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Greater Subjective Cognitive Decline Severity is Associated with Worse Memory Performance and Lower Entorhinal Cerebral Blood Flow in Healthy Older Adults

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Abstract

Objective: Subjective cognitive decline (SCD) is a potential early risk marker for Alzheimer's disease (AD), but its utility may vary across individuals. We investigated the relationship of SCD severity with memory function and cerebral blood flow (CBF) in areas of the middle temporal lobe (MTL) in a cognitively normal and overall healthy sample of older adults. Exploratory analyses examined if the association of SCD severity with memory and MTL CBF was different in those with lower and higher cardiovascular disease (CVD) risk status.

Methods: Fifty-two community-dwelling older adults underwent magnetic resonance imaging, neuropsychological testing, and were administered the Everyday Cognition Scale (ECog) to measure SCD. Regression models investigated whether ECog scores were associated with memory performance and MTL CBF, followed by similar exploratory regressions stratified by CVD risk status (i.e., lower vs higher stroke risk).

Results: Higher ECog scores were associated with lower objective memory performance and lower entorhinal cortex CBF after adjusting for demographics and mood. In exploratory stratified analyses, these associations remained significant in the higher stroke risk group only.

Conclusions: Our preliminary findings suggest that SCD severity is associated with cognition and brain markers of preclinical AD in otherwise healthy older adults with overall low CVD burden and that this relationship may be stronger for individuals with higher stroke risk, although larger studies with more diverse samples are needed to confirm these findings. Our results shed

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Disclosure Statement

The authors report no conflicts of interest.

light on individual characteristics that may increase the utility of SCD as an early risk marker of cognitive decline.

Keywords

cognitive complaints; memory complaints; arterial spin labeling MRI; neuropsychology; memory; cognitive aging

Background

The worldwide older adult population continues to grow steadily each year, and this growth is accompanied by increasing prevalence rates of various chronic conditions (Tkatch et al., 2016) and Alzheimer's disease (AD) and related dementias (ADRD) (Barnes & Yaffe, 2011). There are approximately 50 million individuals currently diagnosed with dementia of various etiologies worldwide, and it is estimated that 152 million will be diagnosed by 2050 due to longer life expectancy and demographic changes (World Health Organization, 2019).

A comprehensive understanding of early risk markers in cognitively normal individuals is critical to accurately detect those at risk for ADRD and implement early interventions prior to symptom manifestation. A plethora of research has found that subjective cognitive decline (SCD), defined as the self-experienced perception of decline in one or more cognitive domains compared to a previous state, may be an early risk marker of AD (Jessen, 2014; Molinuevo et al., 2017), and is related to brain abnormalities consistent with AD pathology (Amariglio et al., 2012; Jessen et al., 2014; Jia, Li, Li, & Cao, 2021; Rabin, Smart, & Amariglio, 2017; Schwarz et al., 2021; Zhao et al., 2019). Since many individuals may report SCD for reasons other than preclinical AD (e.g., depression and other mood disturbances, poor physical health) (Molinuevo et al., 2017; Rabin et al., 2017), a deeper understanding of the individual characteristics that strengthen the ability of SCD severity to predict cognition and AD biomarkers is needed.

Several studies have demonstrated that higher SCD reporting is associated with lower objective cognition in various community-based older adult samples (Blom et al., 2019; Burmester, Leatham, & Merrick, 2016; Corlier et al., 2020; Jessen, 2014; Kielb, Rogalski, Weintraub, & Rademaker, 2017; Nakhla et al., 2021; Studart Neto & Nitrini, 2016; Zlatar et al., 2022) and increases the risk of progressing to dementia (Mazzeo et al., 2020; Mendonça, Alves, & Bugalho, 2016; Mitchell, Beaumont, Ferguson, Yadegarfar, & Stubbs, 2014). However, other studies have shown that SCD may be related more closely to depression than objective cognition (Molinuevo et al., 2017; Slavin et al., 2010; Zlatar et al., 2014). Given conflicting findings, it is important to study if the severity of SCD reporting is sensitive to cognitive abilities and markers of brain health in non-clinic-based community samples, while accounting for depressive symptoms (Jessen et al., 2020, 2014).

AD pathology is linked to preclinical changes in cerebrovascular function and cardiovascular disease (CVD) risk factors such as hypertension, hyperlipidemia, diabetes, and metabolic syndrome, which increase the risk of developing dementia (Knopman & Roberts, 2010). The two-hit vascular hypothesis of AD (Zlokovic, 2011) posits that damage to the brain's microcirculation (hit one) initiates a cascade of vascular-related

neuronal dysfunction, mediated by changes in blood-brain barrier function and reductions in cerebral blood flow (CBF). These vascular changes lead to a second hit, which arises from increased amyloid- β accumulation and impaired amyloid- β clearance mechanisms, which exert neurotoxic effects on the brain leading to degeneration and dementia. Given the involvement of cerebrovascular dysfunction in preclinical AD, and more specifically decreased CBF, it is important to study if SCD severity relates to CBF in cognitively normal individuals.

However, research studying the association of SCD with CBF is sparse. One study found that greater CBF did not support memory performance in those with SCD, whereas greater CBF was associated with better memory performance in those without SCD, suggesting neurovascular dysregulation in those with SCD (Hays, Zlatar, Campbell, Meloy, & Wierenga, 2018). Another community-based study also found higher CBF in the left parahippocampal gyrus of individuals with SCD compared to those without SCD (Wenyi Li et al., 2022), suggestive of neurovascular dysregulation (Hays, Zlatar, & Wierenga, 2016; Østergaard et al., 2013; Wierenga, Hays, & Zlatar, 2014). Moreover, a longitudinal study showed that baseline SCD (measured as a continuous variable in a community-based sample) was associated with reduced global CBF in older adults over a 3.8 year follow-up period (Kresge et al., 2020). Given the importance of CBF to maintaining brain health and supporting cognitive function, and its role as a potential early marker of cognitive decline (Hays et al., 2016; Rabin et al., 2017; Wierenga et al., 2014), research is needed to better understand if SCD is associated with CBF in older adults.

We examined if SCD severity (with SCD as a continuous variable rather than a diagnostic criterion) is associated with memory performance and with CBF in areas of the middle temporal lobe (MTL) that are implicated in preclinical AD. We hypothesized that greater SCD severity would be associated with worse memory performance and lower CBF in the MTL, adjusting for demographics and mood. To identify individual characteristics that may increase the likelihood that SCD reporting may be due to preclinical AD rather than other mood or health characteristics, we explored if those with greater CVD risk showed a stronger association of SCD severity with memory performance and CBF in the MTL.

Method

Participants

Participants were 52 community-dwelling research volunteers from the community with normal cognition and who were overall healthy, with mostly low CVD risk. They were recruited from ongoing aging studies at the UC San Diego's (UCSD) Wellness Initiative for Senior Enrichment (WISE) Lab and Veteran Affairs San Diego Healthcare System (VASDHS). Participants were recruited from Research Match, registries, word of mouth, and community outreach. Study protocols were approved by UCSD or VASDHS Institutional Review Boards, and all participants provided written informed consent. Research was completed in accordance with the Helsinki Declaration.

Inclusion criteria for this sample consisted of individuals between the ages of 65 to 85 years, who are English-speaking as needed to complete cognitive testing, have no contraindications

for magnetic resonance imaging, and ambulate independently. Exclusionary criteria included a pre-existing diagnosis of mild cognitive impairment (MCI) or dementia, history of vascular events (e.g., myocardial infarction, transient ischemic attacks, stroke), diabetes, chronic psychiatric conditions, major neurologic disorders, history of falls resulting in hospitalization in the past two years, and poorly controlled chronic conditions. Cognitive impairment for exclusion was based on comprehensive neuropsychological testing and followed the recommendation outlined by Jak and colleagues, which was defined by performance greater than one standard deviation below the norm on at least two measures within the same cognitive domain (Jak et al., 2009).

