

The roles of biological sex and cognitive reserve in shaping sleep-cognition dynamics

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BACKGROUND

- Poor sleep is a risk factor for Alzheimer's disease^{1,2}.
- Compared to males, females have a higher risk of developing Alzheimer's disease and report poorer sleep with age^{3,4,5}.
- Poor sleep contributes to early amyloid- β accumulation and hippocampal atrophy, which precede memory decline and predict Alzheimer's disease symptom progression^{6,7}.
- It is unclear whether there are sex differences in how sleep shapes the link between hippocampal structure and memory in older adults.

STUDY OBJECTIVE

This study examined how perceived sleep quality and hippocampal structure influence memory in males and females, with the aim of understanding sex differences in sleep-cognition relationships.

PARTICIPANTS

- Cognitively unimpaired (CU): $n=169$, 65% female
- Subjective cognitive impairment (SCI): $n=222$, 68% female
- Amnesic mild cognitive impairment (aMCI): $n=380$, 43% female

Table 1. Participant characteristics by group

	Group	Total	Females $n=298$	Males $n=278$	Effect size (Cohen's d)
		Mean (SD)	Mean (SD)	Mean (SD)	Females – Males
Age (Years)	CU	70.5 (6.1)	70.8 (5.9)	70.0 (6.5)	0.14
	SCI	70.9 (5.5)	71.0 (5.4)	70.5 (5.5)	0.08
	aMCI	73.6 (6.6)	73.0 (6.5)	74.1 (6.7)	-0.17
Education (Years)	CU	15.5 (2.9)	14.8 (2.5)	16.8 (3.1)	-0.67
	SCI	15.7 (2.9)	15.5 (2.8)	16.1 (3.0)	-0.18
	aMCI	15.0 (3.1)	14.6 (3.0)	15.2 (3.2)	-0.19
MoCA (Total score /30)	CU	27.6 (1.8)	27.7 (1.7)	27.5 (2.0)	0.06
	SCI	27.2 (2.1)	27.2 (1.9)	27.1 (2.3)	0.02
	aMCI	23.4 (3.0)	23.4 (3.0)	23.3 (3.0)	0.03
					Effect size (Cohen's w)
		n (%)	n (%)	n (%)	
Race (White)	CU	158 (94.0)	103 (95.4)	55 (91.7)	0.09
	SCI	207 (95.0)	141 (95.3)	66 (94.3)	0.09
	aMCI	329 (86.8)	138 (85.2)	191 (88.0)	0.07

