Supplemental Material

Supplemental Methods

Hippocampal Volume MRI Acquisition and Processing. Sagittal T_1-weighted 3D fast spoiled gradient echo (FSPGR) sequences were acquired with the same scanners (TE=3.164 msec, TR=8.084 msec, TI=600 msec, flip angle=8°, matrix=256 x 192, in-plane resolution=1 x 1 mm, slice thickness=1.2 mm, slices=172). MR images were processed using as described previously but updated with latest software (Kremen et al., 2010). Briefly, this involved correction of distortion due to gradient nonlinearity (Jovicich et al., 2006), image intensity normalization, rigid registration into standard orientation with 1 mm isotropic voxel size, and removal of non-brain tissue. As an update from Kremen et al. (2010, Wave 3 atlas-based volumetric segmentation (Fischl et al., 2002; Fischl et al., 2004) was performed using FreeSurfer version 6.0 (http://surfer.nmr.mgh.harvard.edu). Subcortical segmentations were visually reviewed, and participants with inaccurate segmentations (defined by obvious overestimation or underestimation on the segmentation atlas via a detailed lab protocol) were excluded from analysis (*n*=24). The analytical sample included 361 participants. Estimated hippocampal volume and estimated total intracranial volume were obtained from FreeSurfer's automated segmentation statistics. Hippocampal volume was adjusted (residualized) for an individual's estimated intracranial volume.

Objective Cognitive Function. Objective cognitive function was measured using a two-step approach in which cognitive domains are modeled as latent variables in SEM models using the larger VETSA samples at Wave 1 (*n*=1237), Wave 2 (*n*=1261), and Wave 3 (*n*=1196), and then are exported as factor scores to analyze within the smaller sample with LC imaging (see Kremen et al, 2019 for a thorough description of these larger samples). The two-step method is

recommended for small samples (Anderson et al., 1988; Burt et al., 1976, Smid & Rosseel, 2020), and most suitable when the factor scores will be independent variables rather than dependent variables (Devlieger et al., 2016). The two-step method also produces results that are more conservative and generalizable in that they can be used by other researchers and/or clinicians to examine relationships in new samples without having to refit new latent variable models.

Regarding the larger SEM model done before exporting factor scores, we inverted scores on time-based measures (i.e., Trails Making Task) prior to estimating the latent variable, so that higher scores on the latent liability indicated better cognitive function. Regarding invariance, latent variables at every VETSA wave were able to have equal factor loadings without significantly worse model fit than a freely estimated model based on the ratio of their loglikelihoods (*ps*>.05), indicating configural and weak invariance. Strong invariance was not assumed. Not only does variance increase with cognitive aging, i.e., cognitive function becomes more heterogeneous (Schaie et al., 1998), but we would not expect equal intercepts. For this reason, strong invariance is not expected for models of developmental change and aging (Haberstumpf et al., 2022; Pentz et al., 1994, Tyrell et al., 2019). All factor scores are standardized with respect to Wave 1. Therefore, the mean at the third wave is negative (reflecting group level decline since Wave 1) and the standard deviation is not exactly 1 (reflecting slight changes in variance since baseline). For our analyses, factor scores at Wave 3 were adjusted for practice effects via methods previously described (Elman et al., 2018). Description of factor scores are listed below:

Episodic memory: The episodic memory factor score is based on the combined number of correctly recalled words on the short and delayed portions and the total number of words

recalled across the five learning trials (i.e., the sum of all correct responses across learning trials 1 through 5) of the California Verbal Learning Test-II (CVLT-II) (Delis, Kaplan, & Kramer, 2001) and the combined number of correctly recalled story details on the immediate and delayed portions of the Wechsler Memory Scale-III Logical Memory test and the WMS-III Visual Reproductions test (Wechsler, 1997, 1997). An SEM model of the larger VETSA sample has shown good overall fit for the latent variable model used to derive the episodic memory factor score (CFI=.98, TLI=.97, RMSEA=.04; Gustavson et al., 2022). More details on these measures and factor score creation are available in prior work (Gustavson et al., 2018; Gustavson et al., 2019; Sanderson-Cimino et al., 2019).

