

CSF Markers of Preclinical AD & Deficits on a Self-Administered Computerized Test Battery

INTRODUCTION

Alzheimer's disease (AD) is characterized by the deposition of amyloid (Aβ) plaques and neurofibrillary tangles (tau) in the brain that produces progressive cognitive and functional impairments. Aβ and tau accumulate for years before impairment is observable¹, a state termed preclinical AD. Aβ or tau levels suggestive of preclinical AD are detectable using analysis of PET imaging or CSF. The latter was used in the present study.

Subtle cognitive changes are detectable in preclinical AD using pen-and-paper²⁻¹¹ and computerized¹²⁻¹⁴ neuropsychological assessments. The present study examined performance on the CANS-MCI, a self-administered computerized assessment.

Preclinical levels of Aβ are associated with slight deficits in the domains of memory^{3,12}, language⁶, visuospatial ability¹², and executive function¹¹. CSF tau levels have also been linked with deficits in memory¹² and executive function¹³. It was hypothesized that CSF Aβ and tau levels indicative of preclinical AD would associate with deficits on CANS-MCI tests of the aforementioned domains.

METHODS & MATERIALS

All participants were cognitively intact when they consented to completing the CANS-MCI and undergoing lumbar puncture. Research was conducted in accordance with UK IRB-approved protocols. Mini-Mental Status Exam (MMSE) was used to assess mental status and Hachinski scale was used to assess cerebrovascular risk factors.

