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22 Semantic Processing and its Relation to Brain Pathology in Individuals with Autosomal Dominant Alzheimer's Disease: Preliminary Findings from the Colombia-Boston Biomarker Study

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Objective: Semantic processing dysfunction has been shown to be an early indicator of cognitive decline in Alzheimer's disease (AD) and has been linked to early accumulation of AD-pathology. We examined semantic processing and its relation to AD pathology in non-demented individuals from a Colombian kindred with autosomal dominant AD due to the Presenilin1 E280A mutation (*PSEN1*).
Participants and Methods: A total of 13 cognitively unimpaired *PSEN1* mutation carriers (mean age: 36.92± 4.94), 7 carriers with mild cognitive impairment (MCI; mean age: 45±2.65), and 17 family non-carriers (mean age: 36±6.38) from the Colombia-Boston (COLBOS) longitudinal biomarker study were included. We used the Batería IV Woodcock-Muñoz verbal analogies and text comprehension subtests to examine semantic processing, the Mini-Mental State Examination (MMSE) to assess global cognition and the CERAD word list delayed recall task to measure verbal memory. Participants also underwent PiB and flortaucipir-PET to measure mean cortical amyloid and regional tau burden (entorhinal cortex and precuneus), respectively. Mann-Whitney U tests and Spearman's Rho correlations compared group differences in semantic processing, and its associations with age and pathological markers. Post-hoc analyses excluded carriers with MCI and controlled for education.
Results: Carriers (including cognitively unimpaired and symptomatic individuals) performed significantly worse on the MMSE (carriers: 14.55, non-carriers: 24.24; U=81.00, p=.006), CERAD word list delayed recall (carriers: 13.63, non-carriers: 25.32; U=48.00, p=.001), and text comprehension (carriers: 16.36, non-carriers: 23.81; U=107.00, p=.042,) than non-carriers, and showed a trend towards worse performance on verbal analogies (carriers: 17.16, non-carriers: 23.68; U=124.50, p=.077). There were no differences in text comprehension or verbal analogies performance between cognitively-unimpaired carriers and non-carriers.Across the whole sample, age was negatively associated with performance on verbal analogies (r=-.341, p=.039), but not text comprehension (r=-.136, p=.428). Among carriers only, better MMSE and CERAD delayed recall performance was associated with higher verbal analogies (r=.561, p=<.001; r=.662, p=<.001, respectively) and text comprehension scores (r=.468, p=.004; r=.480, p=.003, respectively). Greater amyloid burden was associated with worse verbal analogies performance (r=-.432, p=.007) and text comprehension (r=-.430, p=.008). Greater entorhinal cortex (r=-.384, p=.016) and precuneus tau burden (r=-.318, p=.049) was associated with worse performance on verbal analogies, but not text comprehension. These associations did not survive when excluding carriers with MCI or controlling for education.
Conclusions: Preliminary results show that non-demented mutation carriers had worse performance in semantic processing than non-carriers and performance was associated with markers of AD pathology. These findings suggest that changes in semantic processing may be early indicators of disease progression in individuals at increased risk for Alzheimer's disease dementia. Future studies with larger samples need to examine the role of education and the longitudinal trajectory of semantic processing dysfunction in AD.

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