METHODS

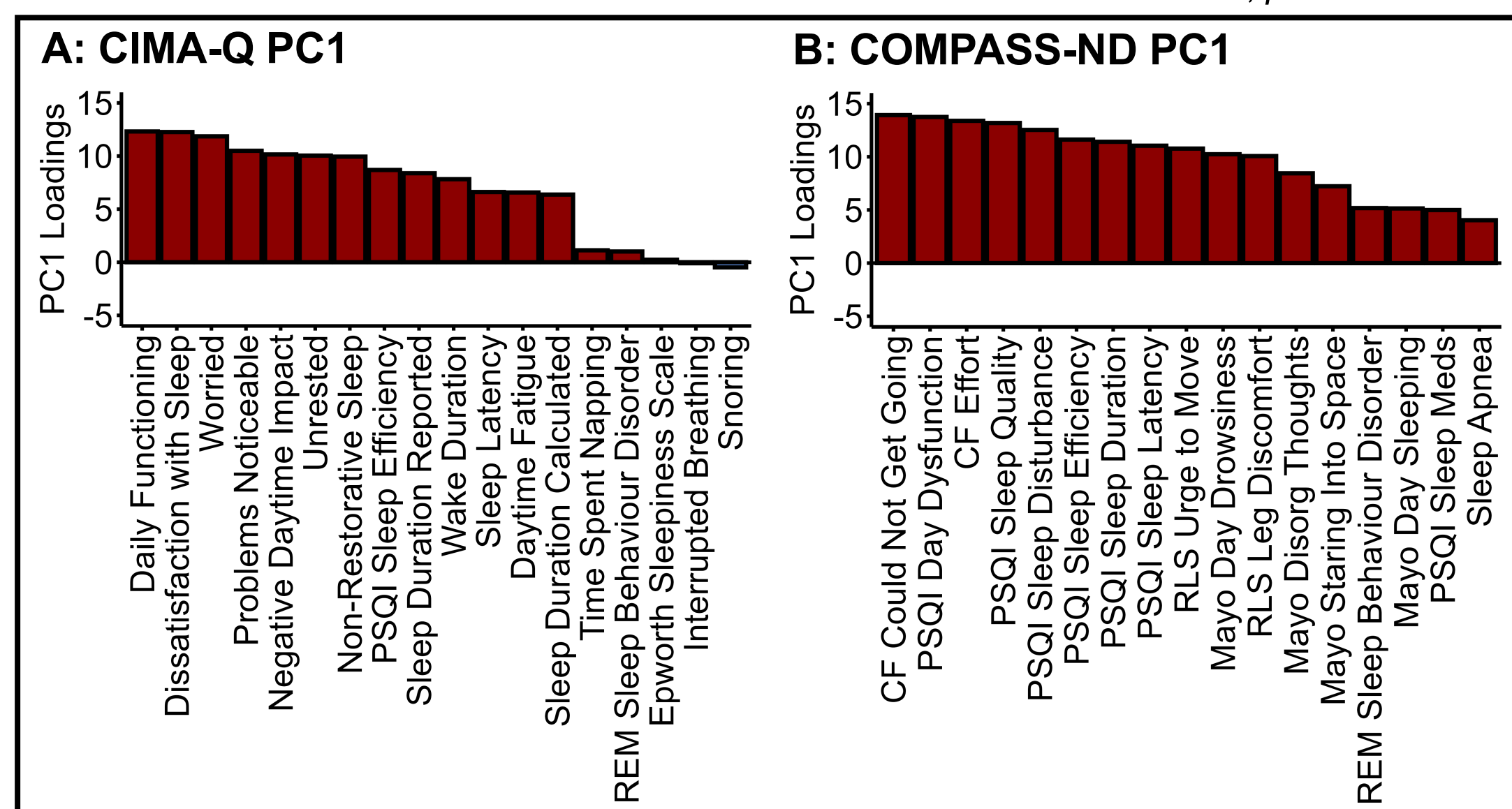
- Data were harmonized across COMPASS-ND and CIMA-Q^{8,9} cohorts.
- Perceived sleep scores were derived using Principal Component Analysis of various self-reported sleep-related variables.
- Hippocampal gray matter volume was extracted from T1-weighted structural MRI scans using ASHS¹⁰.
- Memory was measured using Rey's Auditory Verbal Learning Test [RAVLT; Recognition d' and recollection retention ratio (A7-A5)/A5].
- A structural equation model tested PC1 as mediator/moderator between hippocampal volume and memory, including sex as a key moderator.

RESULTS

Principal component 1 (PC1) represented global sleep quality (higher scores = poorer sleep and daytime function).

