Relations between pattern separation ability and hippocampal subfield volume in childhood

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Introduction

Pattern separation (PS) refers the ability to keep similar memories separate (e.g., where you parked your car today versus yesterday; Bakker et al., 2008).

Recent behavioral research examining PS showed significantly worse PS ability in 4-year-olds compared to 6-year-olds and adults (Ngo et al., 2017).

fMRI research in adults suggests subfields of the hippocampus, dentate gyrus (DG) and CA3, work together to facilitate PS (Baker et al., 2008; Yassa & Stark, 2011; Reagh & Yassa, 2014).

Neuroanatomical studies in non-human primates examining the development of the hippocampus suggests that DG and CA3 exhibit a slower and prolonged developmental time course, with maturity emerging between ages 5 and 7 (Serres, 2001; Lavenex & Banta Lavenex, 2013).

Structural MRI research in 6- to- 14-year-olds (Keresztes et al., 2017) shows an association between increased hippocampal maturity and PS (as opposed to pattern completion; see also Schlichting et al., 2017).

Both behavioral and neuroanatomical studies suggest early childhood (5-7 years) is an age of interest, both in terms of PS ability and hippocampal development.

The current study examined relations between performance on a modified Mnemonic Similarity Test, which reflects PS ability, and hippocampal subfield volumes in 4- to- 8-year-old children.

Methods

Participants

- A total of 67 4- to- 8-year-old children (N_{female}=37, M_{age}=6.63 years, SD_{age}=1.30 years) provided both useable behavioral and neuroimaging data.

Modified Mnemonic Similarity Task (Ngo et al., 2017)

Encoding

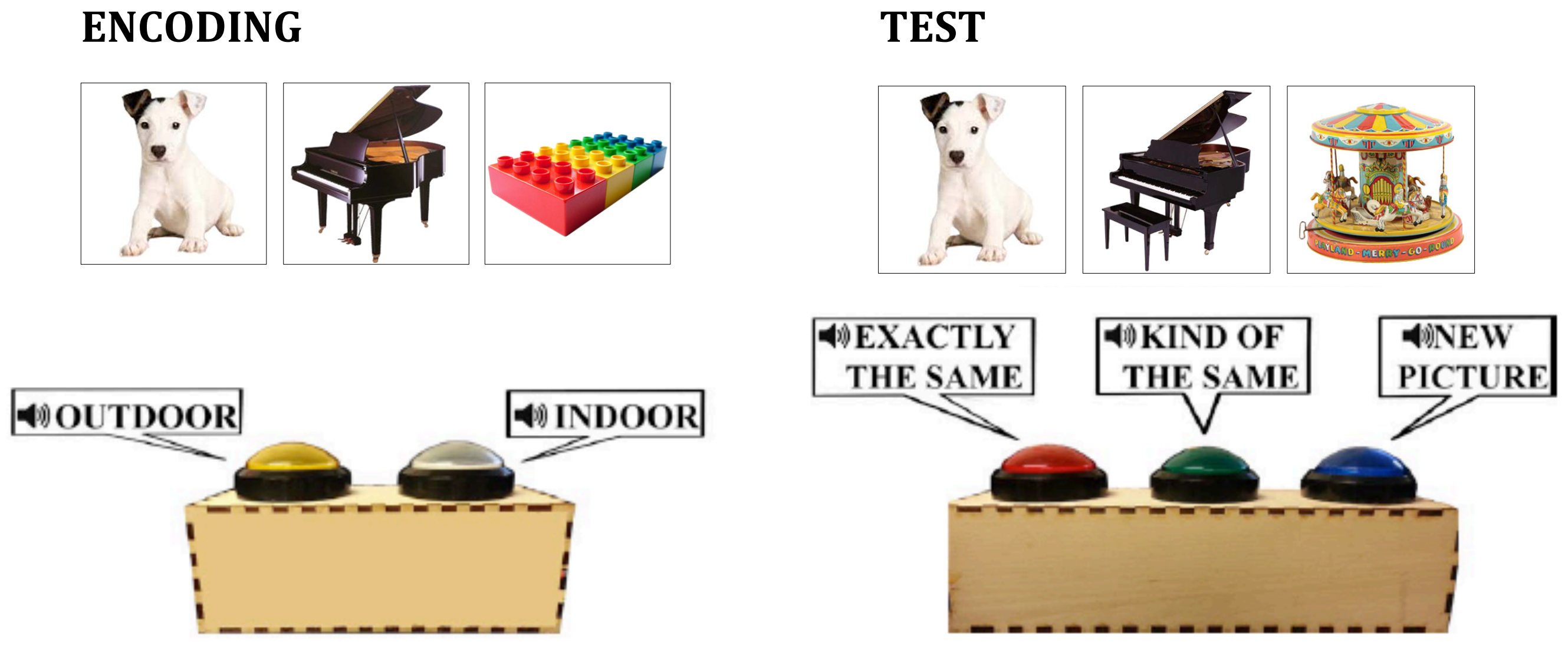
Viewed 66 objects sequentially and decided whether the object belonged "indoors" or "outdoors" using a 2-button box.

