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Association of Subjective Cognitive Decline with Markers of Brain Pathology in Preclinical Autosomal Dominant Alzheimer's Disease

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The first (JRG) and senior (YTQ) authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
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INTRODUCTION:

Subjective cognitive decline (SCD) has been implicated as an early marker of subtle cognitive change in preclinical Alzheimer's disease (AD)(1). The relationship between SCD and molecular markers of disease progression in AD is poorly understood. Carriers of the *presenilin* (*PSEN-1* E280A) mutation from the Colombian kindred(2) are a compelling group in which to study SCD, as they will develop dementia with certainty, and have a well-characterized disease trajectory from pre-symptomatic to clinical stages (2).

SCD has been associated with markers of AD pathology in older adults at risk for late-onset sporadic AD(3). We showed previously that self-reported subjective memory complaints (SMC), a proxy for SCD, were elevated in cognitively unimpaired *PSEN1* mutation carriers, and that study-partner-reported SMC were correlated with age and negatively correlated with hippocampal volume(4). In the present study, we explored the extent to which SCD relates to markers of brain pathology—*in vivo* amyloid and/or tau. We hypothesized that SCD would be related to neocortical amyloid and regional tau levels. Findings have the potential to inform whether SCD might be a sensitive marker of AD related pathology and disease trajectory in the preclinical stage of AD.

METHODS:

Participants were twenty-one *PSEN1* E280A mutation carriers and twenty-seven age-, sex- and education-matched non-carrier family members recruited from the Alzheimer's Prevention Initiative (API) Registry. All had at least one parent who bore the *PSEN1* E280A mutation but were blind to their genetic status, in accordance with cultural norms and ethical regulations in this community.

Clinical assessments, including neurological exam and psychiatric questionnaires probing depression and anxiety were completed at the University of Antioquia. SCD was assessed using both the self-report and study-partner-based versions of the Memory Complaint Scale (MCS), Spanish version(Appendix 1). PET imaging was done in Boston, Massachusetts USA.

Exclusion criteria included chronic major neurological or psychiatric disorders. Inclusion criteria were: no cognitive impairment, a Clinical Dementia Rating global score of 0 and a Mini-Mental State Examination (MMSE) score of 26 or higher(Appendix 1).

The study was approved by the institutional review boards of Massachusetts General Hospital (USA), and the University of Antioquia (Colombia). Participants completed informed consent at both institutions.

Cortical-to-cerebellum [$_{11}$C] Pittsburgh Compound B (PiB) distribution volume ratio (DVR) and $_{18}$F-Flortaucipir (FTP) standardized uptake volume ratio (SUVR) values were derived as previously described (Appendix 2), and used to characterize mean cortical Aβ burden, and tau in two regions (bilateral entorhinal cortex (EC) and inferior temporal cortex (IT)) that have been shown to have elevated tau PET signal at early stages of both sporadic and dominantly inherited AD(5).

Spearman's correlations were used to examine relationships among SCD, amyloid and EC or IT tau using SPSS Version 23 (IBM, Armonk, NY) (Appendix 3). Exploratory whole-brain vertex-wise analyses of pathology markers and SCD were also carried out (Appendix 4).

RESULTS:

Carriers and non-carriers did not differ in education, age, gender ratio or MMSE (see Supplemental Table 1 for more detail). Self-reported SCD did not differ between carriers and non-carriers (carriers: 11.3+/−8.0, non-carriers: 10.2+/−7.5 p=0.50), while the group difference in study-partner-based SCD approached significance (carriers: 8.6 +/− 6.7, non-carriers: 5.4 +/− 4.7, p=0.063; Supplemental Table 1). Carriers showed elevated mean cortical amyloid [$_{11}$C] PiB DVR (carriers: 1.59 +/− 0.30; non-carriers: 1.12 +/−0.05, p<0.001) and elevated tau [18F-FTP] SUVR in the EC (carriers: 1.56 +/− 0.53, non-carriers: 1.02 +/−0.22, p<0.001) and in the IT (carriers: 1.31 +/−0.21, non-carriers: 1.18 +/− 0.12; p=0.023) (Supplemental Table 2).