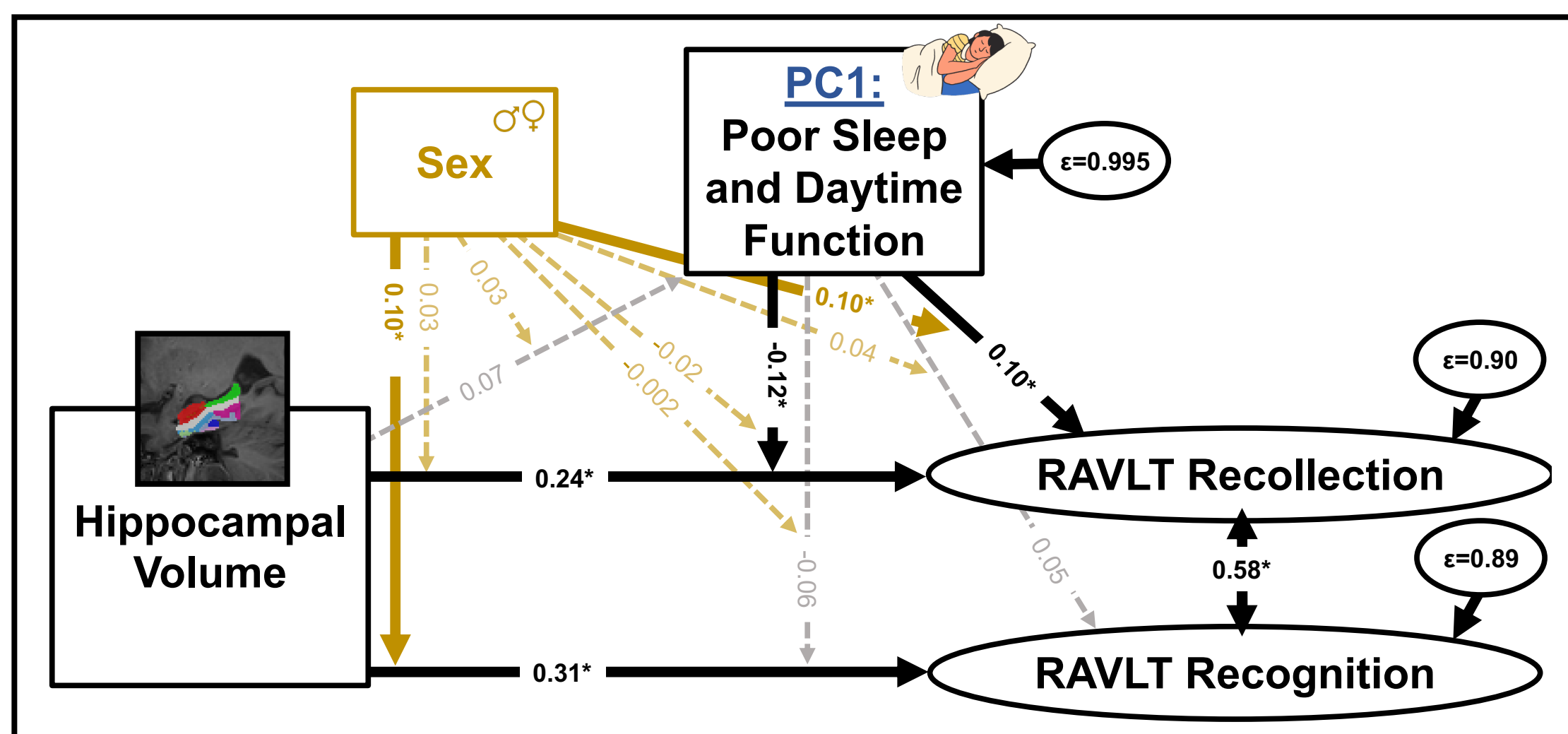
PC1 analysis loading profiles for A) CIMA-Q (30.8% variance explained) and B) COMPASS-ND (19.3% variance explained)

