Research Article

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 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 139 million will be diagnosed by 2050 due to longer life expectancy and demographic changes (World Health Organization, 2022).

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 et al., 2021; Rabin et al., 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 et al., 2016; Corlier et al., 2020; Jessen, 2014; Kielb et al., 2017; Nakhla et al., 2021; Rabin et al., 2020; Studart Neto & Nitrini, 2016; Zlatar et al., 2022) and increases the risk of progressing to dementia (Mazzeo et al., 2020; Mendonça et al., 2016; Mitchell et al., 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; Rabin et al., 2020).

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 et al., 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 et al., 2016; Østergaard et al., 2013; Wierenga et al., 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).

SCD 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 et al., 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 RAVLT (Schmidt, 1996), and participants from the VASDHS Lab (n = 13) were administered the CVLT-II (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 et al.,

2019; Grimes et al., 2017; Samudra et al., 2020; Stallings et al., 1995), particularly for raw scores (Stallings et al., 1995; Wiens et al., 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 et al., 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 suggest 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 CVD (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 was 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 = 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 et al., 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, postlabeling 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 offline 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 et al., 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 (Zlatar 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 postlabeling 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 et al., 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 noninvasive, 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 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 and the European Consortium for ASL in Dementia including a PCASL labeling approach and a relatively long postlabeling 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). 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 $rs < .6$). 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 et al., 2014; Molinuevo et al., 2017). 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, and (4) 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

Table 1. Descriptive and demographic information (n = 52)

Variable Name	M (SD)
Demographic Characteristics	
Age (years)	72.90 (4.53)
Education (years)	16.98 (2.28)
Males:Females (total)	16:36
Mood & SCD	
m-GDS Score	2.60 (2.86)
ECog Total	51.65 (10.42)
CVD Risk	
FSRP Score	8.12 (5.34)
Average CBF (ml/100g/min)	
Hippocampal	40.86 (9.72)
Parahippocampal	38.89 (9.61)
Entorhinal	39.24 (15.29)
Cognition	
Memory (z-scores)	.00 (.81)
Raw Scores	
WMS-R Logical Memory I [range 0–50]	28.79 (6.51)
WMS-R 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)

Note. 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-R = Wechsler Memory Scale - Revised; RAVLT = Rey Auditory Verbal Learning Test; CVLT-II = California Verbal Learning Test-2nd Edition.
All values listed are means (standard deviations) unless otherwise indicated.

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, 72.90 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).

Table 2. ECog scores predicting memory and CBF in the total sample (n = 52)

					95% Confidence Interval for B	
	B (SE)	β	t	p	Lower Bound	Upper Bound
Cognition						
Memory	−.03 (.01)	−.42	−2.51	.016*	−.06	−.01
Average CBF (ml/100g/min)						
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

Note. *$p < .05$, **$p < .01$, ***$p < .001$. 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.
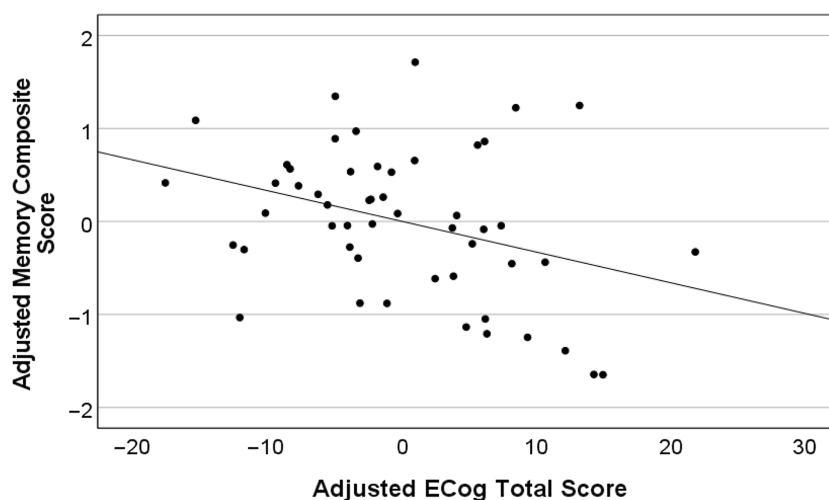Abbreviations: ECog = Everyday Cognition Scale; CBF = cerebral blood flow.

