippocampal dysfunction in preclinical and prodromal Alzheimer’s disease.

Acknowledgment

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