Fitness and Stress as Modulators of Hippocampal Subfield Structure and Function in Aging

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Background

Both cognitive aging and chronic stress are associated with reduced hippocampal integrity, which results in episodic memory impairments.

- Accurate episodic memory formation requires pattern separation, a neurocomputational process that is reliant on the dentate gyrus (DG) subfield of the hippocampus and is responsible for disambiguating similar stimulus input during neural encoding.[1]
- Cognitive aging is associated with decreased accuracy on mnemonic discrimination tasks,[2,3,4,5] which are putative measures of behavioral pattern separation.

Whereas aging and stress are associated with blunted hippocampal plasticity, increasing cardiorespiratory fitness is associated with enhanced hippocampal plasticity.

- In young adults, increasing fitness is associated with increased left anterior DG/CA3 volume[6] and improved mnemonic discrimination.[6,7,8]
- In older adults, increasing fitness is associated with increased hippocampal volume[9] and hippocampal cerebral blood flow.[10] However, a clear understanding of how fitness differentially affects the hippocampal subfields of older adults remains elusive.

Studying these relationships is critical, given the known effects of aging and stress on hippocampal integrity.

Predictions:

1. Older adults will demonstrate the lowest accuracy in the MDT condition with the highest stimuli similarity. Both DG/CA3 volume and fitness positively will predict performance in this condition.
2. Fitness will positively predict DG/CA3 volume, as evidenced by our laboratory in young adults[6], and may also demonstrate positive effects on other hippocampal subfields, including the CA1 and subiculum, as evidenced in other older adult literature[11, 12]

Methods: Participants, Fitness Assessment, and Mnemonic Discrimination Task

Participants: N = 65 (39 female) healthy volunteers; age range 55 – 85 years (mean 65.66 ± 6.97 years)

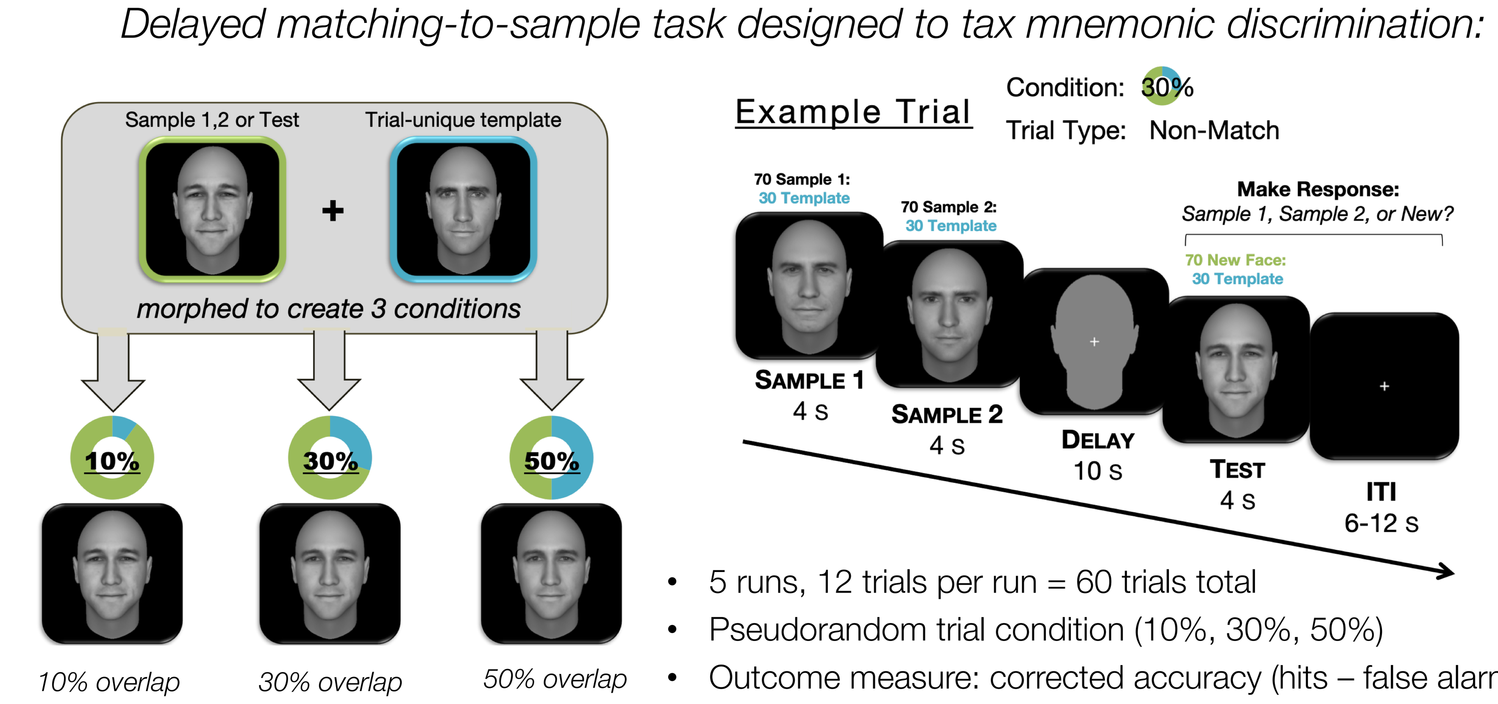
Fitness assessment - VO_{2MAX} estimation:

Graded submaximal treadmill test of cardiorespiratory fitness (modified Balke protocol) to 85% age-predicted HR_{MAX} [13]

Stress assessment - perceived stress:

Perceived stress was examined with the Perceived Stress Scale.[14]

Delayed matching-to-sample task designed to tax mnemonic discrimination:



- 5 runs, 12 trials per run = 60 trials total
- Pseudorandom trial condition (10%, 30%, 50%)
- Outcome measure: corrected accuracy (hits – false alarms)

Methods: MRI and Delineation of ROIs

MRI data was acquired on two different scanners from 52 participants. Behavioral data was acquired from an additional 13 participants.

MRI dataset 1 acquisition (N = 25):

- 3T Phillips Achieva; 8 channel head coil
- T1w MPRAGE structural scan (0.98 × 0.98 × 1.20 mm³ voxels)
- T2w structural scan (0.4 × 0.4 × 2.0 mm³ voxels)

MRI dataset 2 acquisition (N = 27):

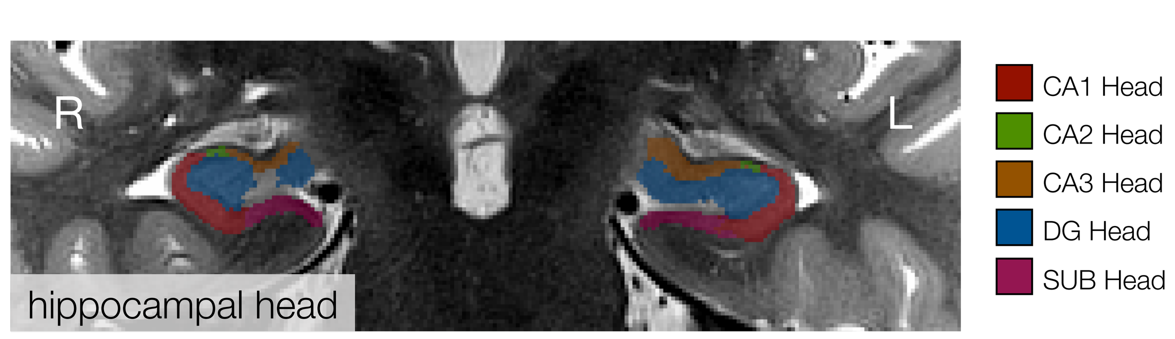
- 3T Siemens MAGNETOM Prisma; 64-channel head coil
- T1w MPRAGE structural scan (1.00 mm³ voxels)
- T2w structural scan (0.39 × 0.39 × 2.0 mm³ voxels)

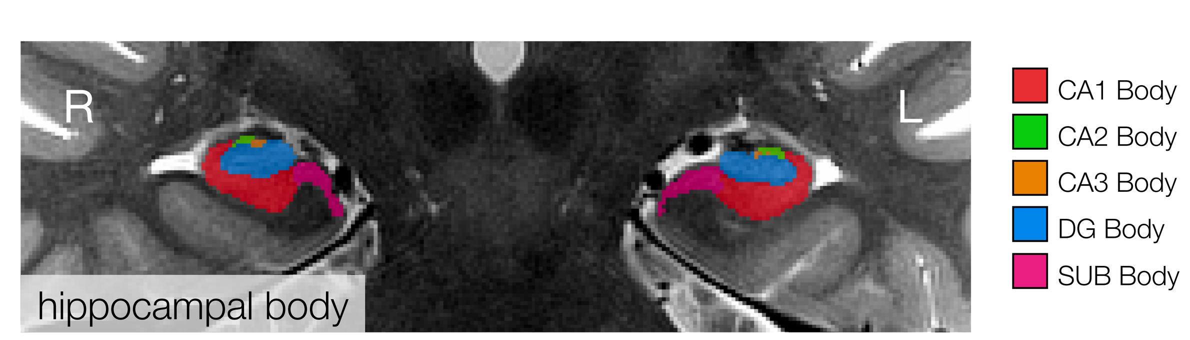
Delineation of Boundaries:

- Automatic Segmentation of Hippocampal Subfields (ASHS) using the Penn Memory Center 3T ASHS Atlas[15], with ROIs including hippocampal subfields (CA1, DG/CA3, subiculum)
- All volumes are corrected for differences in intracranial volume, as in the literature[16, 17]
- 8 participants lost due to head motion; 2 participants lost due to incidental findings (N = 42)

Manual segmentation of head, body, and tail:

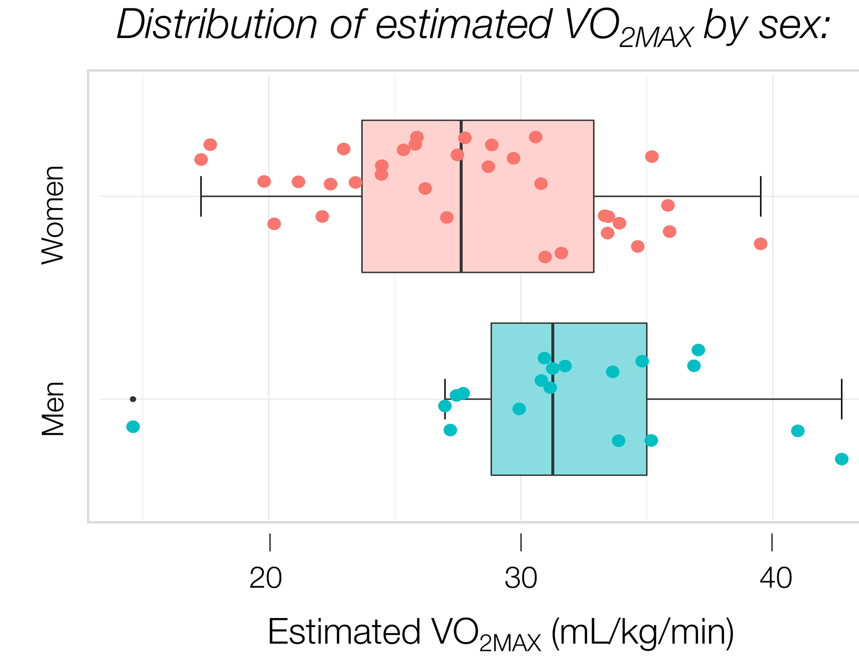
- Manual segmentation of subfields into head, body, and tail based on anatomical relation to the uncal apex and the wing of the ambient cistern, as in established guidelines[18]
- Example head (left) and body (right) coronal slices shown below



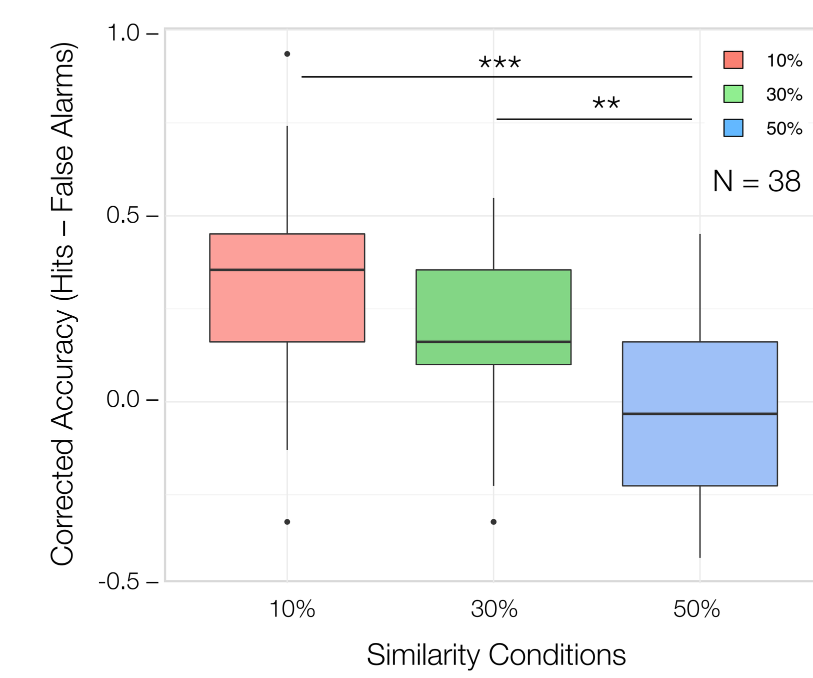


Results: Older adults demonstrate a range of fitness levels and decreased mnemonic discrimination task accuracy on trials with high stimuli similarity.