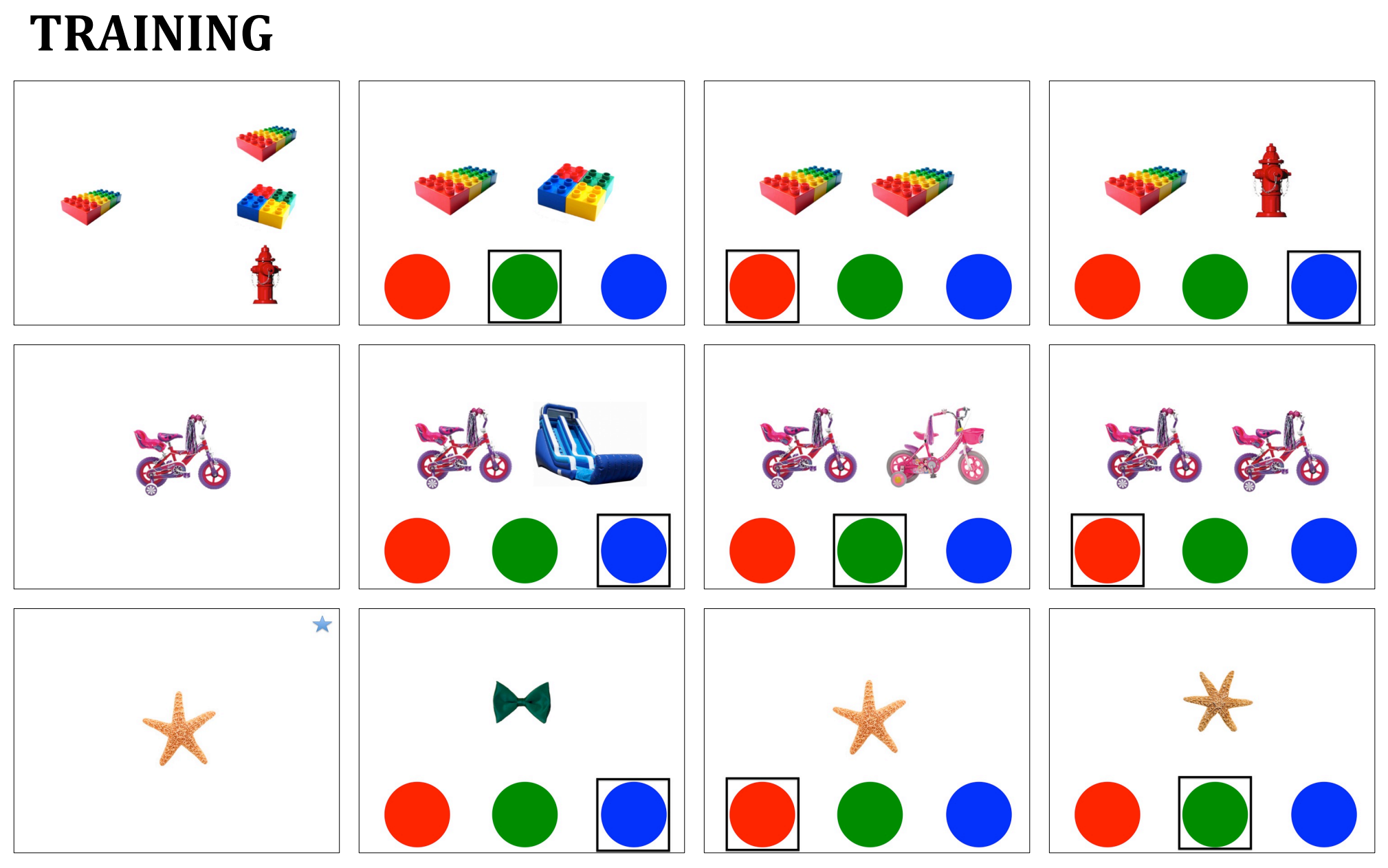
Training

~10 minute training-delay. Required to pass one of two sets of 6 training trials with 100% accuracy.

Test

Viewed 66 objects (22 targets, 22 lures, and 22 foils) and decided if each object was "old", "new", or "similar" using a 3-button box





Behavioral Measure of Pattern Separation Ability

- Proportions of memory responses (old, similar, and new) for each item type (target, lure, and foil) were calculated for each participant.
- Proportion of old responses to lures ("old" | "lure") were subtracted from the proportion of old responses to targets ("old"| "old") to create a bias-corrected measure of lure discrimination (Loiotile & Courtney, 2015; Leal, Tighe, Jones, & Yassa, 2014).
- Positive values denote successful discrimination between targets and lures. Negative values denote a higher tendency to over-generalize between two similar items.
- A value of zero denotes chance-level discrimination.

Methods (cont.)