Executive function: We derived a factor score of executive function using measures of inhibition (color-word trial of the Golden and Freshwater (2002) Stroop test adjusted for non-interference conditions); shifting (reaction time on Condition 4 of the Delis-Kaplan Executive Function System Trail Making task (Delis, Kaplan, & Kramer, 2001; Delis et al., 2001), and working memory span (total number of trials completed on the Letter-Number Sequencing and Digit Span tasks from Wechsler Memory Scale (Wechsler, 1997). An SEM model of the larger VETSA sample has shown good overall fit for the latent variable model used to derive the executive function factor score (CFI=.98, TLI=.97, RMSEA=.03; Gustavson et al., 2022). More details on these measures and factor score creation are available in prior work (Gustavson et al., 2018; Gustavson et al., 2019; Sanderson-Cimino et al., 2019).

Verbal fluency: DKEFS Letter and Category fluency were used to capture verbal fluency. The factor score was derived from the total number of correctly named words in selected Letters and Categories. An SEM model of the larger VETSA sample has shown good overall fit for the latent variable model used to derive the episodic memory factor score

(CFI=.99, TLI=.96; RMSEA=.03; Gustavson et al., 2019). More details on these measures and factor score creation are available in prior work (Gustavson et al., 2018; Gustavson et al., 2019; Sanderson-Cimino et al., 2019)).

Visuospatial ability: Visuospatial ability was captured using accuracy scores on the Gottschaldt Hidden Figures task (Gottschaldt, 1929) and the WMS-III Visual Reproductions Copy task (Wechsler, 1997). We calculated an SEM model from the larger VETSA sample and found that the latent variable model used to derive the visuospatial factor score had good overall fit (CFI=.97, TLI=.95; RMSEA=.03).

Global cognition: This factor score was derived using an SEM model estimating latent variables for each wave from the aforementioned factor scores at each wave. We calculated an SEM model from the larger VETSA sample and found that the latent variable model used to derive the global cognition factor score had good overall fit (CFI=.96, TLI=.95; RMSEA=.05).

Young-adult cognitive ability. Young adult cognitive ability was measured using the Armed Forces Qualification Test (AFQT) that was given to all participants at average age 20. The AFQT test is highly correlated with the Weschler Adult Intelligence Scale (*r*=.84) (Lyons et al., 2017; Lyons et al., 2009). This measure was used to adjust for longstanding differences in cognitive ability. Education is commonly used as an estimate of earlier/premorbid cognitive ability, but we were able to take advantage of having an actual measure of general cognitive ability. We have shown that the AFQT is much more sensitive measure than education (Vuoksimaa et al., 2013). In supplemental analyses, we examined education instead as a comparison.

Depressive symptoms. Depressive symptoms at Wave 3 were assessed using the 20-item Center of Epidemiological Studies Depression scale (CES-D) (Radloff, 2016). Individuals rated how often they experienced 20 symptoms of depression in the last 2 weeks on a five-point Likert-type scale: Not at all or less than one day (0); 1-2 days (1), 3-4 days (2), 5-7 days (3); Nearly every day for 2 weeks (4). Four items were rated in reverse fashion. Scores are summed into a total depressive symptoms score.

Physical morbidities. Physical morbidities at Wave 3 included the total number of self-reported medical conditions, including heart attack, heart failure, peripheral vascular disease, thrombolysis, hypertension, angina, diabetes, bronchitis, asthma, cancer, osteoarthritis, rheumatoid arthritis, and cirrhosis. These conditions were selected as they are noted on the Charlson, an index of major deadly conditions (Charlson, Pompei, Ales, & MacKenzie, 1987).

Objective Cognitive Decline. Objective cognitive decline was obtained using data in a subset of individuals (n=287) who completed tests at Wave 1, which occurred around 12 years before Wave 3. Task-measured objective cognitive decline was measured as the change in outputted factor scores (standardized to baseline mean and standard deviation) from Wave 1 to Wave 3. This was acceptable due to configural and weak invariance, i.e., equivalent factor loadings at Waves 1 and 3. Subtracting Wave 3 scores from Wave 1 scores (Wave 1-Wave 3) were used to capture individual-specific cognitive decline. Measures of objective cognitive decline were calculated for episodic memory, executive function, verbal fluency, visuospatial ability, and global cognitive function.