Distribution of estimated VO_{2MAX} by sex:



53 participants successfully completed VO_{2MAX} testing.

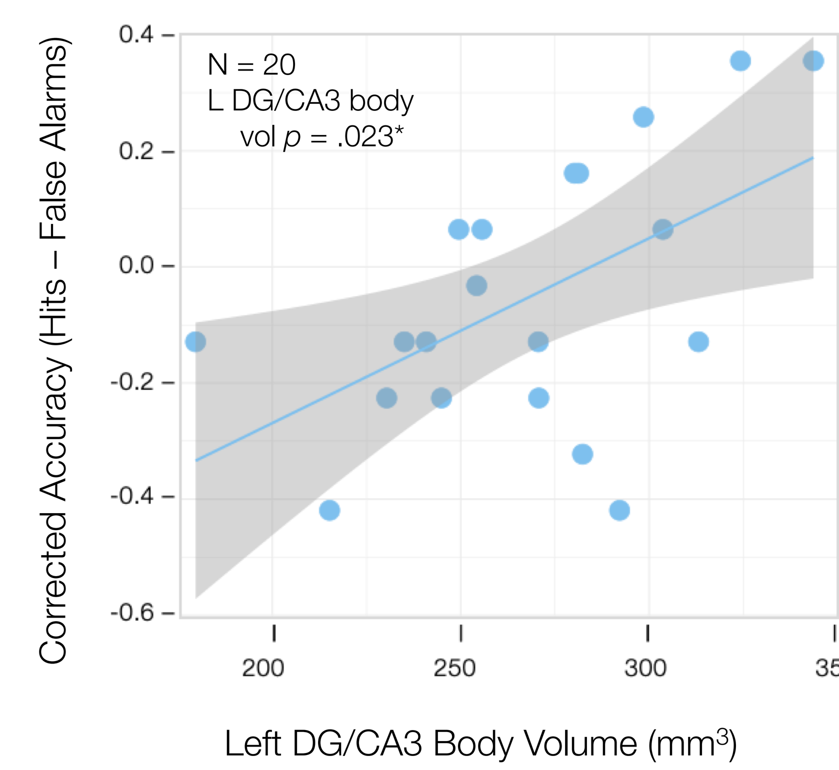


Mnemonic discrimination task – behavioral results:

- ANOVA revealed main effect of trial similarity (F =39.75, $p < .001$***)
- Tukey test revealed significant differences between conditions:
  - 50% vs. 30% ($p < .01$**)
  - 50% vs. 10% ($p < .001$***)

Results: DG/CA3 body volume, but not fitness, predicts performance on trials with high stimuli similarity.

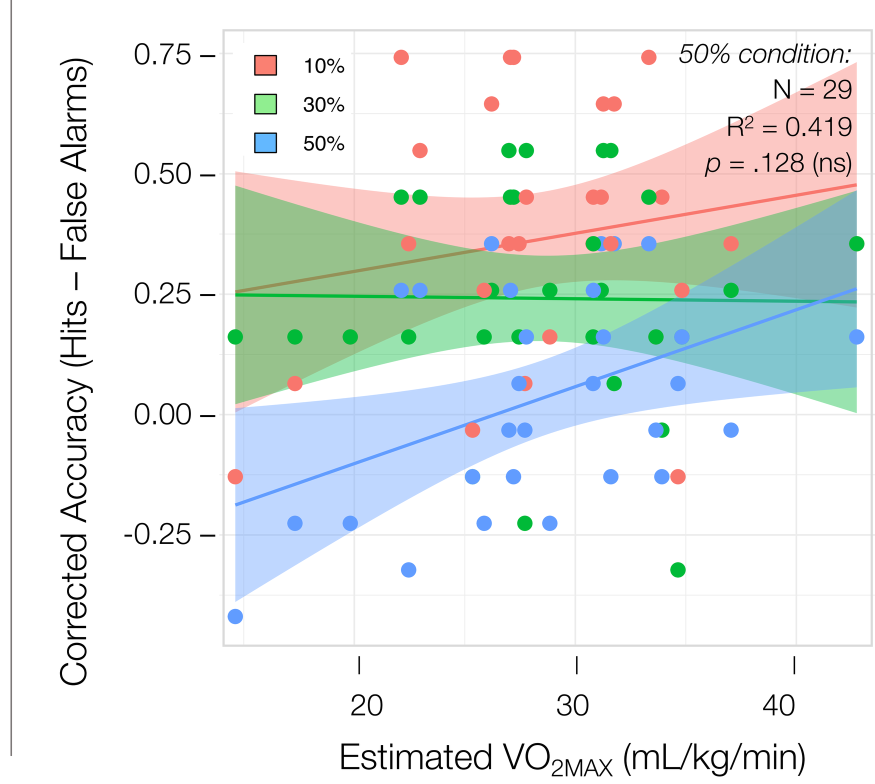
Left DG/CA3 body volume predicts mnemonic discrimination:



Linear regression analyses examined ROI volumes as predictors of corrected accuracy (covariates: age, sex, and education).

- **Left DG/CA3 body volume significantly predicts corrected accuracy in the 50% condition.**

Fitness does not predict mnemonic discrimination:



Linear regression analyses examined estimated VO_{2MAX} as a predictor of corrected accuracy in each similarity condition (covariates: age, sex, education, and dataset).

- VO_{2MAX} does not predict accuracy in 10%, 30%, or 50% conditions.

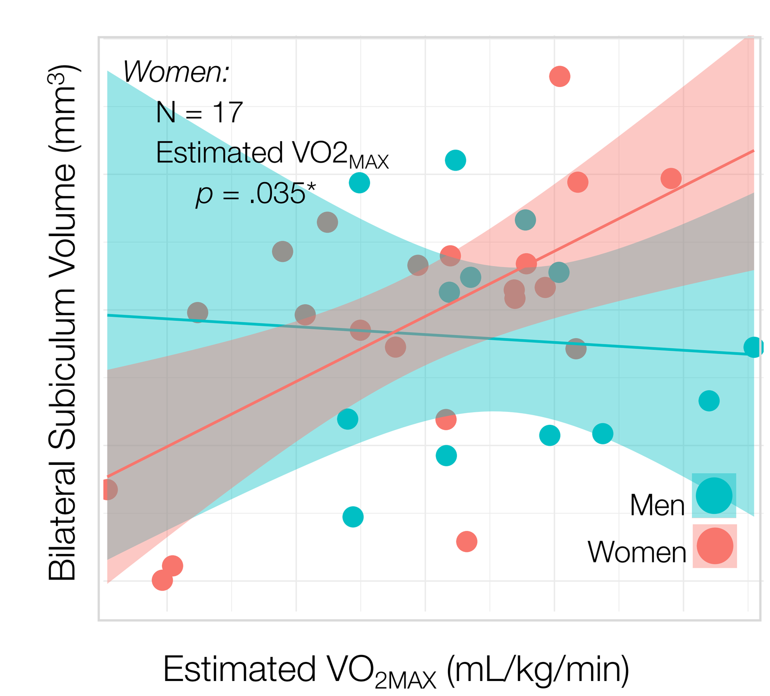
Results: Fitness predicts subiculum volume in women; stress does not predict hippocampal subfield volumes.

In young adults, fitness is associated with increased left anterior DG/CA3 volume.[6] In older adults, fitness may also modulate CA1 and subiculum volume.[11,12]

Linear regression analyses examined estimated VO_{2MAX} as a predictor of ICV-corrected ROI volumes (covariates: sex, age, and education).

- **VO_{2MAX} significantly predicts bilateral ICV-corrected subiculum volume in women only** (N = 17).

In older adults, perceived stress is associated with decreased hippocampal volume,[19,20] which may be due to smaller CA2/CA3 and DG/CA4 subfield volumes.[20]



Spearman's rank correlations examined the relationships between Perceived Stress Scale score and hippocampal subfield volumes.

- Perceived Stress Scale score did not correlate with CA1, DG/CA3, or SUB volumes.

Summary & Conclusions

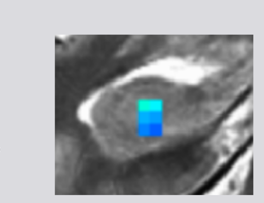
Left DG/CA3 body volume significantly predicted mnemonic discrimination task accuracy in the condition with the greatest stimuli similarity. There was no relationship between fitness and mnemonic discrimination.

Fitness predicted subiculum volume in women.

There were no observed relationships between Perceived Stress Scale score and hippocampal subfield volumes or MDT performance.

These findings provide support for a role of the DG in pattern separation in humans and suggest that fitness may have differential effects on hippocampal subfield integrity in young and older adults.

Future directions: does fitness modulate DG/CA3 BOLD signal during mnemonic discrimination?



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