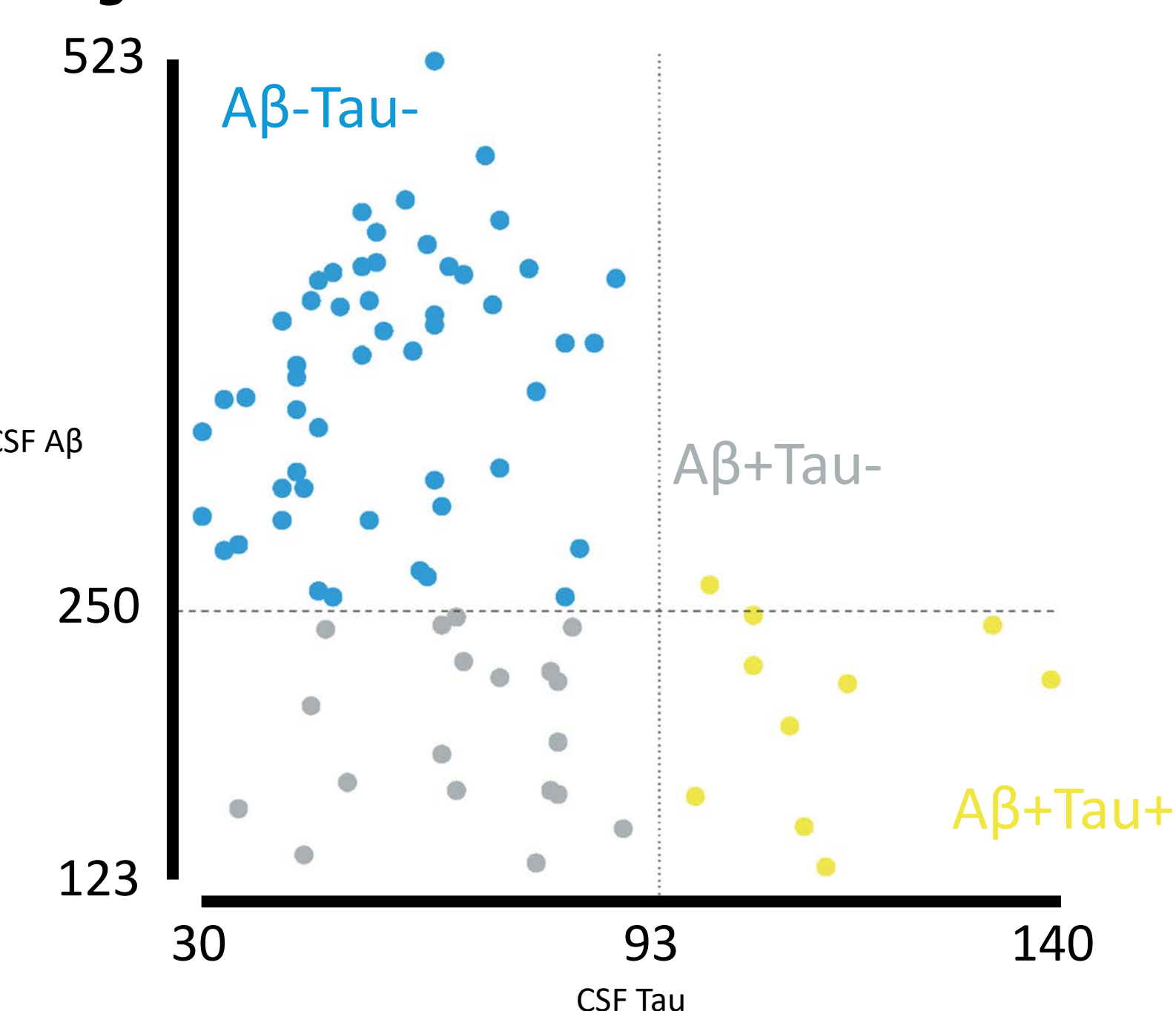
CSF Collection & Analysis

CSF was collected after ≥8 hours fasting, stored in -80°C freezer prior and shipped on dry ice. Measurement of Aβ and tau concentrations is described elsewhere¹⁶. Lower CSF Aβ indicates higher brain Aβ deposition; greater CSF tau indicates higher brain tau deposition.

Classification

CSF Aβ threshold was set at 250pg/ml¹⁷. CSF tau threshold was set at 93pg/ml¹⁶. This yielded three groups: Aβ-Tau-, Aβ+Tau-, and Aβ+Tau+. One participant was Tau+ and Aβ- but was assigned to the Aβ+Tau+ group because visual inspection shows the nearest neighbors were in that group. See Figure 1.