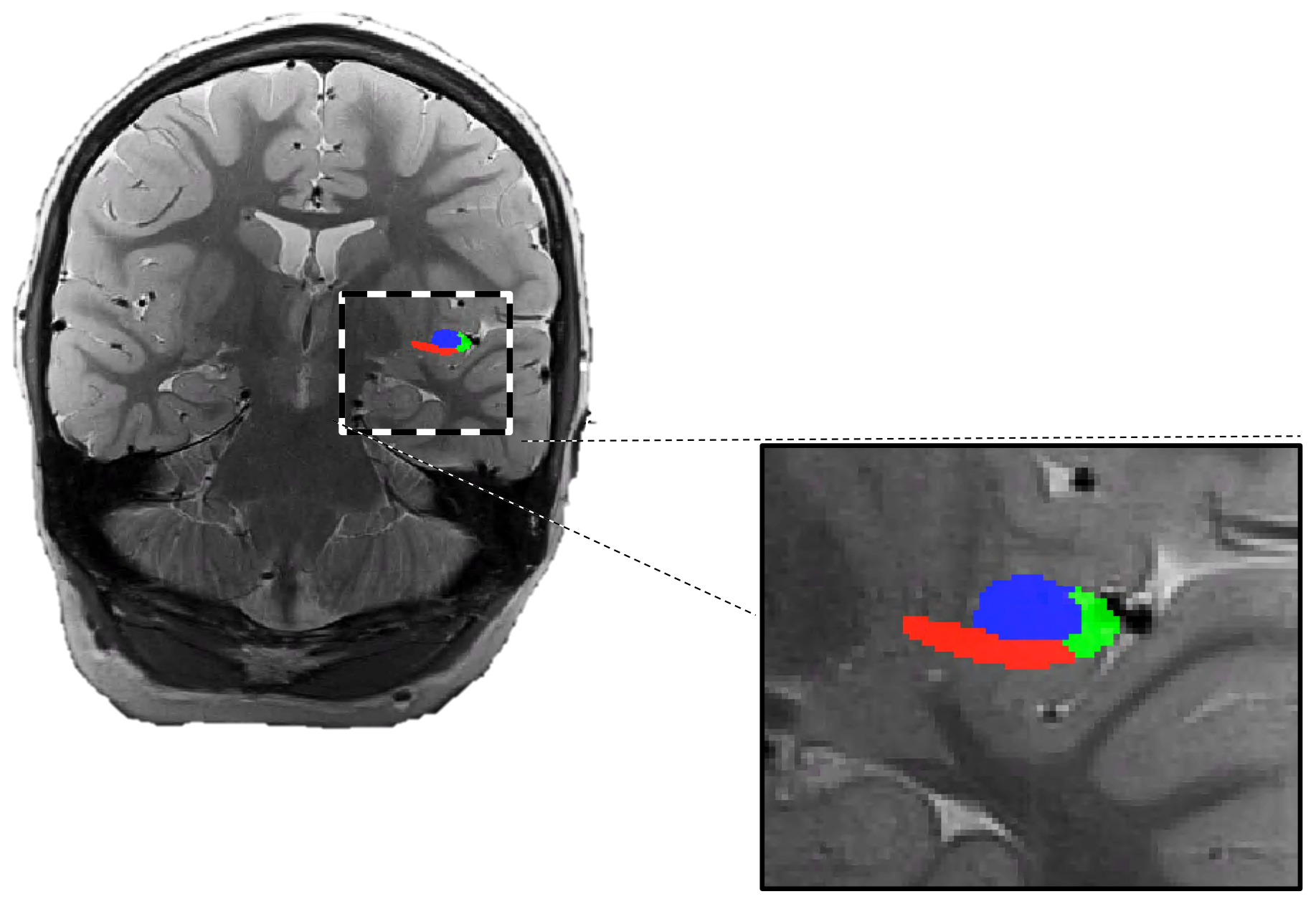
MRI Data Acquisition and Analyses

MRI Data Collection

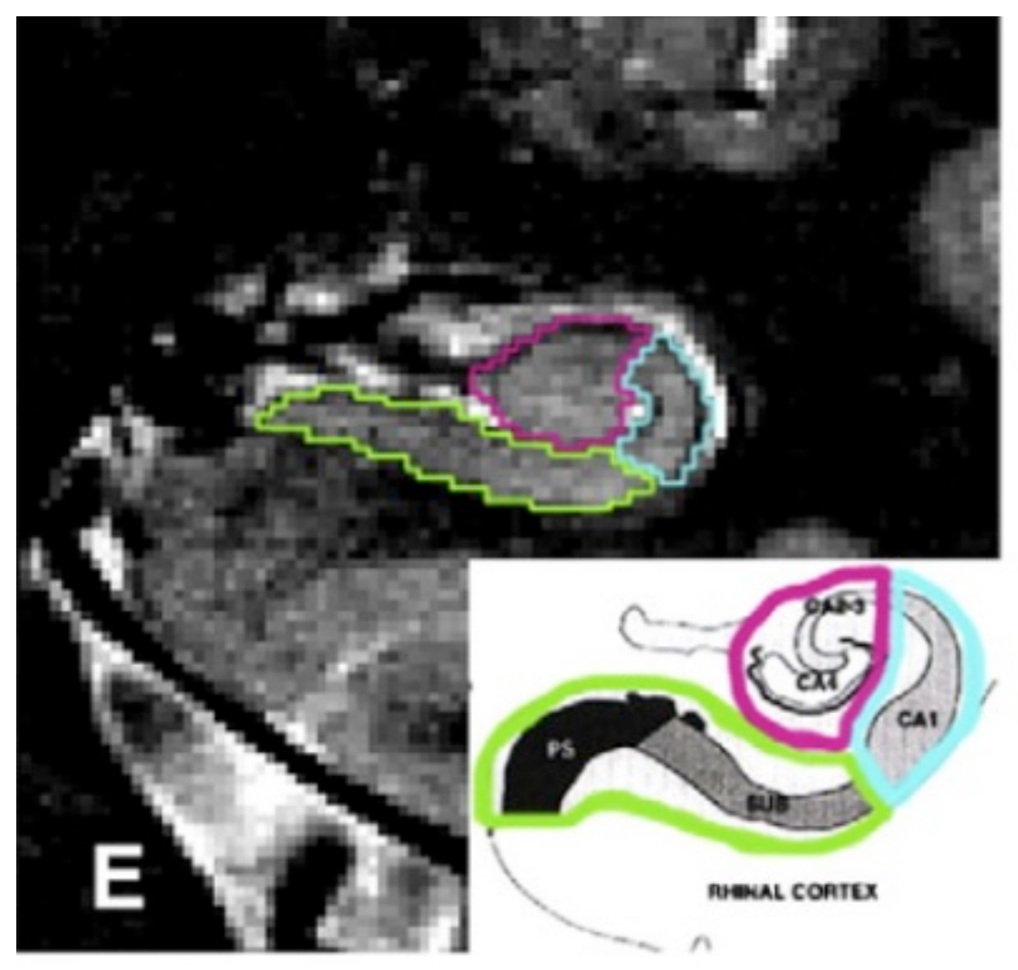
- Ultra-high resolution (.4mm x .4mm x 2mm) structural scans of medial temporal lobe (MTL) were acquired with a T2-weighted fast spin echo sequence (TR=4120ms, TE=41ms, 24 slices, 149 degree flip angle).