Subjective Cognitive Decline Measurement

SCD severity was measured as a continuous variable with the Everyday Cognition Scale (ECog) (Farias et al., 2008), a questionnaire of perceived cognitive decline compared to ten years inquiring about the loss in cognitively mediated functional abilities (e.g., remembering recent events, communicating thoughts, planning a shopping trip, multitasking). The ECog has been validated in older adults with normal cognition, MCI, and dementia and has the following subscales: Global Function, Memory, Language/Semantic, Visuospatial, and Executive: Planning, Organization, Divided Attention (Farias et al., 2008). The questionnaire consists of 39 items each scored on a scale of 1–4 (1= better or no change, 2= questionable/ occasionally worse; 3= consistently a little worse; 4= consistently much worse) (Farias et al., 2008). Total raw scores range from 39 to 156 points, with higher scores reflecting perception of more severe cognitive decline.

Memory Assessment

All participants completed a comprehensive neuropsychological battery. A Memory Composite Score was calculated based on *a priori* tests of immediate and delayed verbal recall by averaging across z-scores derived from each tests' raw score. The memory tests included in the composite were: Wechsler Memory Scale-Revised (WMS-R) Logical Memory (LM)-I immediate recall (Wechsler, 1987); WMS-R LM-II delayed recall (Wechsler, 1987); Rey Auditory Verbal Learning Test (RAVLT) – Trials 1–5 Total (Schmidt, 1996) [OR] California Verbal Learning Test 2nd Edition (CVLT-II) – Trials 1–5 Total (Delis, Kramer, Kaplan, & Ober, 2000); RAVLT – Short Delay Free Recall (Schmidt, 1996) [OR] CVLT-II – Short Delay Free Recall (Delis et al., 2000); RAVLT – Long Delay Free Recall (Schmidt, 1996) [OR] CVLT-II – Long Delay Free Recall (Delis et al., 2000). Participants from the WISE Lab (n = 39) were administered the Rey Auditory Verbal Learning Test (RAVLT) (Schmidt, 1996), and participants from the VASDHS Lab (n = 13) were administered the California Verbal Learning Test (CVLT-II) 2nd Edition (Delis et al., 2000). Given that the CVLT-II and RAVLT differ in word list length, we standardized the raw scores based on the means and standard deviations of each test prior to creating the memory composite. Previous research has supported the comparability between the CVLT-II and RAVLT (Beier, Hughes, Williams, & Gromisch, 2019; Grimes, Zanjani, & Zakzanis, 2017; Samudra, Jacobs, Aulino, & Abou-Khalil, 2020; Stallings, Boake, & Sherer, 1995), particularly for raw scores (Stallings et al., 1995; Wiens, Tindall, & Crossen, 1994).

Assessment of Depression

Depressive symptomatology was assessed with the Geriatric Depression Scale (**GDS**) – a 30-item, self-report questionnaire, with higher scores reflecting worse depressive symptoms (Yesavage et al., 1982). Total scores of 0–4 suggest no depression, 5–8 suggest mild depression, 9–11 suggest moderate depression, and 12–15 suggest severe depression (Greenberg, 2012). Since the GDS contains cognitive items (Montorio & Izal, 1996) that may increase the shared variance with the ECog, we created a modified GDS score by removing the following items from our total score: *item 14* “Do you feel like you have more problems with memory than most?”; *item 26*: “Do you have trouble concentrating?”; *item 29*: “Is it easy for you to make decisions?”. The modified GDS score (m-GDS) was used as a covariate in all analyses.

CVD Risk Assessment

The Framingham Stroke Risk Profile (FSRP) (D’Agostino, Wolf, Belanger, & Kannel, 1994) is a scale that evaluates the probability [percentage] of stroke occurrence over a 10-year period in adults ages 55 and older. FSRP scores of less than 10% suggest low stroke risk, 10–19% suggest moderate stroke risk, and 20% or more suggests high stroke risk (Bosomworth, 2011; D’Agostino et al., 1994). The FSRP is corrected for sex and accounts for several risk factors: age (in years), systolic blood pressure (mm Hg), history of cardiovascular disease (e.g., myocardial infarction, coronary insufficiency, congestive heart failure), left ventricular hypertrophy, and/or atrial fibrillation, diabetes mellitus, cigarette smoking, and use of antihypertensive medications.

Brain Imaging Acquisition and Processing

Magnetic resonance imaging (MRI) data were acquired on a GE Discovery MR 750 3T whole-body system with a body transmit coil and an 8-channel receive-only head coil at the UCSD’s Center for functional MRI. The structural brain sequence was a high-resolution T1-weighted Fast Spoiled Gradient Recall (3DFSPGR) scan: 172 1mm contiguous sagittal slices, field of view (FOV)=25 cm, repetition time (TR)=8 ms, echo time (TE)=3.1 ms, flip angle=12, inversion time (TI)=600 ms, 256×192 matrix, Bandwidth=31.25 kHz, frequency direction=S-I, NEX=1, scan time=8 min and 13 s. T1-weighted images were processed using FreeSurfer 6.0 software. The images underwent skull stripping, B1 bias field correction, gray matter-white matter segmentation, reconstruction of cortical surface models, and parcellation and labeling of cortical surface regions and subcortical structures (Dale, Fischl, & Sereno, 1999; Fischl et al., 2002).

CBF was assessed with a 2D Pseudo Continuous Arterial Spin Labeling (ASL) MRI (2DPCASL) sequence; TR=4500 ms, TE=3.2 ms, FOV=24 cm, labeling duration=1800 ms, post-labeling delay=2000 ms, with a single shot spiral acquisition and a total scan time of 4:30 min plus a 40.5 s calibration scan. The calibration scan was acquired immediately after the ASL scan using a spiral readout with TR=4.5 s and TE=3.2 ms with 8 dummy radiofrequency (RF) pulses (amplitude set to zero) to generate a 36 s delay followed by a 90-degree RF pulse in the last repetition interval to generate proton density-weighted contrast. Two field map scans were collected for off-line field map correction for signal bunching and dropouts in the frontal/medial temporal lobes.

CBF quantification was conducted using the Cerebral Blood Flow Biomedical Informatics Research Network (CBFBIRN) database and analysis pipeline (Shin, Ozyurt, & Liu, 2013). CBFBIRN quantifies CBF and adjusts for partial volume effects (Shin et al., 2013) by using a combination of custom MATLAB (MathWorks, 1996) routines and various Analysis of Functional Neuroimages (AFNI) (Cox, 1996) and FMRIB Software Library (FSL) (Smith et al., 2004) functions (Zlatař et al., 2019). We used MATLAB to form a mean ASL image from the average difference of the control and tag images. For CBF calibration, we used a proton density image for conversion of the ASL difference signal into physiological units (ml/100g/min). Slice timing delays were accounted for, making the post-labeling delay slice specific. Skull stripping of the high-resolution T1-weighted image was performed using AFNI's 3dSkullStrip. We used FSL's Automated Segmentation Tool (FAST) algorithm to define cerebrospinal fluid, gray matter, and white matter regions. To correct CBF for partial volume effects and ensure that CBF values were not influenced by known decreased perfusion in the white matter or increased volume of cerebrospinal fluid, we used a linear regression method (Asllani, Borogovac, & Brown, 2008) with a 5×5 regression kernel to obtain corrected gray matter CBF measurements. For each participant's partial volume corrected quantified CBF map (in units of ml/100 g tissue/min), voxels with negative intensities were replaced with zero.

We used FreeSurfer 6.0 software to create anatomical ROIs for the CBF data. For each participant, using AFNI's @SUMA_AlignToExperiment program, the FreeSurfer formatted T1-weighted brain volume was registered to the ASL CBF-aligned T1-weighted anatomical image which was derived from CBFBIRN. The resulting co-registration matrix was used to align the FreeSurfer aparc+aseg segmentation volume to the ASL CBF-aligned T1-weighted image using AFNI's 3dAllineate program. The CBF-aligned FreeSurfer volumes were visually inspected to ensure proper alignment and were then downsampled to the resolution of the CBF ASL image using AFNI's 3dfractionize program. Mean CBF was extracted for each FreeSurfer ROI for each participant, which were entered as outcome variables in our models. We focused on investigating average CBF in AD-related regions of the MTL (hippocampal, parahippocampal, and entorhinal cortex) to determine their association with ECog total scores.

