Subjective Visuospatial Decline in Cognitively Unimpaired Individuals

Deepti Putcha[1,3*], Michael Properzi[2], Kathryn Papp[2,3], Keith Johnson[2,3,4], Reisa Sperling[2,3], Dorene Rentz[2,3], and Rebecca Amariglio[2,3]

[1] Department of Psychiatry, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA, [2] Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA,
[3] Department of Neurology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA , [4] Department of Radiology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

Key Take Aways: (1) Subjective visuospatial decline as measured by the Everyday Cognition Scale (ECOG) is associated with amyloid positivity in cognitively normal older adults. (2) Subjective visuospatial decline is associated with tau PET signal in a spatiotemporal cortical pattern that is distinct from that of subjective memory decline. (3) The ECOG may be a useful biomarker-validated tool to identify subjective visuospatial decline that could place individuals at higher risk for developing atypical syndromes of AD (e.g., PCA) and should be evaluated in a younger cohort of adults (ages 50-65).

BACKGROUND

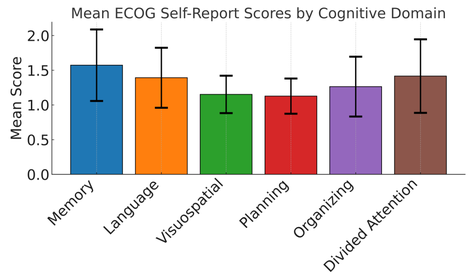
- Subjective cognitive decline (SCD) in cognitively unimpaired (CU) individuals represents a significant risk factor for progression from the preclinical to the symptomatic stage of AD (Munro et al., 2023)
- The study of SCD has thus far primarily focused on **subjective memory decline**, measured by instruments such as the Everyday Cognition Scale (ECOG) memory subscale, that has been linked with the development of an amnestic syndrome of AD (Buckley et al., 2017).
- However, AD pathology also gives rise to atypical non-amnestic syndromes thought to comprise up to a third of all early-onset AD cases and ~6% of older-onset cases (Koedam et al., 2012; Tort-Merino et al., 2022). Atypical AD syndromes, such as a visuospatial variant called Posterior Cortical Atrophy, are often underdiagnosed and have a significantly longer interval between the onset of symptoms and accurate diagnosis (van Vliet et al,. 2013).
- We do not yet have a biologically-validated tool to assess **subjective visuospatial decline (SVD)**. We seek to evaluate the ECOG visuospatial subscale as a possible screening tool to assess SVD, for use in evaluating pre-symptomatic stages of AD across the phenotypic continuum.

MATERIALS AND METHODS

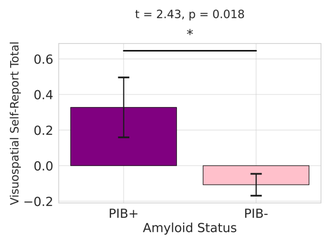
- Responses on the Everyday Cognition (ECOG) scale were analyzed from 247 cognitively unimpaired (CU) older adults from the Harvard Aging Brain Study who received amyloid PET and tau PET imaging at the same timepoint.
- Total self-report scores on the ECOG visuospatial subscale were evaluated as a measure of subjective visuospatial decline (SVD). As SVD and subjective memory decline were highly correlated, we residualized each variable from the other. The residuals from this model, representing the variance in each variable independent of the other, were extracted and used in all subsequent analyses.
- Bivariate correlation analyses were conducted to determine if SVD was associated with demographic factors (age, sex, education), clinical functional severity (CDR-SB), and objective cognitive test performance on a global cognitive screening test (Mini-Mental State Examination (MMSE) and a measure of visuospatial cognition (Benton Visual Form Discrimination Test).
- Independent samples *t*-test and bivariate correlation were utilized to evaluate the association between residualized SVD and dichotomized amyloid status (PIB positivity) as well as a continuous measure of cortical amyloid burden (PiB PET FLR DVR).
- Whole-cortex general linear modeling of tau PET was conducted with residualized variables measuring SVD and subjective memory decline, respectively to determine the association between subjective concerns and tau PET signal across the cortex, with post-hoc correlation analysis focused on specific regions of interest relevant to each domain of interest.

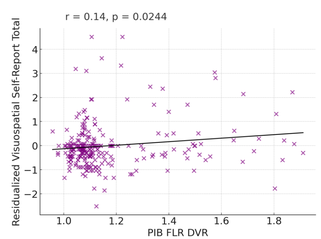
RESULTS

Demographic	N=247 CU
Age (years)	72.0 ± 8.9 (min 50, max 91)
Education (years)	16.4 ± 2.8 (mix 6, max 20)
Sex (M/F)	102 M / 145 F
CDR	CDR 0 (n=235) CDR 0.5 (n=11)
CDR Sum-Of-Boxes	0.12 ± 0.3
MMSE (/30)	29.2 ± 1.1
Amyloid Status	PiB+ (n= 57) PiB- (n= 185)