MRI Data Processing and Analysis

- Bilateral subiculum, CA1, and DG/CA2-4 volumes were derived using a protocol adapted from Joie and colleagues (2010) and used in conjunction with the Automatic Segmentation of Hippocampal Subfields software (ASHS, Yushkevich et al., 2014) to yield volumes for all participants. All resulting segmentations were checked manually.



Figures depicting boundaries and tracings used for hippocampal subfield segmentation. **Above**: Example segmentation from the present report's sample; **Below**: Segmentation from Joie et al., 2010.



- Bilateral volumes were collapsed across hemisphere and adjusted for intracranial volume (ICV) (see Keresztes et al., 2017) for all reported analyses.

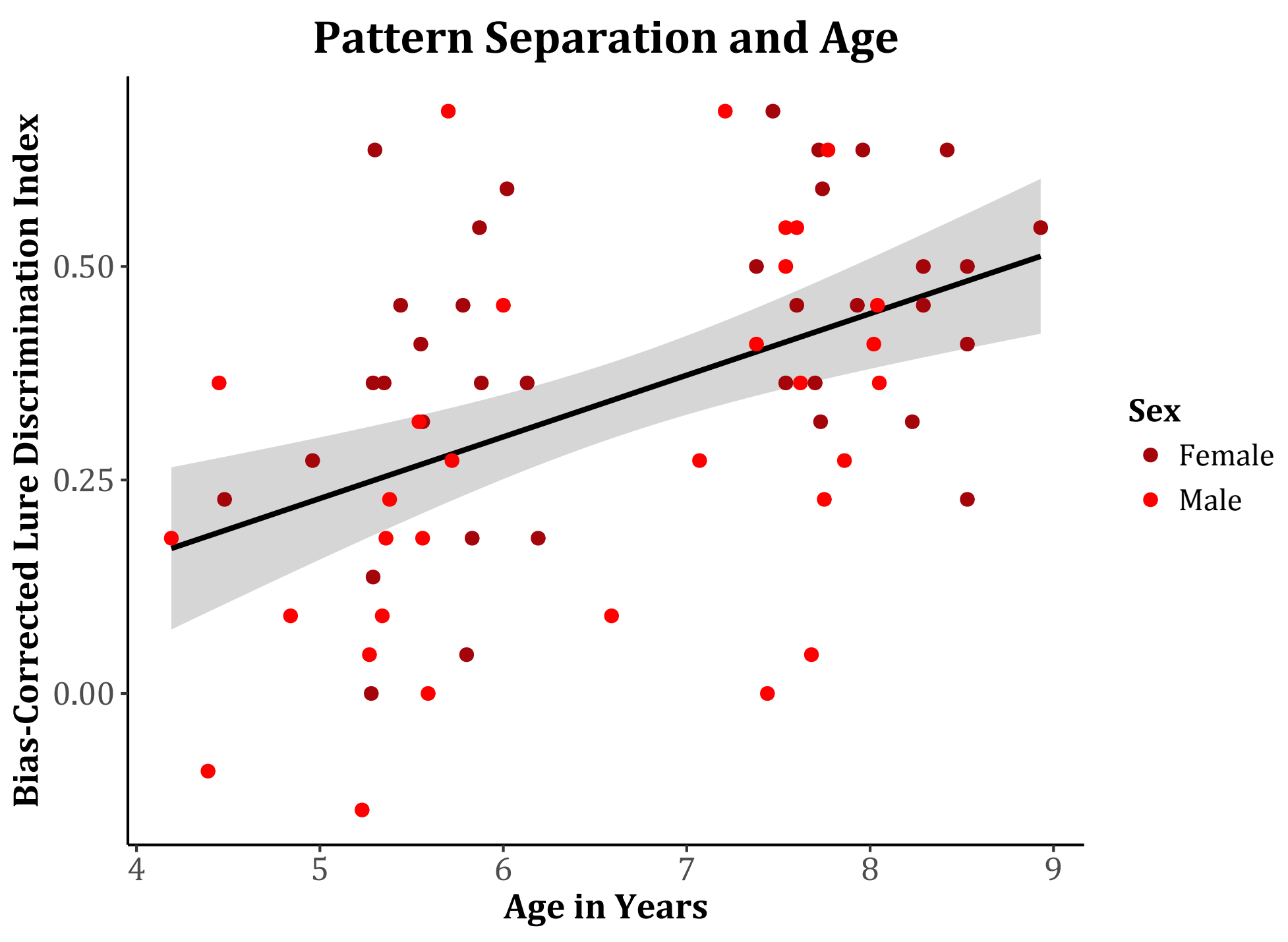
Statistical Analyses

- Multiple linear regression analyses were used to investigate the possible relation between hippocampal subfield volumes and PS ability. The first model tested for main effects of Age and Volume for each of the three subfields, controlling for Sex. A second model included the main effects plus Volume × Age interactions for all three subfields, controlling for Sex.

Behavioral Results

Pattern Separation Ability Improves with Age

- A linear regression analysis was performed to assess the degree to which Age predicted performance on the MST (lure discrimination), controlling for Sex. The model was significant, with both Age and Sex predicting PS ability.


Pattern Separation and Age

- *Adj. R^2*= 0.25, *F*(2, 64)= 11.93, *p* < .001; reliability of age effect: β= 0.42*, *p* < .001; sex effect β = 0.24, *p* = .03. *all statistics reflect standardized β
- This suggests that PS ability improves with age in 4- to- 8-year-old children.
- Due to the effect of Sex, when assessing the relation between hippocampal subfields and lure discrimination, Sex was controlled.

