

Cortical Microstructural MRI Changes Are Associated With CSF APP Across The Alzheimer’s Disease Clinical Continuum

P4-07
Wednesday-0659
Saturday-AIC-299

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Cortical diffusion MRI (PerpPD⁺) is closely associated with CSF APP, supporting its potential as a sensitive imaging biomarker of neuronal integrity across the Alzheimer's disease continuum.

INTRODUCTION

Amyloid precursor protein (APP) is a transmembrane protein highly expressed in cortical neurons and involved in synaptic function, neuronal development, and neuronal activity (1). Although APP is the precursor of amyloid-β, changes in total APP levels primarily reflect neuronal integrity rather than amyloid deposition, as APP has documented physiological roles in neuronal survival, neurite outgrowth, and neurorepair beyond amyloid generation (2). Previous studies investigated the association between APP-derived peptides and cortical macrostructural MRI measures in FTLD (3). In this study, we used the proteomic CSF measure of total APP as an index of cortical integrity and investigated its relationship with MRI-derived cortical macrostructural and microstructural measures in Alzheimer’s Disease.

METHODS

We analyzed data from ADNI including cognitively normal (CN=29), mild cognitive impairment (MCI=43), and Alzheimer’s disease (AD=28) participants who were all amyloid PET positive (Table1). For each participant with CSF APP P05067 available, T1-structural and diffusion-weighted MRI scans were used to extract cortical thickness and cortical diffusivity perpendicular to cortical minicolumns (PerpPD⁺ (4) at both whole-brain and regional levels. Associations between APP_P05067 and MRI measures were assessed to characterize relationships between proteomic markers of neuronal integrity and cortical structure. Associations between APP_P05067 levels and cortical whole-brain and regional metrics were tested with linear models, adjusting for age, sex, and variations in scanner model or protocol, with false discovery rate correction (pFDR<0.05).

RESULTS

Table 1 - Demographic and clinical characteristics

	CN A+ (n=29)	MCI A+ (n=43)	AD A+ (n=28)
Age mean (sd)	73.6 (5.6)	73.8 (6.8)	75.7 (9.2)
Sex female % (n)	72.4 (21)	41.9 (18)*	32.1 (9)*
ApoE4 carrier % (n)	65.5 (19)	62.8 (27)	75 (21)
Education mean (sd)	16.7 (2.2)	15.6 (2.7)	15.9 (2.7)
MMSE mean (sd)	29.2 (0.8)	26.6 (2.3)*	23 (1.9)*#
CDR global mean (sd)	0	0.5 (0)*	1.1 (0.25)*#
CDR Sum of Boxes mean (sd)	0	1.5 (0.7)*	3.9 (0.7)*#
Cortical Volume Fraction mean (sd)	0.298 (0.02)	0.286 (0.02)	0.270 (0.02)*#
Hippocampal Volume Fraction mean (sd)	0.0052 (0.0005)	0.0047 (0.0006)*	0.0042 (0.0005)*#

*Significantly different compared to Controls; # Significantly different compared to MCI.

Figure 1 – Regional Proteomics/MRI associations

CONCLUSIONS

These findings support the role of PerpPD⁺ as a sensitive MRI measure of microstructural neurodegeneration across the Alzheimer’s Disease spectrum. The observed regional patterns further align with known trajectories of Alzheimer’s disease pathology, reinforcing the relevance of multimodal proteomic-imaging approaches for characterizing cortical neurodegeneration in Alzheimer’s disease.

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