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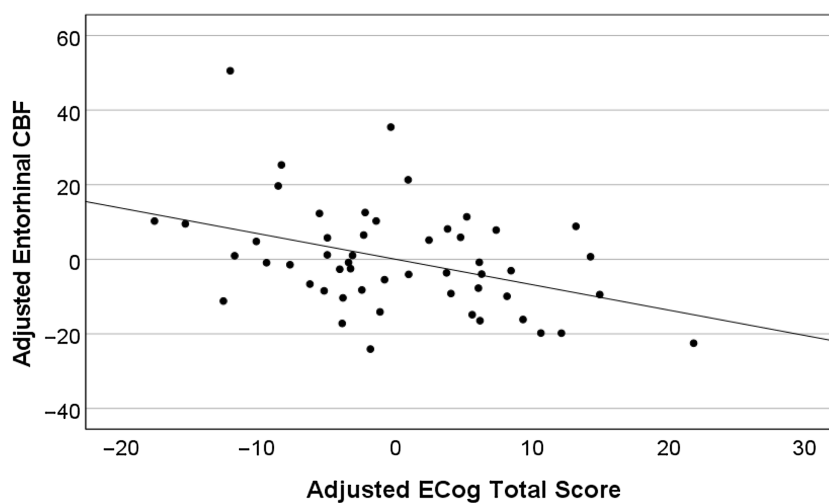

Figure 2. Higher ECog total scores predict lower entorhinal CBF in the total sample (n = 52). Partial regression plot depicts residual values adjusted for age, years of education, sex, and modified GDS scores.

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.

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
Demographic Characteristics				
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
CVD risk				
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
Mood & Cognition				
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
Average CBF (ml/100g/min)				
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

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

					95% Confidence Interval for B	
Variable	B (SE)	β	t	p	Lower Bound	Upper Bound
Outcome: Memory						
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
Outcome: Entorhinal CBF						
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

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

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 et al., 2019; Corlier et al., 2020; Farias et al., 2013; Kielb et al., 2017; Li, Yue, et al., 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 et al., 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 Aβ production and are thought to be an early risk marker of AD (Hays et al., 2016; Korte et al., 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 (Li, Jiang 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 an increased risk of developing AD (Song et al., 2021). Our findings suggest that SCD severity in individuals
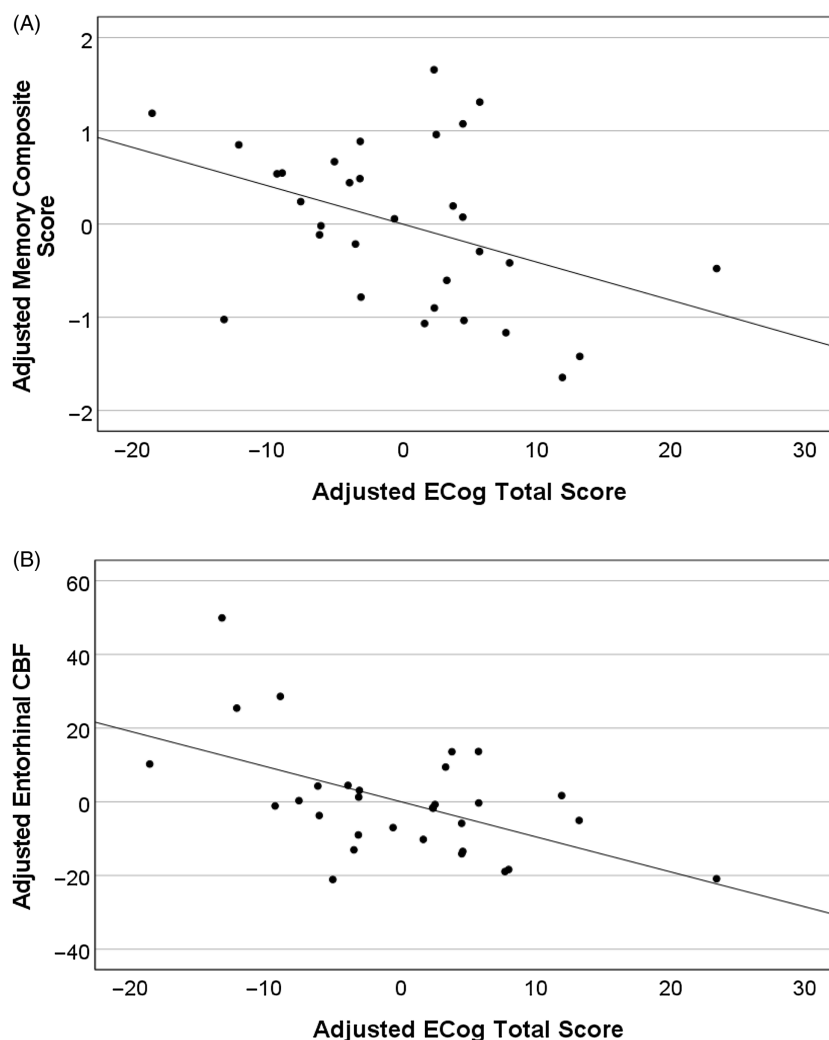
(A)

(B)

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

with a 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 disorders (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 (Gu et al., 2013; Molinuevo et al., 2017; Rabin et al., 2017; Sajjad et al., 2015), 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 SCD severity have a higher chance of progression to MCI and AD over time.

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