ASL MRI studies of older adults show similar patterns of regional CBF compared to studies using fluorodeoxyglucose positron emission tomography (FDG-PET) and single photon emission computed tomography (SPECT) (Chen et al., 2011; Takahashi et al., 2014). ASL has advantages over PET and SPECT given its use of a non-invasive, endogenous tracer rather than an intravenously administered contrast agent and also allows quantification of cerebral perfusion (in milliliters per 100 g of tissue per minute). Notably, the use of ASL in older adult populations may give rise to unique challenges given that the signal to noise ratio (SNR) may be lower due to reduced CBF and potential vascular changes with aging. Age-related partial volume effects due to tissue atrophy and prolonged transport time from the labeling position to the tissue (i.e., arterial transient time) due to factors such as internal carotid stenosis or vessel tortuosity may affect the ASL signal and lead to underestimation or overestimation of CBF (Kilroy et al., 2014). To minimize the effects of these potential issues, we followed the white paper recommendations for the implementation of ASL published by the International Society for Magnetic Resonance in Medicine (ISMRM) and

the European Consortium for ASL in Dementia including a PCASL labeling approach and a relatively long post labeling delay (i.e., 2,000 ms in older adults rather than the standard 1,800 ms) (Alsop et al., 2015). Future studies using angiograms to improve tagging efficiency and quantifying arterial transit time delays may improve quantification of CBF among older adults (Alsop et al., 2015).

Statistical Analyses

Analyses were conducted using IBM SPSS Version 28.0 (IBM, 2021). Data were screened for normality by inspecting skewness and kurtosis limits (Field, 2009), and no significant outliers were detected for the memory outcome variable. There was one outlier for the ECog total scores (>4 standard deviations above the mean), which was removed.

We removed one participant that had CBF values (i.e., entorhinal) outside of the expected physiological range (<10 or >150 ml/100g/min) (Bangen et al., 2014; Marshall & Mayer, 2007; Mount & Das, 2020). There were also three statistical outliers in the dataset with mean regional CBF values within the range that our group has considered physiologically plausible (i.e., >10 and <150; Bangen et al., 2014, 2018), but were excluded given statistical considerations (>3 standard deviations above the mean). This is not uncommon since several studies have shown that older adults at risk for cognitive decline demonstrate elevated CBF, which may represent a compensatory mechanism and/or neurovascular dysregulation (Bangen et al., 2012; Thomas et al., 2022). Altogether, a total of 5 outliers (1 ECog + 4 CBF) were removed, which resulted in a final sample of 52 participants for all analyses.

Pearson correlations between the predictor variables were within acceptable limits (all r s < .6). For all regression models, tolerance levels were >.1 and variance inflation factors <.2, indicating no evidence of multicollinearity (Field, 2009). Covariates of interest were theoretically selected based on the SCD literature and following best practices (Jessen, 2014; Jessen et al., 2014). As such, we included age, sex, years of education, and m-GDS scores in all regression models.

Relationship Between ECog, Objective Memory, and CBF in the total sample (n=52)

Linear regression models were conducted to determine the association of continuous ECog scores with 1) memory composite scores, 2) CBF in the hippocampus, 3) CBF in the parahippocampal gyrus, 4) and CBF in the entorhinal cortex. All models were adjusted for age, sex, years of education, and m-GDS scores.

Exploratory Analysis: ECog, Objective Memory, and CBF Stratified by CVD Risk

Linear regression models stratified by FSRP scores were conducted to determine if the association of ECog with memory and CBF was higher in those with greater FSRP scores. We dichotomized the continuous FSRP% Stroke Risk variable into “lower FSRP scores” (n=21) and “higher FSRP scores” (n=31) groups based on a median split (median value= 6%). Only 14 participants in the sample had FSRP scores 10 suggestive of medium to high stroke risk (Bosomworth, 2011; D’Agostino et al., 1994), which was too small to dichotomize groups based on this criteria. Since we are studying a healthy sample of older adults, and our strict inclusion criteria excluded individuals with very high CVD risk, results

are interpreted in the context of those with overall low CVD risk. *T*-tests and chi-square analyses explored differences in demographics and mood, FSRP scores, blood pressure, CBF, and memory performance between lower and higher FSRP score groups. We adjusted for demographic characteristics (age, sex, education) and mood (m-GDS scores).

Results

Participants' characteristics are displayed in Table 1. They were, on average, 72.9 years old (range=65–83 years), mostly female (69%), relatively well-educated (mean=16.98 years, SD= 2.28 years), predominantly Caucasian/White (87%), and with overall low CVD risk status as indicated by FSRP scores (mean=8.12, SD=5.34).

Relationship Between ECog, Objective Memory, and CBF in the total sample (n=52)

Fully adjusted linear regression models (Table 2 & Figures 1 and 2) revealed that higher ECog total scores were significantly correlated with lower memory performance after adjusting for age, sex, education, and m-GDS. Similarly, higher ECog total scores were associated with lower CBF in the entorhinal cortex after adjusting for age, sex, education, and m-GDS. Results did not change when using the total GDS scores instead of the m-GDS scores as a covariate.

Exploratory Analysis: ECog, Objective Memory, and CBF Stratified by CVD Risk

Lower and higher FSRP score groups did not significantly differ in years of education, m-GDS scores, memory performance, ECog total scores, or CBF (hippocampal, parahippocampal, entorhinal). The sex distribution and age were statistically different between the lower and higher FSRP score groups. The higher FSRP score group had significantly greater FSRP% stroke risk scores and systolic blood pressure (Table 3). There was a significant association of greater ECog scores with lower memory performance (Figure 3A) and entorhinal CBF (Figure 3B) only for those in the higher FSRP score group. Memory performance and entorhinal CBF were not associated with ECog scores in the lower FSRP score group (Table 4). Results did not change when using the total GDS scores instead of the m-GDS scores as a covariate.

Discussion

This study investigated the association of SCD severity with objective memory performance and CBF in areas implicated in preclinical AD in older cognitively normal research volunteers. We also explored if those with greater CVD risk severity showed a stronger correlation of ECog scores with memory performance and CBF. We found that greater SCD severity, measured with the ECog, was associated with lower memory performance in our sample of cognitively normal older adults, after controlling for demographic characteristics and mood. This is consistent with other studies (Brailean, Steptoe, Batty, Zaninotto, & Llewellyn, 2019; Corlier et al., 2020; Farias et al., 2013; Kielb et al., 2017; Wei Li, Yue, & Xiao, 2022), and highlights that SCD severity in community-based samples may be sensitive to concurrent memory difficulties, even in individuals who are cognitively normal, non-medical help-seeking, and have overall low CVD risk profiles.

We also found an association between greater SCD severity and lower entorhinal CBF across the total sample, even after adjusting for demographics and mood. The entorhinal cortex is thought to be one of the first regions to be affected in AD and a strong predictor of disease progression from MCI to AD (Khan et al., 2014; Zhou, Zhang, Zhao, Qian, & Dong, 2016). In fact, reduced CBF in the MTL has been predictive of faster rates of cognitive decline, neurodegeneration and white matter hyperintensity progression (Bangen et al., 2021), and decline in daily functioning (i.e., instrumental activities of daily living) (Sanchez et al., 2020). Dysfunction in the entorhinal cortex is thought to precede dysfunction in the hippocampal circuit (Khan et al., 2014), a brain region that is associated with hallmark memory deficits observed in AD (Babcock et al., 2021; Chen et al., 2021; Setti et al., 2017). Reductions in CBF have been associated with increased A β production and are thought to be an early risk marker of AD (Hays et al., 2016; Korte, Nortley, & Attwell, 2020; Park et al., 2019; Wierenga et al., 2014; Zlokovic, 2011). As such, our findings provide evidence that SCD severity is not only associated with objective memory, but also with one of the earliest brain signatures of AD in a cognitively normal, community-based sample. These findings are consistent with recent literature showing that CBF alterations in the MTL are an independent risk factor for SCD (Wenyi Li et al., 2022), and that, compared to healthy controls, those with SCD show lower CBF in areas of the MTL (Yang et al., 2021).

