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IMAGING CORRELATES OF COGNITION AND BIOMARKERS

Plasma NfL predicts default mode network functional connectivity in older adults at higher risk for Alzheimer's disease

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Abstract

Background: Neurofilament light (NfL) is a measure of neuronal damage and has the potential as a monitoring and prognostic biomarker of Alzheimer's disease (AD) (Mattsson et al., 2019). Likewise, alterations in default mode network (DMN) functional connectivity (FC) may predict AD progression (Jones et al., 2016). Here, we investigated the relationship between plasma NfL levels and DMN FC along the continuum of AD, and explored whether APOE ε4 status influenced this relationship.

Method: Resting-state functional MRI data and blood samples were available for 103 older adults (17 with AD dementia, age: 69.2±6.9; m/f: 8/9; CDR: 0.7±0.3; and 86 without dementia (includes amnestic MCI and control), age: 71.7±7.4; m/f: 21/65; CDR: 0.3±0.2). Plasma NfL was measured using a single-molecule array (Simoa) assay. We calculated DMN FC using 32 high consensus DMN ROIs from Dworetsky et al. (2021). DMN FC was defined as the average correlation between the mean time-series of three ROIs labeled as posterior cingulate cortex and those of all the other ROIs. Participants' APOE status was defined as APOE ε4 carriers (ε3/ε4 or ε4/ε4) and noncarriers (ε3/ε3). Multiple regression was run with DMN FC as the outcome variable, plasma NfL as the predictor, and age and sex as covariates.

Result: Plasma NfL levels were higher in those with dementia compared to those without dementia ($t = 4.4608$, $p = 0.0002$) but did not differ between amnestic MCI and control ($t = 1.6116$, $p = 0.1130$). Across all participants, plasma NfL did not predict DMN FC ($B = 0.0045$, $p = 0.4830$). However, higher plasma NfL was marginally associated with higher DMN FC in those with dementia ($B = 0.0045$, $p = 0.0657$) but not in those without dementia ($B = 0.0021$, $p = 0.3160$). Moreover, in those without dementia, higher plasma NfL predicted higher DMN FC in APOE ε4 carriers ($B = 0.0079$, $p = 0.0312$) but not in APOE ε4 noncarriers ($B = 0.0023$, $p = 0.4871$).

Conclusion: Our results indicate that the increase of DMN FC, seen at early stages of AD (Damoiseaux et al., 2012), is significantly associated with more neuronal damage in APOE ε4 carriers without dementia.

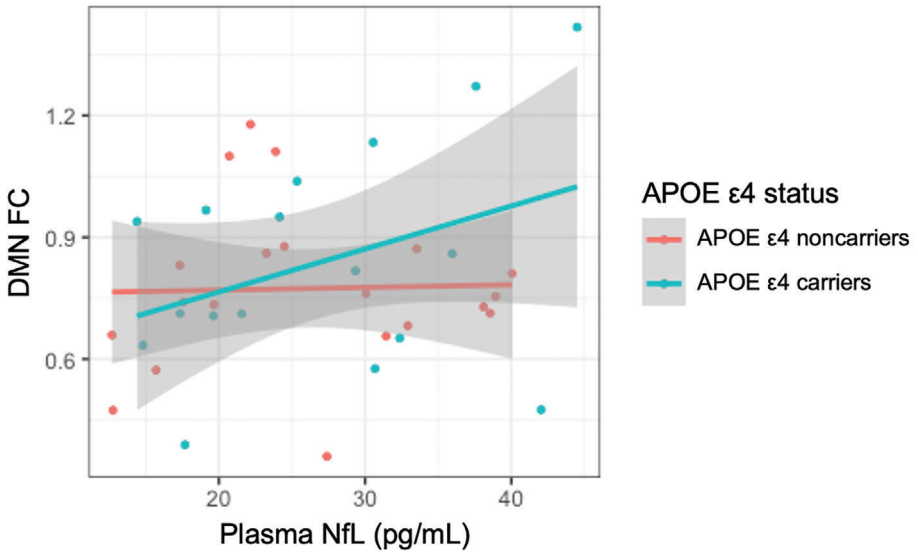

Figure. Relationship between plasma neurofilament light (NfL) and default mode network (DMN) functional connectivity (FC) by APOE ε4 status in participants without dementia