Mild Cognitive Impairment. MCI classification at Wave 3 followed the Jak-Bondi approach that only uses objective cognitive performance (Bondi et al., 2014; Jak et al., 2009). Specifically, MCI was defined as performing >1.5 *SD*s on 2 or more tasks within a cognitive domain after

adjusting for age and education. We also adjusted for young-adult cognitive ability using a measure of general cognitive ability completed at average age 20 (Armed Forces Qualification Test) when VETSA participants were inducted into the Armed Forces. Adjustment for young-adult cognitive ability has been shown to improve the detection of MCI, which is related to AD polygenic risk scores (Logue et al., 2019) and lower hippocampal volume (Jak et al., 2015). We also adjusted test scores for practice effects using data from attrition replacements who completed cognitive tests for the first time at Wave 2 (n=179). We have previously shown in VETSA that adjusting for practice effects identified a greater number of MCI cases that were less likely to revert to normal performance (Elman et al., 2018).

Supplemental Results

Covariates and ECOG Scores. In the analyses with rostral-middle LC as the main predictor, greater depressive symptoms were related to greater decline in participant-rated subjective memory (β=.20, 95%CI [.10, .30], p<.001), subjective executive function (β=.24, 95% CI [.24, .34], p<.001), subjective language (β=.25, 95% CI [.15, .35], p<.001), and subjective visuospatial ability (β=.18, 95% CI [08, .28], p=.005). A higher number of physical morbidities related to greater decline in participant-rated subjective memory (β=.13, 95% CI: [.03, .22], p=.033) but no other participant-rated ECOG subscale (ps>.05). Older age was related to greater decline in participant-rated subjective language (β=.13, 95% CI .[03, .23], p=.033) but no other participant-rated ECOG subscale (ps>.05).

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Supplemental Tables

Table S1. Correlations between Everyday Cognition (ECOG) subscales for participant ratings (left of diagonal) and informant ratings (right of diagonal) (*n*=381).

	Subjective Memory Decline	Subjective Executive Function Decline	Subjective Language Decline	Subjective Visuospatial Decline
	r	*r*	*r*	*r*
Subjective Memory Decline	-	.53***	.64***	.38***
Subjective Executive Function Decline	.54***	-	.55**	.44***
Subjective Language Decline	.57***	.68***	-	.48*
Subjective Visuospatial Decline	.35***	.36***	.48***	-

Note. Correlations among participant-rated ECOG subscales are to the left of the diagonal; correlations among informant-rated ECOG subscales are to the right of the diagonal. Correlations are calculated using Spearman-Rank.
*p<.05
**p<.01
***p<.001

Table S2. Correlations of major variables with objective cognitive decline (*n*=287).

	Objective Cognitive Decline	Objective Memory Decline	Objective Executive Function Decline	Objective Fluency Decline	Objective Visuospatial Decline
	r	*r*	*r*	*r*	*r*
Rostral-Middle LC	.03	-.02	-.02	-.02	.08
Caudal LC	.06	.06	.05	.01	.06
ECog Scale					
Participant Ratings					
Subjective Cognitive Decline	-.03	.10	.003	.08	.04
Subjective Memory Decline	-.01	.11*	-.01	.10	.01
Subjective Executive Function Decline	-.001	.08	.01	.09	.02
Subjective Language Decline	-.06	.05	.01	.04	.05
Subjective Visuospatial Decline	-.02	.14**	.01	.03	.02
Informant Ratings					
Subjective Cognitive Decline	.07	.16**	.06	-.03	.18**
Subjective Memory Decline	.08	.13*	.10	.05	.11*
Subjective Executive Function Decline	.05	.11*	.02	-.04	.13*
Subjective Language Decline	.08	.18**	.003	-.05	.18**
Subjective Visuospatial Decline	-.02	.05	-.02	-.06	.11

Note. Correlations are calculated using Spearman-Rank. ECOG=Everyday Cognition scale; LC=locus coeruleus.
*p<.05
**p<.01
***p<.001

Table S3. Associations between Locus Coeruleus and ECOG scales when adjusting for education (*n*=381).