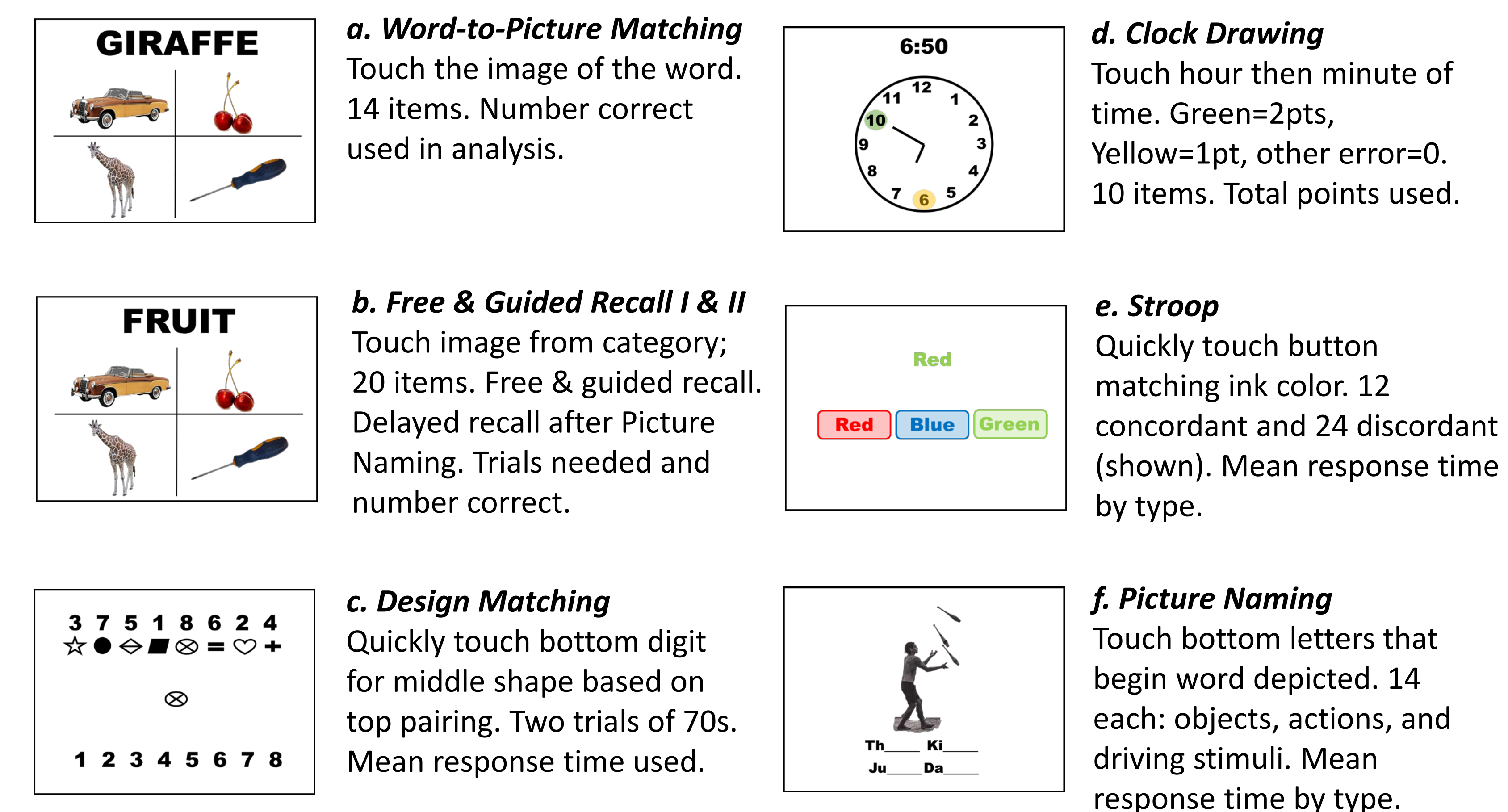
Figure 1



CANS-MCI

The CANS-MCI is validated for use in older adults¹⁸. It also contains 10 items from the Geriatric Depression Scale and questions about head injury, exercise, and prescription and other drug use. Figure 2a-f are in order of administration and are recreations of test stimuli.