Consistent with our hypothesis, exploratory stratified analyses within FSRP score groups suggest that the relationship of SCD severity with memory performance and entorhinal CBF in our sample of cognitively normal older adults may be driven by those with higher risk for developing AD by virtue of their CVD burden. That is, the association of greater SCD severity with worse memory performance and lower entorhinal cortex CBF was only significant within the higher FSRP score group. As previously noted, SCD is associated with an increased risk for dementia (Jessen, 2014; Mendonça et al., 2016; Mitchell et al., 2014; Molinuevo et al., 2017) for some individuals. Similarly, those with greater CVD burden also have increased risk of developing AD (Song et al., 2021). Our findings suggest that SCD severity in individuals with higher CVD burden may be more closely associated with cognition and brain markers of preclinical AD than in those with lower CVD burden. These exploratory results shed light on a potential variable that may help increase the clinical utility of SCD reporting in cognitively normal and overall healthy individuals, although larger studies with more diverse individuals (i.e., with greater CVD risk and from different ethnic and socioeconomic backgrounds) are needed to replicate these findings.

It is important to keep in mind that not everyone who reports SCD will progress to AD since SCD reporting may reflect other conditions such as depression, anxiety, or other neurologic conditions (Jessen et al., 2014; Molinuevo et al., 2017; Slavin et al., 2010; Zlatar et al., 2014). As such, finding individual characteristics that increase the clinical utility of SCD to predict preclinical AD and later progression warrants further study. Alternatively, our findings could also indicate that cognitively normal individuals with a higher CVD burden may also be more aware of subtle changes in their memory performance and/or may be at greater risk for memory difficulties.

Limitations of this study include a cognitively normal older adult community-based sample that was mostly Caucasian/White, female, and highly educated, limiting the generalizability

of our findings. Individuals in our sample generally reported minimal to no depressive symptoms and reported low SCD severity. Similarly, we had strict inclusion criteria, excluding individuals with a history of vascular events (e.g., myocardial infarction, transient ischemic attacks, stroke) and diabetes, which are components of the FSRP score we used to characterize CVD risk. This resulted in an overall healthy sample with low CVD risk burden. Thus, our results cannot be generalized to individuals with high CVD burden, a diagnosis of SCD, and/or clinical samples seeking medical help for cognitive decline. Since CVD risk and other health conditions may influence SCD reporting, future research with larger and more diverse samples, including individuals with high CVD risk burden is warranted. Moreover, our small sample size may have obscured potential associations of SCD with CBF in other MTL regions due to lack of power. Notably, this study was cross-sectional, and therefore, we cannot determine if SCD predicts changes in objective cognition or CBF over time. Future longitudinal studies would be beneficial in elucidating these important relationships. Lastly, inclusion of other measures of CVD risk (including relevant variables such as hyperlipidemia, hypercholesterolemia, body mass index, renal function) (Bosomworth, 2011) and other markers of brain health would be beneficial to increasing our understanding of how CVD risk may impact the relationship of SCD severity with memory and CBF.

In summary, findings provide evidence that SCD severity is associated with objectively measured cognition and CBF in regions implicated in preclinical AD, and further suggest that those with greater CVD risk may be driving this relationship. Findings are aligned with previous studies suggesting that the ECog can be used as a clinically valuable prescreening tool (Corlier et al., 2020; Farias et al., 2013; Rueda et al., 2015; Shokouhi et al., 2019). In this case, the ECog seems particularly sensitive to memory performance and neural markers of preclinical AD in individuals with greater CVD risk. Future studies should investigate if individuals who present with greater CVD burden and report greater SCD severity have a higher chance of progression to MCI and AD over time.

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References

- Alsop DC, Detre JA, Golay X, Günther M, Hendrikse J, Hernandez-Garcia L, ... Smits M (2015). Recommended implementation of arterial spin-labeled perfusion MRI for clinical applications: A consensus of the ISMRM perfusion study group and the European consortium for ASL in dementia. *Magnetic Resonance in Medicine*, 73(1), 102–116. 10.1002/mrm.25197 [PubMed: 24715426]
- Amarglio RE, Becker JA, Carmasin J, Wadsworth LP, Lorus N, Sullivan C, ... Rentz DM (2012). Subjective cognitive complaints and amyloid burden in cognitively normal

- older individuals. *Neuropsychologia*, 50(12), 2880–2886. 10.1016/j.neuropsychologia.2012.08.011 [PubMed: 22940426]
- Asllani I, Borogovac A, & Brown TR (2008). Regression algorithm correcting for partial volume effects in arterial spin labeling MRI. *Magnetic Resonance in Medicine: An Official Journal of the International Society for Magnetic Resonance in Medicine*, 60(6), 1362–1371. 10.1002/mrm.21670
- Babcock KR, Page JS, Fallon JR, & Webb AE (2021). Adult hippocampal neurogenesis in aging and Alzheimer's disease. *Stem Cell Reports*, 16(4), 681–693. 10.1016/j.stemcr.2021.01.019 [PubMed: 33636114]
- Bangen KJ, Kaup AR, Mirzakhani H, Wierenga CE, Jeste DV, & Eyler LT (2012). Compensatory brain activity during encoding among older adults with better recognition memory for face-name pairs: an integrative functional, structural, and perfusion imaging study. *Journal of the International Neuropsychological Society*, 18(3), 402–413. 10.1017/S1355617712000197 [PubMed: 22433609]
- Bangen KJ, Nation DA, Clark LR, Harmell AL, Wierenga CE, Dev SI, ... Bondi MW (2014). Interactive effects of vascular risk burden and advanced age on cerebral blood flow. *Frontiers in Aging Neuroscience*, Vol. 6, p. 159. 10.3389/fnagi.2014.00159 [PubMed: 25071567]
- Bangen KJ, Thomas KR, Sanchez DL, Edmonds EC, Weigand AJ, Delano-Wood L, ... Initiative ADN (2021). Entorhinal perfusion predicts future memory decline, neurodegeneration, and white matter hyperintensity progression in older adults. *Journal of Alzheimer's Disease*, 81(4), 1711–1725. 10.3233/JAD-201474
- Bangen KJ, Werhane ML, Weigand AJ, Edmonds EC, Delano-Wood L, Thomas KR, ... Liu TT (2018). Reduced regional cerebral blood flow relates to poorer cognition in older adults with type 2 diabetes. *Frontiers in Aging Neuroscience*, 10, 270. 10.3389/fnagi.2018.00270 [PubMed: 30250430]
- Barnes DE, & Yaffe K (2011). The projected effect of risk factor reduction on Alzheimer's disease prevalence. *The Lancet Neurology*, 10(9), 819–828. 10.1016/S1474-4422(11)70072-2 [PubMed: 21775213]
- Beier M, Hughes AJ, Williams MW, & Gromisch ES (2019). Brief and cost-effective tool for assessing verbal learning in multiple sclerosis: Comparison of the Rey Auditory Verbal Learning Test (RAVLT) to the California Verbal Learning Test–II (CVLT-II). *Journal of the Neurological Sciences*, 400, 104–109. 10.1016/j.jns.2019.03.016 [PubMed: 30913522]
- Blom K, Koek HL, Zwartbol MHT, van der Graaf Y, Kessler L, Biessels GJ, ... Doevendans PA (2019). Subjective cognitive decline, brain imaging biomarkers, and cognitive functioning in patients with a history of vascular disease: The SMART-Medea study. *Neurobiology of Aging*, 84, 33–40. 10.1016/j.neurobiolaging.2019.07.011 [PubMed: 31479862]
- Bosworth NJ (2011). Practical use of the Framingham risk score in primary prevention: Canadian perspective. *Canadian Family Physician*, 57(4), 417–423. Retrieved from <https://pubmed.ncbi.nlm.nih.gov/21626897> [PubMed: 21626897]
- Brailean A, Steptoe A, Batty GD, Zaninotto P, & Llewellyn DJ (2019). Are subjective memory complaints indicative of objective cognitive decline or depressive symptoms? Findings from the English Longitudinal Study of Ageing. *Journal of Psychiatric Research*, 110, 143–151. 10.1016/j.jpsychires.2018.12.005 [PubMed: 30639919]
- Burmester B, Leatham J, & Merrick P (2016). Subjective cognitive complaints and objective cognitive function in aging: A systematic review and meta-analysis of recent cross-sectional findings. *Neuropsychology Review*, 26(4), 376–393. 10.1007/s11065-016-9332-2 [PubMed: 27714573]
- Chen Song, X., Beyea S, D'Arcy R, Zhang Y, & Rockwood K (2011). Advances in perfusion magnetic resonance imaging in Alzheimer's disease. *Alzheimer's & Dementia*, 7(2), 185–196. 10.1016/j.jalz.2010.04.004
- Chen X, Farrell ME, Rundle MM, Chan MY, Moore W, Wig GS, & Park DC (2021). The relationship of functional hippocampal activity, amyloid deposition, and longitudinal memory decline to memory complaints in cognitively healthy older adults. *Neurobiology of Aging*, 105, 318–326. 10.1016/j.neurobiolaging.2021.04.020 [PubMed: 34147860]
- Corlier FW, Shaw C, Hayes-Larson E, Mungas D, Farias ST, Glymour MM, ... Mayeda ER (2020). Association between cognitive test performance and subjective cognitive decline in a diverse cohort of older adults: Findings from the KHANDLE study. *Alzheimer Disease & Associated Disorders*, 34(3), 198–205. 10.1097/WAD.0000000000000383 [PubMed: 32427599]