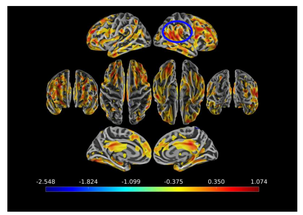


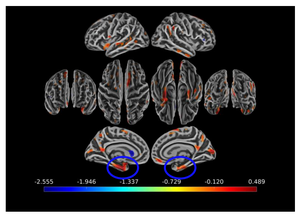
SVD is associated with amyloid positivity



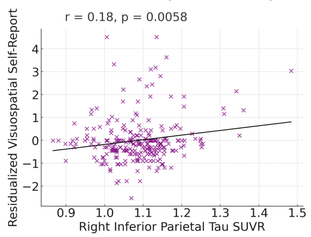


SVD is associated with tau in right-hemisphere predominant cortical regions while subjective memory concerns are associated with tau in the entorhinal cortex



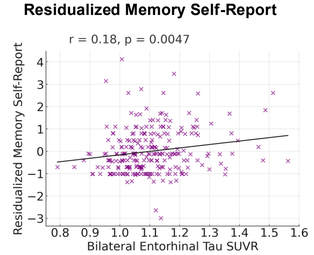


Residualized Visuospatial Self-Report



Residualized Visuospatial Self-Report concerns are associated with **right-hemisphere inferior parietal tau SUVR** (t=0.2, p=0.006) but not left-hemisphere inferior parietal (p>0.05) or entorhinal tau SUVR (p>0.05).

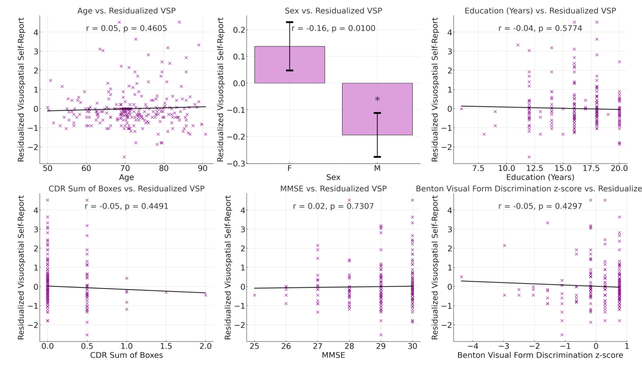
Residualized Memory Self-Report



Residualized Memory Self-Report concerns are associated with both left-hemisphere (r=0.2, p= 0.001) and right-hemisphere (r=0.14, p=0.04) **entorhinal tau SUVR** but not inferior parietal tau SUVR (p>0.05).

RESULTS, CONT'D

SVD differs by sex, but is not significantly associated with age, education, functional severity (CDR-SB), or objective cognition.



CONCLUSIONS

- SVD is associated with amyloid positivity in older cognitively unimpaired individuals, separate from the effects of subjective memory decline.
- SVD is associated with a spatial distribution of tau PET signal in distinct cortical regions (including right-hemisphere predominant inferior parietal cortex) from tau PET signal associated with subjective memory concerns (entorhinal cortices).
- SVD differs by sex such that females report greater concerns compared to males. This was also observed with subjective memory concerns.
- SVD is not associated with age, education, overall clinical impairment (CDR-SB), or cognitive performance (MMSE or Benton Visual Form Discrimination).
- The ECOG visuospatial subscale shows promise as a tool to measure SVD and should be further evaluated in a younger cognitively unimpaired sample who may be at risk for developing an atypical early-onset syndrome of AD such as Posterior Cortical Atrophy.

REFERENCES & ACKNOWLEDGMENTS

1. Buckley RF, Hanseeuw B, Schultz AP, et al. Region-Specific Association of Subjective Cognitive Decline With Tauopathy Independent of Global beta-Amyloid Burden. JAMA Neurol. Dec 1 2017;74(12):1455-1463. doi:10.1001/jamaneurol.2017.2216
2. Koedam EL, Lauffer V, van der Vlies AE, van der Flier WM, Scheltens P, Pijnenburg YA. Early-versus late-onset Alzheimer's disease: more than age alone. J Alzheimers Dis. 2010;19(4):1401-8. doi:10.3233/JAD-2010-1337
3. Munro CE, Boyle R, Chen X, et al. Recent contributions to the field of subjective cognitive decline in aging: A literature review. Alzheimers Dement (Amst). Oct-Dec 2023;15(4):e12475. doi:10.1002/dad2.12475
4. Tort-Merino A, Falgas N, Allen IE, et al. Early-onset Alzheimer's disease shows a distinct neuropsychological profile and more aggressive trajectories of cognitive decline than late-onset. Ann Clin Transl Neurol. Dec 2022;9(12):1962-1973. doi:10.1002/acn3.51689
5. van Vliet D, de Vugt ME, Bakker C, et al. Time to diagnosis in young-onset dementia as compared with late-onset dementia. Psychol Med. Feb 2013;43(2):423-32. doi:10.1017/S0033291712001122

This work was supported by NIH grants K23 236450 (Putcha), and P01 AG036694 (Sperling and Johnson).

We gratefully acknowledge our participants, without whom this work would not be possible.

Please contact Deepti Putcha, PhD (dputcha@mgh.harvard.edu) with any questions.