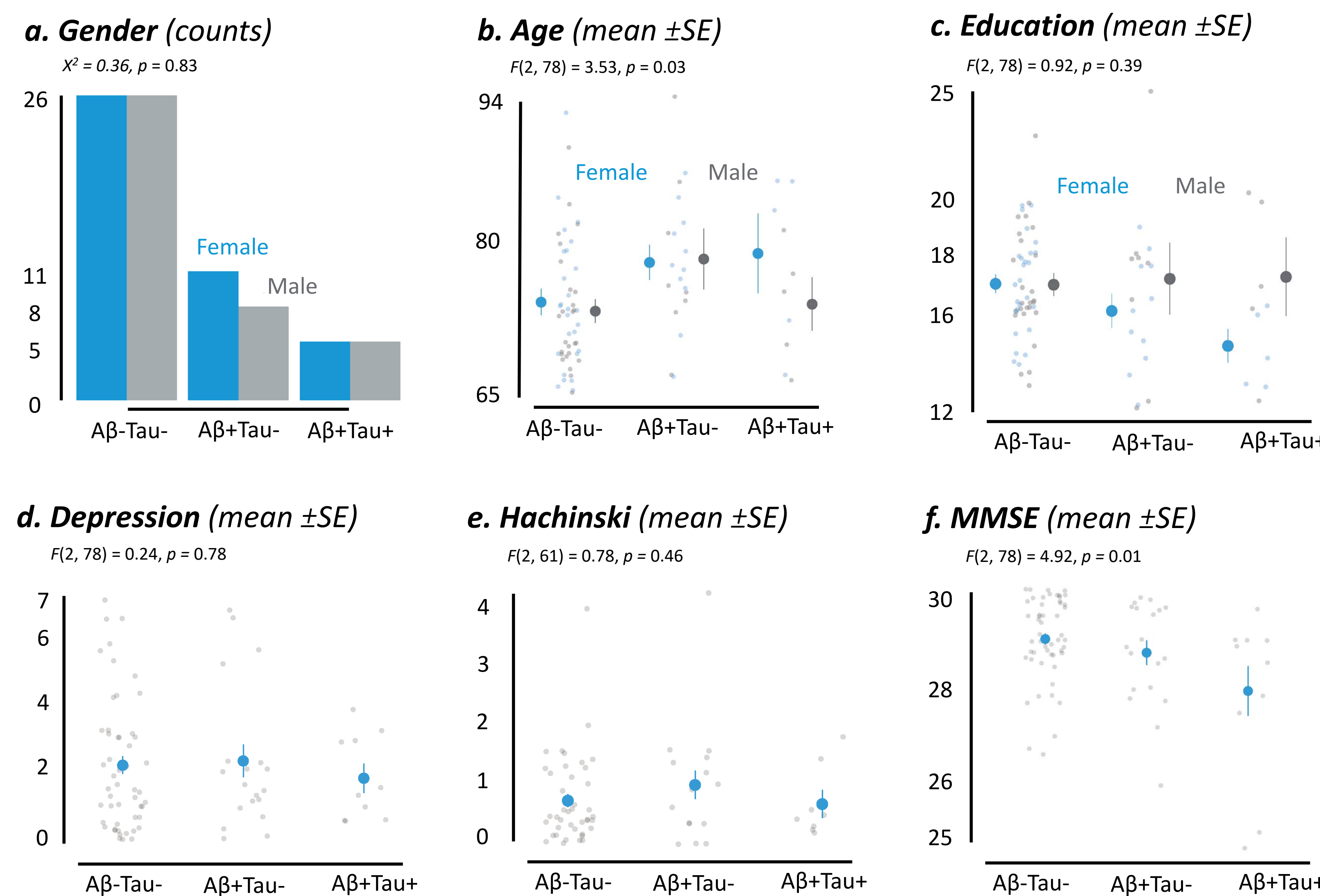
Figure 2



RESULTS

The characteristics of 81 participants are shown in Figure 3; three were ethnic minorities. 18 (22.2%) participants had 1 or 2 prior CANS-MCI administrations, with no difference between groups. CSF was collected a mean 33.96 days prior (SD = 81 days) to the CANS-MCI, with no group differences. Processing speed significantly slowed with age, $r = 0.27$, $p = 0.02$, and was included in models with response time as a dependent variable.