- Cox RW (1996). AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Computers and Biomedical Research*, 29(3), 162–173. 10.1006/cbmr.1996.0014 [PubMed: 8812068]
- D’Agostino RB, Wolf PA, Belanger AJ, & Kannel WB (1994). Stroke risk profile: Adjustment for antihypertensive medication. *The Framingham Study. Stroke*, 25(1), 40–43. 10.1161/01.STR.25.1.40 [PubMed: 8266381]
- Dale AM, Fischl B, & Sereno MI (1999). Cortical surface-based analysis: I. Segmentation and surface reconstruction. *Neuroimage*, 9(2), 179–194. 10.1006/nimg.1998.0395 [PubMed: 9931268]
- Delis DC, Kramer JH, Kaplan E, & Ober BA (2000). *California Verbal Learning Test—Second Edition. Adult Version. Manual* The Psychological Corporation: San Antonio, TX.
- Farias ST, Mungas D, Reed BR, Cahn-Weiner D, Jagust W, Baynes K, & DeCarli C (2008). The measurement of everyday cognition (ECog): Scale development and psychometric properties. *Neuropsychology*, 22(4), 531. 10.1037/0894-4105.22.4.531 [PubMed: 18590364]
- Farias ST, Park LQ, Harvey DJ, Simon C, Reed BR, Carmichael O, & Mungas D (2013). Everyday cognition in older adults: Associations with neuropsychological performance and structural brain imaging. *Journal of the International Neuropsychological Society*, 19(4), 430–441. 10.1017/S1355617712001609 [PubMed: 23369894]
- Field A (2009). *Discovering Statistics Using SPSS: 3rd Edition*. SAGE Publications Inc.
- Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, ... Klaveness S (2002). Whole brain segmentation: Automated labeling of neuroanatomical structures in the human brain. *Neuron*, 33(3), 341–355. 10.1016/S0896-6273(02)00569-X [PubMed: 11832223]
- Greenberg SA (2012). The geriatric depression scale (GDS). *Best Practices in Nursing Care to Older Adults*, 4(1), 1–2.
- Grimes KM, Zanjani A, & Zakzanis KK (2017). Memory impairment and the mediating role of task difficulty in patients with schizophrenia. *Psychiatry and Clinical Neurosciences*, 71(9), 600–611. 10.1111/pcn.12520 [PubMed: 28294468]
- Hays CC, Zlatar ZZ, Campbell L, Meloy MJ, & Wierenga CE (2018). Subjective cognitive decline modifies the relationship between cerebral blood flow and memory function in cognitively normal older adults. *Journal of the International Neuropsychological Society*, 24(3), 213–223. 10.1017/S135561771700087X [PubMed: 28974274]
- Hays CC, Zlatar ZZ, & Wierenga CE (2016). The utility of cerebral blood flow as a biomarker of preclinical Alzheimer’s disease. *Cellular and Molecular Neurobiology*, 36(2), 167–179. 10.1007/s10571-015-0261-z [PubMed: 26898552]
- Jak AJ, Bondi MW, Delano-Wood L, Wierenga C, Corey-Bloom J, Salmon DP, & Delis DC (2009). Quantification of five neuropsychological approaches to defining mild cognitive impairment. *The American Journal of Geriatric Psychiatry*, 17(5), 368–375. 10.1097/JGP.0b013e31819431d5 [PubMed: 19390294]
- Jessen F (2014). Subjective and objective cognitive decline at the pre-dementia stage of Alzheimer’s disease. *European Archives of Psychiatry and Clinical Neuroscience*, 264(1), 3–7. 10.1007/s00406-014-0539-z [PubMed: 23942824]
- Jessen F, Amariglio RE, Buckley RF, van der Flier WM, Han Y, Molinuevo JL, ... Saykin AJ (2020). The characterisation of subjective cognitive decline. *The Lancet Neurology*, 19(3), 271–278. 10.1016/S1474-4422(19)30368-0 [PubMed: 31958406]
- Jessen F, Amariglio RE, Van Boxtel M, Breteler M, Ceccaldi M, Chételat G, ... Van Der Flier WM (2014). A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer’s disease. *Alzheimer’s & Dementia*, 10(6), 844–852. 10.1016/j.jalz.2014.01.001
- Jia F, Li Y, Li M, & Cao F (2021). Subjective cognitive decline, cognitive reserve indicators, and the incidence of dementia. *Journal of the American Medical Directors Association*, 22(7), 1449–1455.e4. 10.1016/j.jamda.2020.08.005 [PubMed: 32967819]
- Khan UA, Liu L, Provenzano FA, Berman DE, Profaci CP, Sloan R, ... Small SA (2014). Molecular drivers and cortical spread of lateral entorhinal cortex dysfunction in preclinical Alzheimer’s disease. *Nature Neuroscience*, 17(2), 304–311. 10.1038/nn.3606 [PubMed: 24362760]