In mutation carriers, greater age was associated with increased SCD based on self-report (ρ=0.70, p=<0.001) and study-partner report (ρ=0.64, p=0.002) (Figure 1, Supplemental Table 3). Study-partner-based SCD correlated with PiB DVR (ρ=0.55, p=0.01) as well as EC (ρ=0.54, p=0.01) and IT [$_{18}$F-FTP] SUVR (ρ=0.50, p=0.02) (Figure 1, Supplemental Table 3). In contrast, self-reported SCD correlated with PiB DVR (ρ=0.56, p=0.009), but not with EC or IT [$_{18}$F-FTP] SUVR (EC: ρ=0.33, p=0.14; IT: ρ=0.38, p=0.09) (Figure 1, Supplemental Figure 1, Supplemental Tables 3-6).

DISCUSSION:

To our knowledge, this is the first study to examine relationships between SCD and molecular markers of AD disease progression—*in vivo* cortical amyloid and regional tau—in preclinical ADAD. A prior study showed that, consistent with the present study, study-partner-based SCD increases with age in cognitively unimpaired carriers, as well as a trend toward a negative correlation between hippocampal volume and study-partner-based SCD(4). Extending this result, we found that SCD was related to biomarkers of AD pathology, amyloid and tau, in cognitively unimpaired carriers. While both self and study-partner-based SCD were related to cortical amyloid, only study-partner-based SCD was significantly associated with both EC and IT tau in carriers (Figure 1). Overall, the current and previous findings in two distinct samples from the Colombian kindred support a close relationship between SCD and underlying pathology and neurodegeneration. Further, while self-reported-SCD may be related to early AD pathology in individuals at increased risk to develop dementia much later, study-partner-based SCD may be a sensitive marker of underlying disease progression, tau-mediated neurodegenerative change, and proximity to clinical onset.

The relation between SCD and tau is consistent with prior studies of SCD in older adults at risk for late-onset sporadic AD(3). However, individuals in our sample may have heightened vigilance for their own memory decline due to experience with their parents and other family members. Thus, the generalizability of these SCD findings to others at risk for ADAD or late-onset sporadic AD is an area in need of further investigation.