Correlation between CIMA-Q and COMPASS-ND PC1 scores: $r=0.53$, $p<0.001$



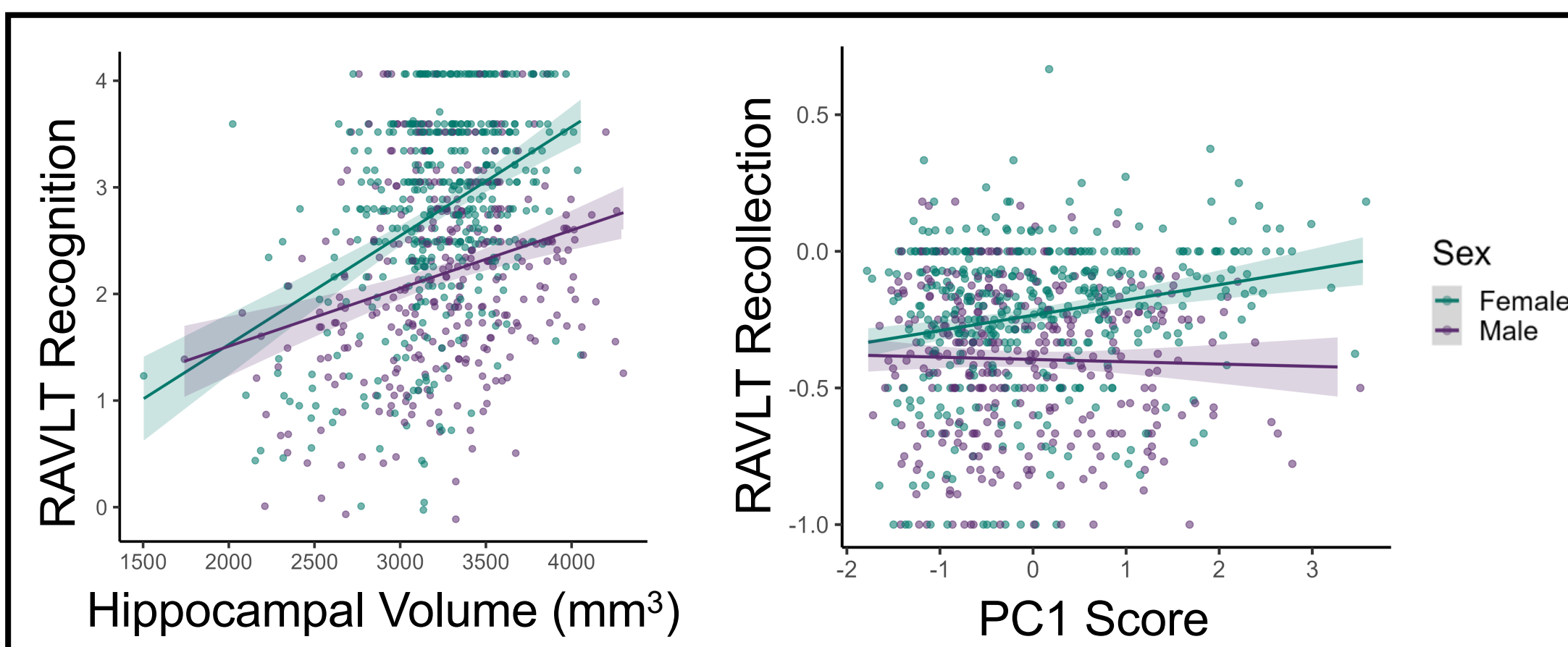
Structural equation model results:

- Larger hippocampal volume was associated with better memory, but perceived sleep did not mediate this relationship.
- Good perceived sleep strengthened volume-memory associations.



Biological sex was a key moderator:

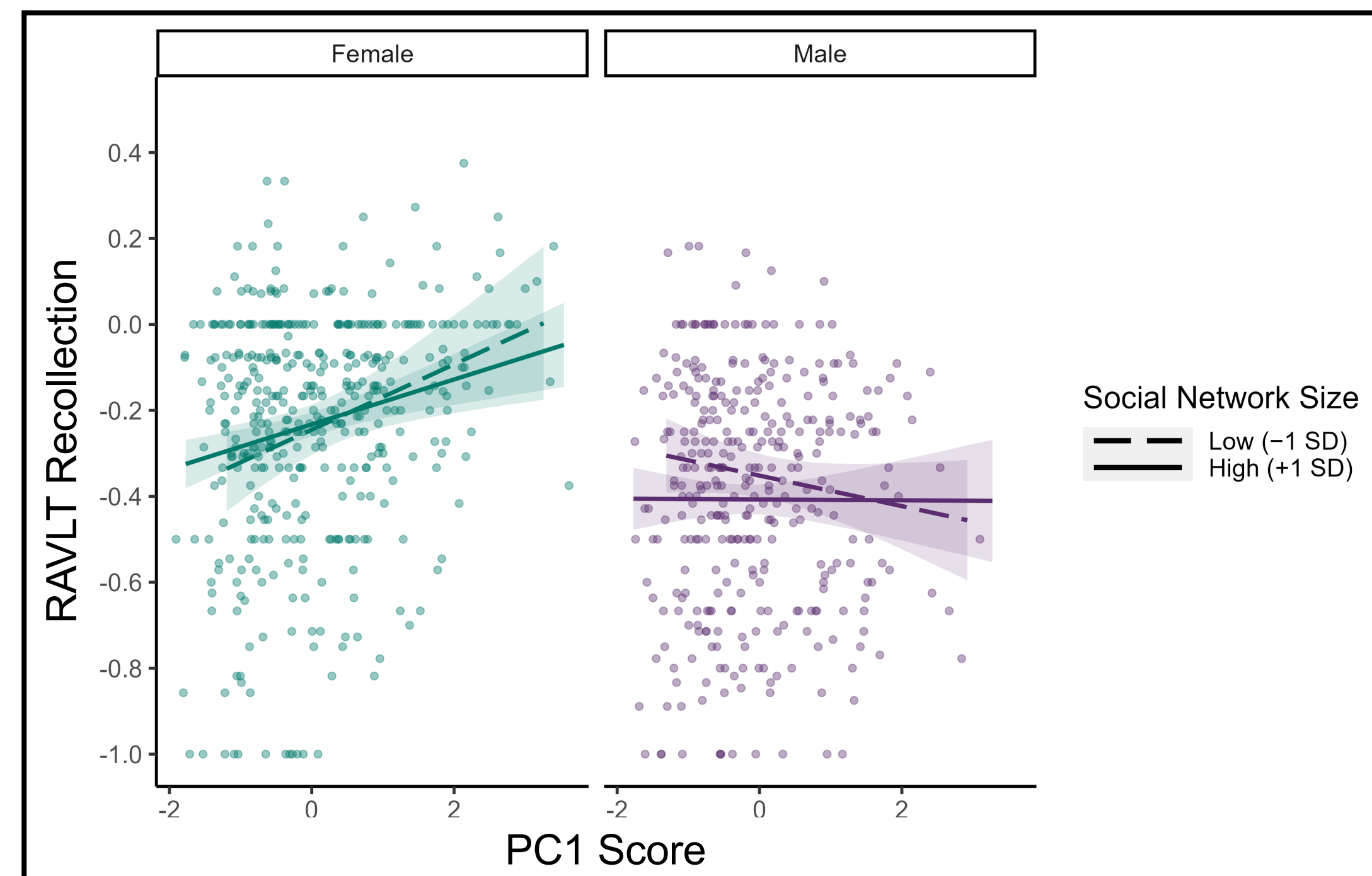
Better perceived sleep enhanced hippocampal-memory associations in both sexes (more strongly in females), but was associated with poorer recollection only in females.



RESULTS

Exploratory cognitive reserve results:

In females, larger social network size may buffer the negative effect of poor perceived sleep on memory.



KEY TAKEAWAYS

- Compared to males, females showed stronger hippocampus-memory coupling and evidence of verbal memory reserve despite hippocampal atrophy¹¹.
- In females, poorer perceived sleep was unexpectedly associated with better recollection, consistent with prior reports of cognitive resilience to reduced sleep quality¹².
 - Exploratory analyses suggest this pattern may relate to cognitive reserve.

A sex- and gender-informed multimodal approach to sleep assessment will be critical for advancing understanding of aging and Alzheimer's disease risk factors.

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FUNDING