- Kielb S, Rogalski E, Weintraub S, & Rademaker A (2017). Objective features of subjective cognitive decline in a United States national database. *Alzheimer's & Dementia*, 13(12), 1337–1344. 10.1016/j.jalz.2017.04.008
- Kilroy E, Apostolova L, Liu C, Yan L, Ringman J, & Wang DJJ (2014). Reliability of 2D and 3D pseudo-continuous arterial spin labeling perfusion MRI in elderly populations—comparison with 15O-water PET. *Journal of Magnetic Resonance Imaging: JMRI*, 39(4), 931. 10.1002/jmri.24246 [PubMed: 24038544]
- Knopman DS, & Roberts R (2010). Vascular risk factors: imaging and neuropathologic correlates. *Journal of Alzheimer's Disease*, 20(3), 699–709.
- Korte N, Nortley R, & Attwell D (2020). Cerebral blood flow decrease as an early pathological mechanism in Alzheimer's disease. *Acta Neuropathologica*, 140(6), 793–810. 10.1007/s00401-020-02215-w [PubMed: 32865691]
- Kresge HA, Liu D, Khan OA, Pamidimukkala U, Cambronero FE, Moore EE, ... Jefferson AL (2020). Subjective cognitive decline is associated with longitudinal cerebral blood flow reductions and gray matter atrophy in older adults: Featured research and focused topic sessions: Examining subjective cognitive decline through an interdisciplinary lens. *Alzheimer's & Dementia*, 16, e043975. 10.1002/alz.043975
- Li Wei, Yue L, & Xiao S (2022). Subjective cognitive decline is associated with a higher risk of objective cognitive decline: A cross-sectional and longitudinal study. *Frontiers in Psychiatry*, 13. 10.3389/fpsyt.2022.950270
- Li Wenyi, Jiang J, Zou X, Zhang Y, Sun M, Jia Z, ... Xu J (2022). The characteristics of arterial spin labeling cerebral blood flow in patients with subjective cognitive decline: The Chinese imaging, biomarkers, and lifestyle study. *Frontiers in Neuroscience*, 16, 961164. 10.3389/fnins.2022.961164 [PubMed: 35983224]
- Marshall RS, & Mayer SABB (Eds.). (2007). 12 - Increased Intracranial Pressure. In *On Call Series* (pp. 155–165). W.B. Saunders. 10.1016/B978-1-4160-2375-3.50019-0
- MathWorks I (1996). *Matlab*. MathWorks. Inc., Natick, Massachusetts, USA.
- Mazzeo S, Padiglioni S, Bagnoli S, Carraro M, Piaceri I, Bracco L, ... Bessi V (2020). Assessing the effectiveness of SCD-plus criteria in predicting the progression to Alzheimer's Disease: A 10-year follow-up study. *Neurology*, (15 Supple), 542.
- Mendonça MD, Alves L, & Bugalho P (2016). From subjective cognitive complaints to dementia: who is at risk?: a systematic review. *American Journal of Alzheimer's Disease & Other Dementias®*, 31(2), 105–114.
- Mitchell AJ, Beaumont H, Ferguson D, Yadegarfar M, & Stubbs B (2014). Risk of dementia and mild cognitive impairment in older people with subjective memory complaints: Meta-analysis. *Acta Psychiatrica Scandinavica*, 130(6), 439–451. 10.1111/acps.12336 [PubMed: 25219393]
- Molinuevo JL, Rabin LA, Amariglio R, Buckley R, Dubois B, Ellis KA, ... Rami L (2017). Implementation of subjective cognitive decline criteria in research studies. *Alzheimer's & Dementia*, 13(3), 296–311. 10.1016/j.jalz.2016.09.012
- Montorio I, & Izal M (1996). The Geriatric Depression Scale: A review of its development and utility. *International Psychogeriatrics*, 8(1), 103–112. 10.1017/S1041610296002505
- Mount CA, & Das JM (2020). Cerebral perfusion pressure. *StatPearls* [Internet].
- Nakhla MZ, Cohen L, Salmon DP, Smirnov DS, Marquine MJ, Moore AA, ... Zlatar ZZ (2021). Self-reported subjective cognitive decline is associated with global cognition in a community sample of Latinos/as/x living in the United States. *Journal of Clinical and Experimental Neuropsychology*, 43(7), 663–676. 10.1080/13803395.2021.1989381 [PubMed: 34709141]
- Østergaard L, Aamand R, Gutiérrez-Jiménez E, Ho Y-CL, Blicher JU, Madsen SM, ... Møller A (2013). The capillary dysfunction hypothesis of Alzheimer's disease. *Neurobiology of Aging*, 34(4), 1018–1031. 10.1016/j.neurobiolaging.2012.09.011 [PubMed: 23084084]
- Park J-H, Hong J-H, Lee S-W, Ji HD, Jung J-A, Yoon K-W, ... Kim HW (2019). The effect of chronic cerebral hypoperfusion on the pathology of Alzheimer's disease: a positron emission tomography study in rats. *Scientific Reports*, 9, 14102. 10.1038/s41598-019-50681-4 [PubMed: 31575996]

- Rabin LA, Smart CM, & Amariglio RE (2017). Subjective cognitive decline in preclinical Alzheimer's disease. *Annual Review of Clinical Psychology*, 13, 369–396. 10.1146/annurev-clinpsy-032816-045136
- Rueda AD, Lau KM, Saito N, Harvey D, Risacher SL, Aisen PS, ... Initiative ADN (2015). Self-rated and informant-rated everyday function in comparison to objective markers of Alzheimer's disease. *Alzheimer's & Dementia*, 11(9), 1080–1089. 10.1016/j.jalz.2014.09.002
- Samudra N, Jacobs M, Aulino JM, & Abou-Khalil B (2020). Baseline neuropsychological characteristics in patients with epilepsy with left temporal lobe encephaloceles compared with left mesial temporal sclerosis. *Epilepsy & Behavior*, 112, 107397. 10.1016/j.yebeh.2020.107397 [PubMed: 32919200]
- Sanchez DL, Thomas KR, Edmonds EC, Bondi MW, Bangen KJ, & Initiative ADN (2020). Regional hypoperfusion predicts decline in everyday functioning at three-year follow-up in older adults without dementia. *Journal of Alzheimer's Disease*, 77(3), 1291–1304. 10.3233/JAD-200490
- Schmidt M (1996). *Rey auditory verbal learning test: A handbook*. Western Psychological Services Los Angeles, CA.
- Schwarz C, Lange C, Benson GS, Horn N, Wurdack K, Lukas M, ... Flöel A (2021). Severity of subjective cognitive complaints and worries in older adults are associated With cerebral amyloid- β load. *Frontiers in Aging Neuroscience*, 13, 675583. [PubMed: 34408640]
- Setti SE, Hunsberger HC, & Reed MN (2017). Alterations in hippocampal activity and Alzheimer's disease. *Translational Issues in Psychological Science*, 3(4), 348–356. 10.1037/tps0000124 [PubMed: 29862310]
- Shin DD, Ozyurt IB, & Liu TT (2013). The Cerebral Blood Flow Biomedical Informatics Research Network (CBFBIRN) database and analysis pipeline for arterial spin labeling MRI data. *Frontiers in Neuroinformatics*, 7, 21. 10.3389/fninf.2013.00021 [PubMed: 24151465]
- Shokouhi S, Conley AC, Baker SL, Albert K, Kang H, Gwirtsman HE, & Newhouse PA (2019). The relationship between domain-specific subjective cognitive decline and Alzheimer's pathology in normal elderly adults. *Neurobiology of Aging*, 81, 22–29. 10.1016/j.neurobiolaging.2019.05.011 [PubMed: 31207466]
- Slavin MJ, Brodaty H, Kochan NA, Crawford JD, Trollor JN, Draper B, & Sachdev PS (2010). Prevalence and predictors of "subjective cognitive complaints" in the Sydney Memory and Ageing Study. *The American Journal of Geriatric Psychiatry*, 18(8), 701–710. 10.1097/JGP.0b013e3181df49fbGet [PubMed: 21491631]
- Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TEJ, Johansen-Berg H, ... Flitney DE (2004). Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage*, 23, S208–S219. 10.1016/j.neuroimage.2004.07.051 [PubMed: 15501092]
- Song R, Pan K, Xu H, Qi X, Buchman AS, Bennett DA, & Xu W (2021). Association of cardiovascular risk burden with risk of dementia and brain pathologies: A population-based cohort study. *Alzheimer's & Dementia*, 17(12), 1914–1922. 10.1002/alz.12343
- Stallings G, Boake C, & Sherer M (1995). Comparison of the California Verbal Learning Test and the Rey Auditory Verbal Learning Test in head-injured patients. *Journal of Clinical and Experimental Neuropsychology*, 17(5), 706–712. 10.1080/01688639508405160 [PubMed: 8557811]
- Studart Neto A, & Nitrini R (2016). Subjective cognitive decline: The first clinical manifestation of Alzheimer's disease? *Dementia & Neuropsychologia*, 10(3), 170–177. 10.1590/S1980-5764-2016DN1003002 [PubMed: 29213452]
- Takahashi H, Ishii K, Hosokawa C, Hyodo T, Kashiwagi N, Matsuki M, ... Murakami T (2014). Clinical application of 3D arterial spin-labeled brain perfusion imaging for Alzheimer disease: Comparison with brain perfusion SPECT. *American Journal of Neuroradiology*, 35(5), 906–911. 10.3174/ajnr.A3780 [PubMed: 24263694]
- Thomas KR, Weigand AJ, Cota IH, Edmonds EC, Wierenga CE, Bondi MW, & Bangen KJ (2022). Intrusion errors moderate the relationship between blood glucose and regional cerebral blood flow in cognitively unimpaired older adults. *Brain Imaging and Behavior*, 16(1), 219–227. 10.1007/s11682-021-00495-8 [PubMed: 34415491]