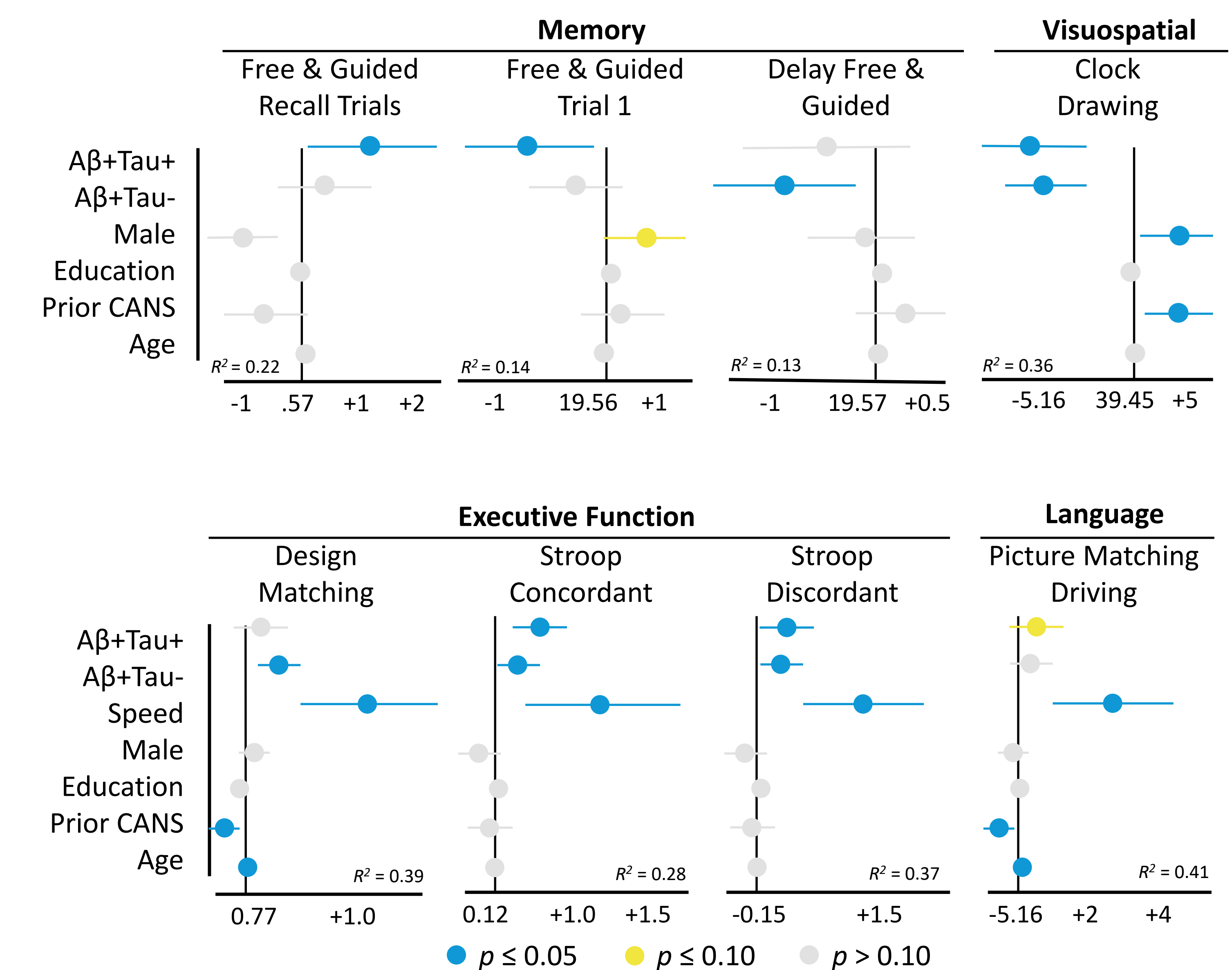
Figure 3



RESULTS Continued

Simple linear regressions were used to examine the relationship between preclinical AD groups and CANS-MCI performance. Aβ-Tau- was the reference group. Only models with a group difference of $p < 0.10$ are shown in Figure 4. Model coefficients in panels by domain and test. Groups were similar on Word-to-Picture Matching and on the other Picture Naming response times.

Figure 4



DISCUSSION

Aβ+Tau- or Aβ+Tau+ group exhibited performance deficits across most tests of the CANS-MCI when controlling for age, sex, education, prior CANS-MCIs and processing speed. The findings indicate a self-administered, computerized neurocognitive test battery is sensitive to CSF markers of preclinical AD, consistent with prior studies using pen-and-paper and computerized assessments.

Limitations

- The study cohort was homogenous, predominantly Caucasian, and well-educated; but, ages 65-late 80s were well-represented.
- Other factors that affect testing such as medical status were not considered; however, vascular risks and depression were similar between groups.
- The Aβ+Tau- and Aβ+Tau+ groups were small, limiting inferences that can be made; however, both evidenced performance deficits.

Future Directions

- Analyze performance within CANS-MCI tests to examine how Aβ and tau CSF levels affect acclimation from beginning to end of test.
- Longitudinal analysis of how CANS-MCI performance changes in relation to changes in Aβ and tau CSF levels.
- Examine utility of CANS-MCI performance to predict preclinical AD as measured by CSF Aβ and CSF tau in larger, more diverse sample.

Acknowledgements

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