	Subjective Cognitive Decline		Subjective Memory Decline		Subjective Executive Function Decline		Subjective Language Decline		Subjective Visuospatial Decline	
Participant Rating	β (95%CI)	*p**	β (95%CI)	*p**	β (95%CI)	*p**	β (95%CI)	*p**	β (95%CI)	*p**
Rostral LC_{CNR}	-.18 (-.28 to -.07)	.001	-.15 (-.25 to -.04)	.008	-.15 (-.26 to -.04)	.007	-.13 (-.24 to -.02)	.018	-.15 (-.26 to -.04)	.007
Caudal LC_{CNR}	.03 (-.08 to .13)	.612	.003 (-.10 to .11)	.953	.002 (-.10 to .11)	.962	.04 (-.06 to .15)	.420	.03 (-.08 to .13)	.637
Education	-.06 (-.11 to -.02)	.005	-.04 (-.08 to .01)	.103	-.05 (-.10 to -.01)	.028	-.06 (-.10 to -.01)	.013	-.06 (-.10 to -.01)	.015
Age (years)	.10 (-.001 to .19)	.050	.09 (-.01 to .19)	.073	.05 (-.05 to .15)	.309	.15 (.05 to .25)	.004	-.002 (-.10 to .10)	.974
Depressive Symptoms	.25 (-.15 to .34)	<.001	.19 (.10 to .29)	<.001	.22 (.12 to .32)	<.001	.23 (.13 to .33)	<.001	.18 (.08 to .28)	<.001
Physical Morbidities	.08 (-.02 to .18)	.101	.12 (-.02 to .22)	.015	.01 (-.09 to .11)	.818	.07 (-.03 to .17)	.157	.05 (-.05 to .15)	.360
Informant Rating										
Rostral LC_{CNR}	-.10 (-.20 -.01)	.074	-.03 (-.15 to .10)	.677	-.05 (-.14 to .05)	.330	.003 (-.17 to .17)	.971	-.04 (-.15 to .08)	.524
Caudal LC_{CNR}	-.07 (-.03 to .16	.188	.06 (-.05 to .16)	.312	.06 (-.03 to .15)	.200	.12 (-.03 to .27)	.104	.09 (-.02 to .19)	.104
Education	-.05 (-.09 to -.004)	.031	-.01 (-.06 to .04)	.737	-.02 (-.06 to .02)	.317	-.05 (-.12 to .03)	.196	-.02 (-.08 to .03)	.417
Age (years)	-.01 (-.11 to .10)	.917	.01 (-.10 to .12)	.828	.10 (.01 to .18)	.039	-.03 (-.19 to .14)	.741	.08 (-.04 to .20)	.171
Depressive Symptoms	-.02 (-.11 to .07)	.719	.05 (-.05 to .14)	.324	-.03 (-.11 to .06)	.543	.02 (-.12 to .16)	.779	-.03 (-.15 to .08)	.564
Physical Morbidities	.05 (-.05 to .15)	.319	-.01 (-.12 to .09)	.792	.01 (-.08 to .09)	.847	-.02 (-.18 to .14)	.810	-.06 (-.19 to .07)	.326

Notes. Each column represents an ECOG domain regressed on predictors shown in the rows. Rows under "Participant Rating" show effects when predicting respective ECOG domains using participant ratings; rows under the "Informant Rating" show effects when predicting respective ECOG domains using informant ratings. Models were assessed in a general estimating equation nesting for twin pairs. CNR=contrast-to-noise ratio; ECOG=Everyday Cognition scale; LC=Locus Coeruleus.

*P-values for effects outside of the hypothesized relationship with rostral-middle LC have been corrected for multiple testing using FDR.

Table S4. Associations between Locus Coeruleus and ECOG scales when excluding people with MCI (*n*=324).