- Tkatch R, Musich S, MacLeod S, Alsgaard K, Hawkins K, & Yeh CS (2016). Population health management for older adults: Review of interventions for promoting successful aging across the health continuum. *Gerontology and Geriatric Medicine*, 2, 1–13. 10.1177/2333721416667877
- Wechsler D (1987). WMS-R: Wechsler Memory Scale-Revised. Psychological Corporation.
- Wiens AN, Tindall AG, & Crossen JR (1994). California verbal learning test: A normative data study. *The Clinical Neuropsychologist*, 8(1), 75–90. 10.1080/13854049408401545
- Wierenga CE, Hays CC, & Zlatar ZZ (2014). Cerebral blood flow measured by arterial spin labeling MRI as a preclinical marker of Alzheimer's disease. *Journal of Alzheimer's Disease*, 42(s4), S411–S419. 10.3233/JAD-141467
- Yang Z, Rong Y, Cao Z, Wu Y, Zhao X, Xie Q, ... Liu Y (2021). Microstructural and cerebral blood flow abnormalities in subjective cognitive decline plus: diffusional kurtosis imaging and three-dimensional arterial spin labeling study. *Frontiers in Aging Neuroscience*, 13, 625843. [PubMed: 33597860]
- Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, & Leirer VO (1982). Development and validation of a geriatric depression screening scale: A preliminary report. *Journal of Psychiatric Research*, 17(1), 37–49. 10.1016/0022-3956(82)90033-4 [PubMed: 7183759]
- Zhao W, Luo Y, Zhao L, Mok V, Su L, Yin C, ... Han Y (2019). Automated brain MRI volumetry differentiates early stages of Alzheimer's disease From normal aging. *Journal of Geriatric Psychiatry and Neurology*, 32(6), 354–364. 10.1177/0891988719862637 [PubMed: 31480984]
- Zhou M, Zhang F, Zhao L, Qian J, & Dong C (2016). Entorhinal cortex: A good biomarker of mild cognitive impairment and mild Alzheimer's disease. *Reviews in the Neurosciences*, 27(2), 185–195. 10.1515/revneuro-2015-0019 [PubMed: 26444348]
- Zlatar ZZ, Hays CC, Mestre Z, Campbell LM, Meloy MJ, Bangen KJ, ... Wierenga CE (2019). Dose-dependent association of accelerometer-measured physical activity and sedentary time with brain perfusion in aging. *Experimental Gerontology*, 125(1), 110679. 10.1016/j.exger.2019.110679 [PubMed: 31382010]
- Zlatar ZZ, Moore RC, Palmer BW, Thompson WK, & Jeste DV (2014). Cognitive complaints correlate with depression rather than concurrent objective cognitive impairment in the successful aging evaluation baseline sample. *Journal of Geriatric Psychiatry and Neurology*, 27(3), 181–187. 10.1177/0891988714524628 [PubMed: 24614203]
- Zlatar ZZ, Tarraf W, González KA, Vásquez PM, Marquine MJ, Lipton RB, ... Youngblood ME (2022). Subjective cognitive decline and objective cognition among diverse US Hispanics/Latinos: Results from the Study of Latinos-Investigation of Neurocognitive Aging (SOL-INCA). *Alzheimer's & Dementia*, 18, 43–52. 10.1002/alz.12381
- Zlokovic BV (2011). Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. *Nature Reviews Neuroscience*, 12(12), 723–738. 10.1038/nature11087 [PubMed: 22048062]

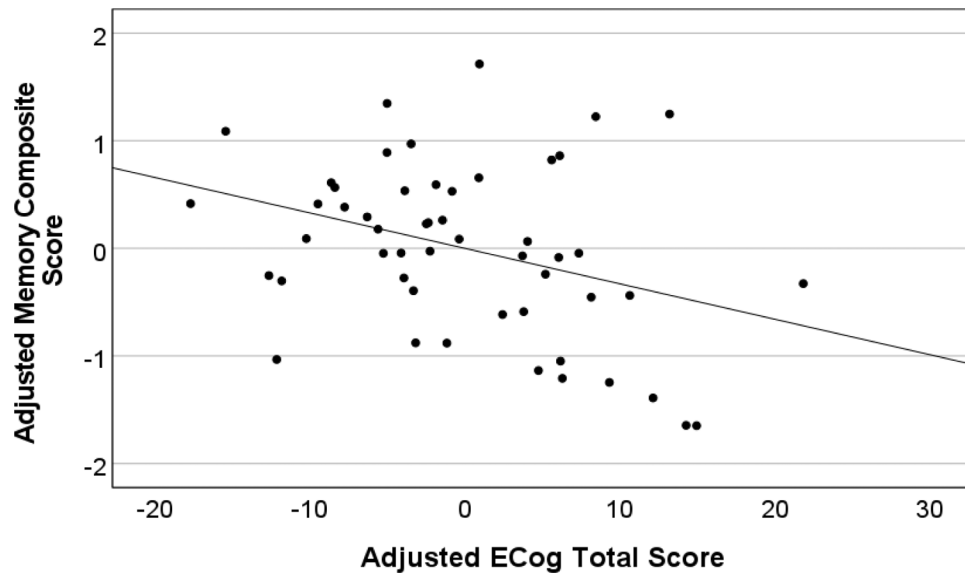


Figure 1.
Higher ECog total scores predict lower memory performance in the total sample (n=52).
Abbreviations: ECog=Everyday Cognition Scale.
Note: Partial regression plot depicts residual values adjusted for age, years of education, sex, and modified GDS scores.

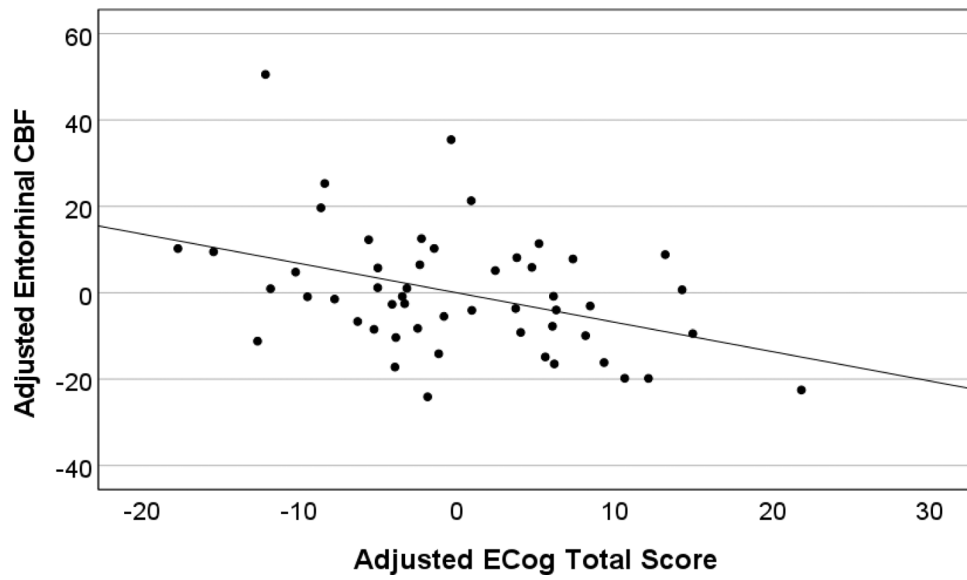


Figure 2.
Higher ECog total scores predict lower entorhinal CBF in the total sample (n=52).
Abbreviations: ECog=Everyday Cognition Scale.
Note: Partial regression plot depicts residual values adjusted for age, years of education, sex, and modified GDS scores.

Figure 3A.