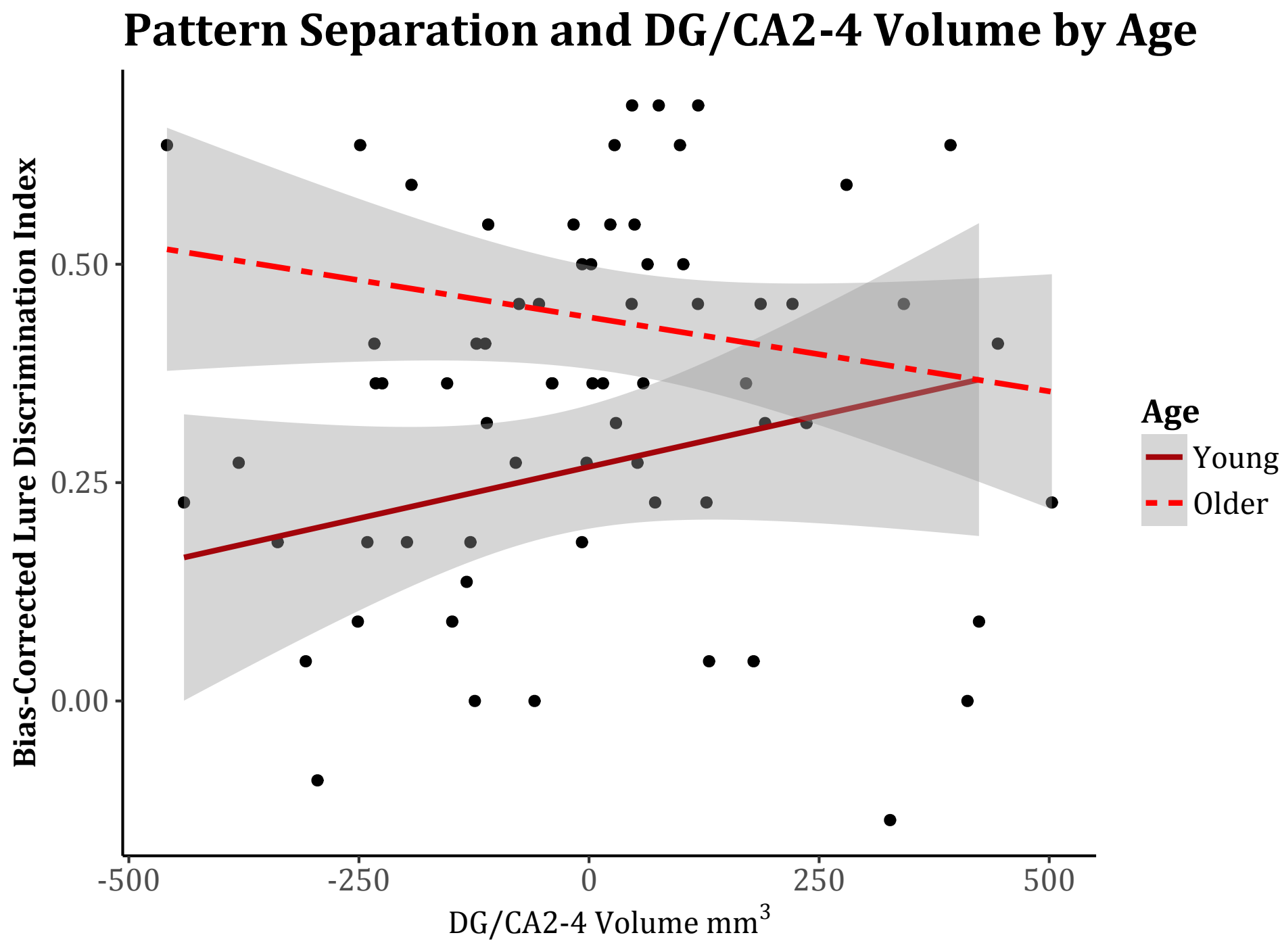
Subfield Volume–Performance Results

DG/CA2-4 Volume Predicts Pattern Separation Ability

- The model that best fit the relation between subfield volume and pattern separation ability was the Volume × Age interaction model; Adjusted R^2= 0.25, *F*(8, 58) = 3.77, *p* = .001.

Lure Discrimination ~ CA1 + DG/CA2-4+ subiculum + CA1 × age +
DG/CA2-4 × age *+ subiculum × age + age + sex*

- DG/CA2-4 volume was the only subfield to show a significant interaction with age (β = -0.31, *p* = .04), with the volume–lure discrimination relation appearing positive in younger children and negative in older children.


Pattern Separation and DG/CA2-4 Volume by Age

Arbitrary groups formed using a median split (Mdn_{age}*=6.59) to illustrate age-related differences.

- Follow-up analyses to explore this relation found it did not differ between hippocampal subregions (head vs. body) but did differ bilaterally (greater right DG/CA2-4 volume in younger children predicted better PS ability).

Discussion

The present report makes several contributions to the literature examining PS ability in children.

Behaviorally, results in the current sample of 4- to- 8-year old children replicate those found previously by Ngo and colleagues (2017), showing PS ability improves with age during childhood.

Importantly, the present report expands previous knowledge in revealing an age-moderated relation between DG/CA2-4 subfield volume and PS ability in 4- to- 8-year-old children. Specifically, larger DG/CA2-4 volume predicts better PS ability in younger children, but not older children. Rather, in older children, smaller volume was related to better PS.

This is consistent with Lavenex & Banta Lavenex's (2013) proposed range of 5-7 as an important developmental period in the trajectory of the DG and CA3 hippocampal subfields thought to support PS ability.

Our results are consistent with findings from Keresztes and colleagues (2017) in younger, but not older, children. This could be due to differences in the defined subfields. Specifically, the present study solely focused on subfield volumes included in the hippocampus proper, with subfields considered individually. Comparatively, Keresztes and colleagues (2017) utilized a latent measure of hippocampal maturity, which included entorhinal cortex.

It is possible that as the hippocampal circuitry supporting PS matures, changes are evident in the volumetric increase hippocampal subfields until a threshold is met.

While this report utilizes the collapsed volume of DG/CA2-4 as an indicator of functional maturity, future work examining fine-grained volumetric and functional differences in subfields between subregions and hemispheres of the hippocampus may provide clarification on the relations between PS ability, age, and hippocampal subfields.

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