	Subjective Cognitive Decline		Subjective Memory Decline		Subjective Executive Function Decline		Subjective Language Decline		Subjective Visuospatial Decline	
Participant Rating	β (95%CI)	*p**	β (95%CI)	*p**	β (95%CI)	*p**	β (95%CI)	*p**	β (95%CI)	*p**
Rostral LC_{CNR}	-.16 (-.27 to -.04)	.007	-.12 (-.23 to .0001)	.050	-.14 (-.26 to -.03)	.018	-.12 (-.24 to -.004)	.043	-.13 (-.24 to -.03)	.013
Caudal LC_{CNR}	.01 (-.10 to .12)	.920	-.04 (-.16 to .07)	.610	-.003 (-.12 to .11)	.957	.02 (-.09 to .13)	.725	.05 (-.05 to .15)	.672
Age (years)	.07 (-.04 to .17)	.265	.05 (-.06 to .16)	.458	.03 (-.08 to .14)	.824	.12 (.01 to .22)	.058	.01 (-.09 to .10)	.858
Depressive Symptoms	.26 (.15 to .36)	<.001	.21 (.10 to .31)	<.001	.25 (-.14 to .35)	<.001	.26 (.15 to .36)	<.001	.13 (.04 to .23)	.024
Physical Morbidities	.09 (-.01 to .19)	.160	.14 (.04 to .25)	.014	.03 (-.08 to .13)	.824	.08 (-.02 to .18)	.176	.03 (-.06 to .12)	.703
Informant Rating										
Rostral LC_{CNR}	-.06 (-.19 to .07)	.336	.01 (-.13 to .15)	.878	-.06 (-.17 to .06)	.312	-.01 (-.21 to .19)	.904	-.10 (-.23 to .03)	.118
Caudal LC_{CNR}	.02 (-.12 to .16)	.829	.07 (-.07 to .20)	.453	.06 (-.06 to .18)	.472	.07 (-.21 to .19)	.780	.18 (.04 to .33)	.052
Age (years)	-.01 (-.14 to .11)	.829	.08 (-.05 to .20)	.453	.09 (-.02 to .19)	.456	-.06 (-.26 to .13)	.780	.09 (-.05 to .23)	.380
Depressive Symptoms	-.02 (-.14 to .09)	.829	.02 (-.08 to .13)	.670	-.06 (-.16 to .04)	.472	.04 (-.12 to .21)	.780	-.04 (-.17 to .09)	.602
Physical Morbidities	.08 (-.04 to .21)	.744	-.06 (-.17 to .05)	.453	.001 (-.10 to .10)	.991	.02 (-.17 to .21)	.794	-.04 (-.18 to .11)	.602

Notes. Each column represents an ECOG domain regressed on predictors shown in the rows. Rows under "Participant Rating" show effects when predicting respective ECOG domains using participant ratings; rows under the "Informant Rating" show effects when predicting respective ECOG domains using informant ratings. Models were assessed in a general estimating equation nesting for twin pairs. CNR=contrast-to-noise ratio; ECOG=Everyday Cognition scale; LC=Locus Coeruleus.

*P-values for effects outside of the hypothesized relationship with rostral-middle LC have been corrected for multiple testing using FDR.

Table S5. Associations of Locus Coeruleus and Hippocampal Volume to ECOG scales (*n*=361).

	Subjective Cognitive Decline		Subjective Memory Decline		Subjective Executive Function Decline		Subjective Language Decline		Subjective Visuospatial Decline	
Participant Rating	β (95%CI)	*p**	β (95%CI)	*p**	β (95%CI)	*p**	β (95%CI)	*p**	β (95%CI)	*p**
Hippocampal Volume	-.04 (-.14 to .06)	.640	-.06 (-.17 to .04)	.452	-.02 (-.12 to .08)	.691	-.05 (-.15 to .05)	.476	.03 (-.06 to .13)	.640
Informant Rating										
Hippocampal Volume	-.05 (-.14 to .05)	.500	-.07 (-.17 to.03)	.318	.02 (-.07 to .11)	.646	-.18 (-.33 to -.02)	.078	-.09 (-.21 to .03)	.224