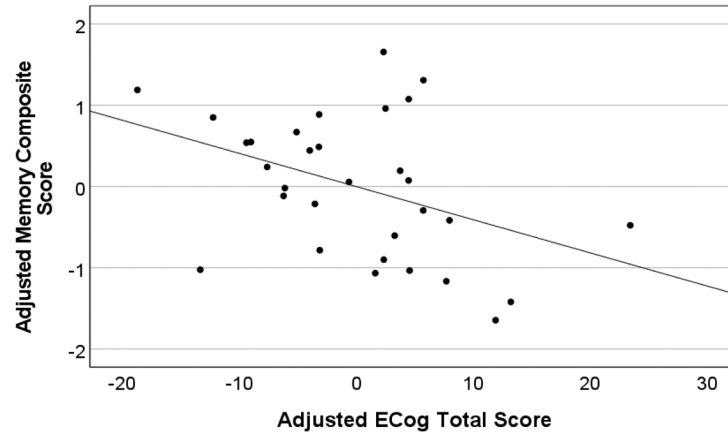


Figure 3B.

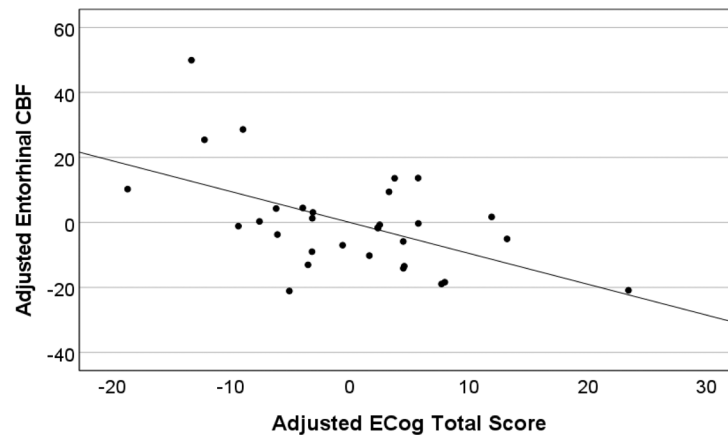


Figure 3. Higher ECog total scores predict lower memory and entorhinal CBF in the higher FSRP score group (n=31). Note: Partial regression plots depict residual values adjusted for age, years of education, sex, and modified GDS scores.

Table 1.

Descriptive and Demographic Information (n=52)

<u>Demographic Characteristics</u>	M (SD)
Age (years)	72.90 (4.53)
Education (years)	16.98 (2.28)
Males:Females (total)	16:36
<u>Mood & SCD</u>	
m-GDS Score	2.60 (2.86)
ECog Total	51.65 (10.42)
<u>CVD Risk</u>	
FSRP Score	8.12 (5.34)
<u>Average CBF (ml/100g/min)</u>	
Hippocampal	40.86 (9.72)
Parahippocampal	38.89 (9.61)
Entorhinal	39.24 (15.29)
<u>Cognition</u>	
Memory (z-scores)	.00 (.81)
<u>Raw Scores</u>	
WMS Logical Memory I [range 0–50]	28.79 (6.51)
WMS Logical Memory II [range 0–50]	26.13 (8.28)
RAVLT Trials 1–5 Total [range 0–75]	49.56 (10.09)
CVLT-II Trials 1–5 Total [range 0–80]	47.54 (10.50)
RAVLT Short Delay Free Recall [range 0–15]	10.92 (2.77)
CVLT-II Short Delay Free Recall [range 0–16]	10.77 (4.15)
RAVLT Long Delay Free Recall [range 0–15]	10.82 (2.94)
CVLT-II Long Delay Free Recall [range 0–16]	10.23 (4.83)

Abbreviations: SCD=subjective cognitive decline; ECog=Everyday Cognition Scale; m-GDS=modified Geriatric Depression Scale; CVD=cardiovascular (risk); CBF=cerebral blood flow; FSRP=Framingham Stroke Risk Profile; WMS>Wechsler Memory Scale; RAVLT=Rey Auditory Verbal Learning Test; CVLT-II=California Verbal Learning Test 2nd Edition.

All values listed are means (standard deviations) unless otherwise indicated.

Table 2.

ECog Scores Predicting Memory and CBF in the Total Sample (n=52)

	B (SE)	β	<i>t</i>	<i>p</i>	95% Confidence Interval for B	
					Lower Bound	Upper Bound
<i>Cognition</i>						
Memory	-.03 (.01)	-.42	-2.51	.016*	-.06	-.01
<i>Average CBF (ml/100g/min)</i>						
Hippocampal	-.24 (.16)	-.26	-1.48	.146	-.57	.09
Parahippocampal	-.28 (.16)	-.31	-1.76	.085	-.61	.04
Entorhinal	-.68 (.23)	-.46	-2.95	.005**	-1.14	-.22

*
p < .05,**
p < .01,***
p < .001.

Note: All models were adjusted for age, sex, years of education, and modified GDS scores. B (SE) denotes unstandardized coefficient and corresponding standard error. β denotes the standardized coefficient.

Abbreviations: ECog=Everyday Cognition Scale; CBF=cerebral blood flow.

Table 3.

Demographic characteristics of the lower (n=21) and higher (n=31) FSRP Score Groups.

	Lower FSRP Score Group (n = 21) Mean (SD)	Higher FSRP Score Group (n = 31) Mean (SD)	p-value	Cohen's d
<i>Demographic Characteristics</i>				
Age (years)	70.10 (3.24)	74.81 (4.32)	<.001 ***	-1.20
Education (years)	17.05 (2.22)	16.94 (2.35)	.864	.05
Male:Female (total)	3:18	13:18	.034 *	.62
<i>CVD risk</i>				
FSRP Score	4.24 (.77)	10.74 (5.52)	<.001 ***	-1.51
Systolic blood pressure	118.52 (16.51)	136.2 (16.33)	<.001 ***	-1.08
Diastolic blood pressure	72.29 (13.25)	78.47 (9.18)	.073	-.56
<i>Mood & Cognition</i>				
m-GDS Score	3.24 (3.39)	2.16 (2.41)	.186	.38
Memory (z-scores)	.10 (.63)	-.07 (.91)	.468	.21
ECog Total	50.90 (9.23)	52.16 (11.28)	.674	-.12
<i>Average CBF (ml/100g/min)</i>				
Hippocampal	41.03 (9.36)	40.75 (10.11)	.919	.03
Parahippocampal	41.52 (10.36)	37.10 (8.80)	.104	.47
Entorhinal	40.33 (12.64)	38.51 (17.01)	.678	.12

*
 $p < .05$,**
 $p < .01$,***
 $p < .001$.

P-values were derived from independent samples t -tests and χ^2 tests. All comparisons based on $df=50$. Abbreviations: CVD=cardiovascular (risk); m-GDS=modified Geriatric Depression Scale; FSRP= Framingham Stroke Risk Profile; CBF=cerebral blood flow; ECog=Everyday Cognition Scale.

All values listed are means (standard deviations) unless otherwise indicated.

Table 4.

Regression models of ECog predicting memory and CBF stratified by CVD risk group.

<i>Outcome: Memory</i>	B (SE)	β	<i>t</i>	<i>p</i>	<i>95% Confidence Interval for B</i>	
					Lower Bound	Upper Bound
Lower FSRP Score Group (n=21)	-.01 (.02)	-.09	-.25	.804	-.06	.04
Higher FSRP Score Group (n=31)	-.04 (.02)	-.50	-2.21	.037*	-.08	-.003
<i>Outcome: Entorhinal CBF</i>						
Lower FSRP Score Group (n=21)	-.18 (.42)	-.13	-.44	.669	-1.08	.71
Higher FSRP Score Group (n=31)	-.95 (.30)	-.63	-3.17	.004**	-1.57	-.33

*
p < .05,**
p < .01,***
p < .001.

Note: Stratified regression models were fully adjusted for age, sex education, and modified GDS scores. B (SE) denotes unstandardized coefficient and corresponding standard error. β denotes the standardized coefficient. Abbreviations: FSRP=Framingham Stroke Risk Profile; CBF=cerebral blood flow.