In conclusion, we showed, for the first time in our sample of a single AD-causing mutation that self-reported and study-partner-based SCD were associated with age and cortical amyloid in cognitively unimpaired mutation carriers, while study-partner-based SCD was additionally related to tau in regions of early deposition. Our findings suggest that SCD may aid in identifying individuals at higher risk for developing AD dementia. Future work with larger samples and longitudinal follow-up will be important to better understand the trajectory of SCD in relationship to AD pathology from preclinical to clinical disease stages.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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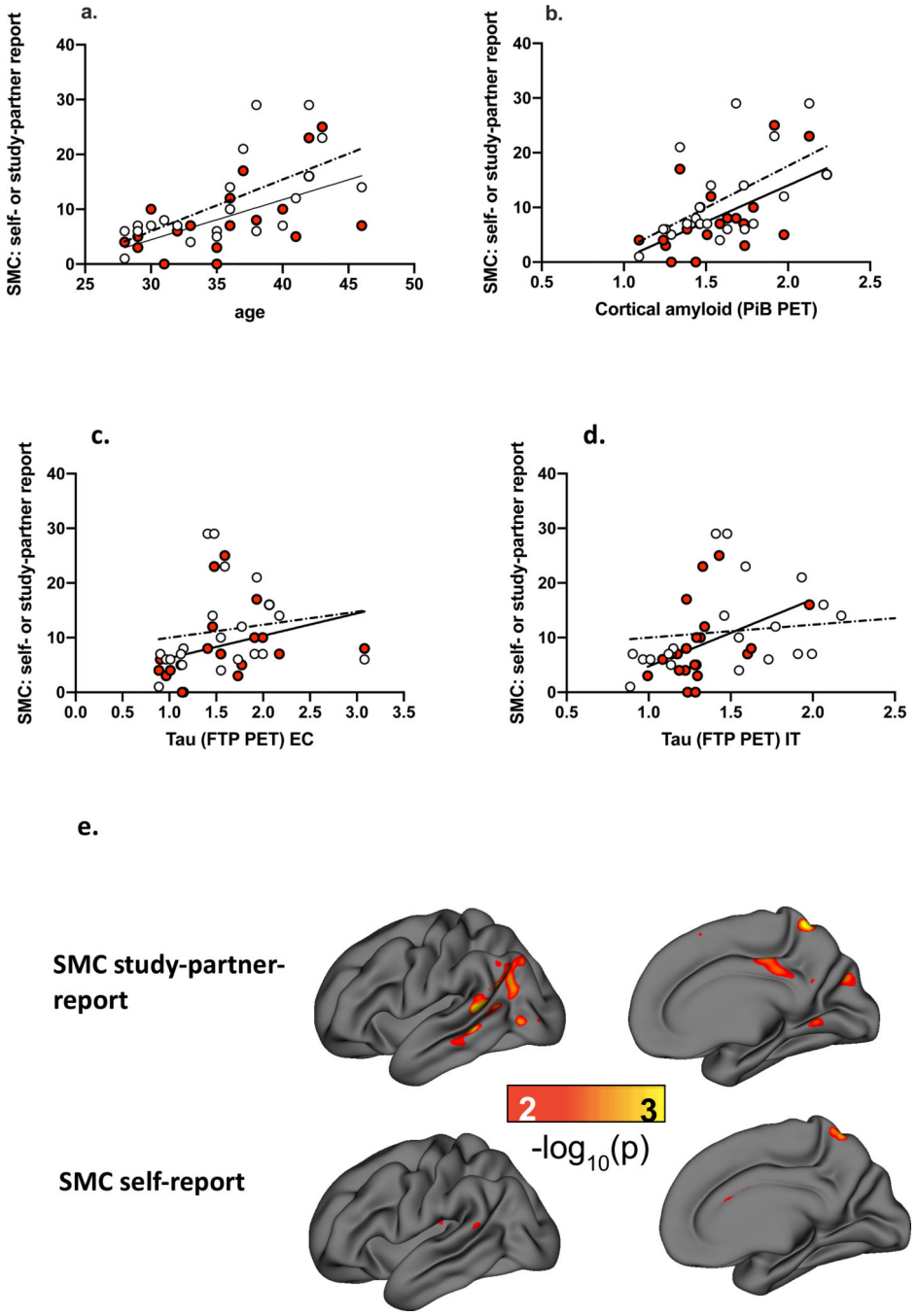

Figure 1.

Scatterplots (a-d) showing the unadjusted correlations between SMC (self-report (unfilled circles, dashed-line) and study-partner-report (filled circles, solid line)) as measured by the Memory Complaint Scale (MCS-Spanish version) and age (a); cortical amyloid (PiB retention) (b); entorhinal cortex (EC) tau (FTP retention) (c); and inferior temporal (IT) tau (FTP retention (d); in *PSEN1* E280A mutation carriers (n=21). e. Whole-brain unadjusted vertex-wise analyses of tau FTP PET SUVR images in relation to SMC study-partner-report (top panel) and self-report (bottom panel) at the $p<0.01$ threshold level show regions in the

temporal and parietal lobes associated with SMC. Results are displayed as - log(p) at the $p<0.01$ (unadjusted) threshold level. SMC=Subjective Memory Complaint Scale, Spanish version; PIB=Pittsburgh Compound B; FTP= Flortaucipir; SUVR=standard uptake volume ratio.