Notes. Each column represents an ECOG domain regressed on predictors shown in the rows. Rows under "Participant Rating" show effects when predicting respective ECOG domains using participant ratings; rows under the "Informant Rating" show effects when predicting respective ECOG domains using informant ratings. Models were assessed in a general estimating equation nesting for twin pairs. Models included early life cognitive ability, age, depressive symptoms, and physical morbidities as covariates. CNR=contrast-to-noise ratio; ECOG=Everyday Cognition scale; LC=Locus Coeruleus.
*P-values for effects outside of the hypothesized relationship with rostral-middle LC have been corrected for multiple testing using FDR.

Supplemental Figure

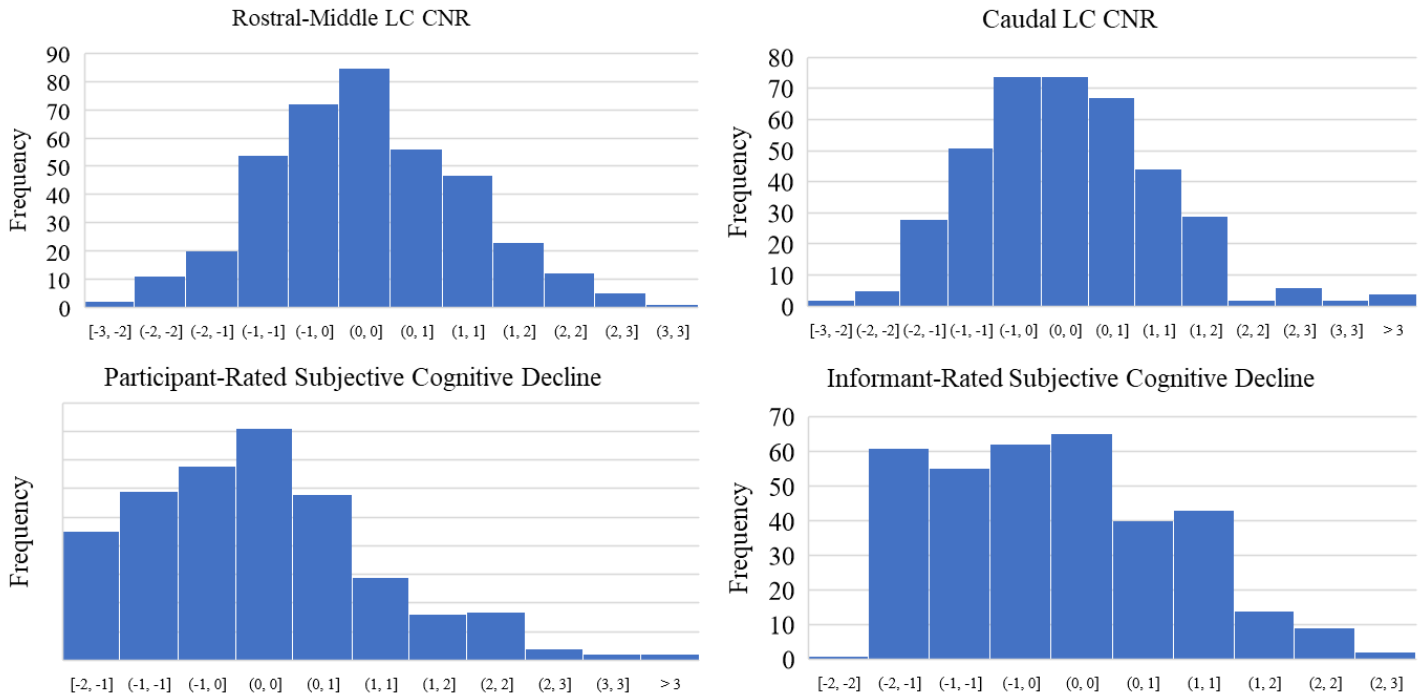

Figure S1. Distributions of major variables using histograms. Note. Participant-rated and informant-rated subjective cognitive decline was log transformed from its original scale. CNR=contrast to noise ratio; LC=locus coeruleus.