

ABSTRACT

Title of Thesis: INVESTIGATING THE RELATION BETWEEN
PATTERN SEPARATION AND HIPPOCAMPAL
SUBREGION ACTIVATION
Jade Dunstan, Master of Science, 2022

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Pattern separation is a key component of episodic memory as it allows us to distinguish between similar events that share overlapping features. Therefore, understanding the development of pattern separation processes can help elucidate individual differences in memory development. Research in children and adults has shown relations between hippocampal structure and pattern separation, indexed behaviorally through a mnemonic discrimination task where participants distinguished between similar stimuli. However, there has been less research investigating relations between hippocampal function and pattern separation processes, all in adult samples. Thus, the current study sought to pilot a child-friendly mnemonic discrimination fMRI paradigm in adults before recruiting a child sample. Results provided some evidence of pattern separation processes as greater differences in activation for Targets relative to Lures predicted better memory performance. Future studies will recruit a child sample to assess group differences in pattern separation processes as well as go beyond mean activation for the conditions by using techniques such as representational similarity analysis to assess patterns of representations for Targets, Lures, and Foils across the voxels of the hippocampus.

INVESTIGATING THE RELATION BETWEEN PATTERN SEPARATION AND
HIPPOCAMPAL SUBREGION ACTIVATION

by

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Thesis submitted to the Faculty of the Graduate School of the
University of Maryland, College Park, in partial fulfillment
of the requirements for the degree of
Master of Science
2022

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Acknowledgements

I would like to thank my advisor and committee chair, Dr. Tracy Riggins for her guidance and endless patience throughout this project and for her invaluable mentorship during my graduate training. I would also like to express my gratitude to Dr. Elizabeth Redcay and Dr. Jeremy Purcell for their critical feedback on this project. Dr. Purcell also offered guidance in the development of the fMRI task used in the current project, which I am thankful for. Finally, I would like to express my appreciation for the participants that completed the study and to the Neurocognitive Development Lab for their role in recruitment and data collection.

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Chapter 1: Introduction

Pattern separation and mnemonic discrimination

Pattern separation is a neurocomputational process by which the patterns of neuronal activation underlying similar memories are made distinct to counteract interference during retrieval (Norman & O'Reilly, 2003). Several studies have implicated the hippocampus, a structure in the medial temporal lobe (MTL) involved in the formation of episodic memories, in pattern separation in adults (for a review, see Yassa & Stark, 2011). Specifically, previous research suggests that the dentate gyrus (DG), a hippocampal subfield located primarily in the hippocampal body (Malykhin et al., 2010) is designed for this process specifically (e.g., Bakker et al., 2008; Lacy et al., 2011; Berron et al., 2016).

Despite our inability to directly measure pattern separation in humans, research suggests that behavioral tasks that require the mnemonic discrimination of similar stimuli can serve as an index of this process (e.g., Kirwan & Stark, 2007; Lacy et al., 2011). During a mnemonic similarity task (MST), participants encode a series of pictures and are then, during retrieval, asked to discriminate between pictures they previously saw during encoding (Targets); completely new pictures they have never seen before (Foils); and pictures that are similar, but not quite the same as the pictures they were previously exposed to (Lures). fMRI studies in adults show a positive relation between DG/CA3 activation and lure discrimination (Lacy et al., 2011; Reagh & Yassa, 2014).

Age-related changes in mnemonic discrimination

Studies comparing behavioral performance of younger adults relative to older adults show that older adults demonstrate impaired lure discrimination (e.g., Yassa et al., 2010; Reagh et al., 2018), suggesting a decline in MST performance with aging. Additionally, reductions in DG/CA3 volume mediate age-related declines in lure discrimination performance (Stark & Stark, 2017; Dillon et al., 2017; Doxey & Kirwan, 2015). However, in older relative to younger adults, increased activity in the DG/CA3 was associated with worse lure discrimination (Reagh et al., 2018).

Findings from child studies show age-related improvements in mnemonic processes, such as binding items in memory (Riggins, 2014) and pattern separation via improvements in mnemonic discrimination (Ngo et al., 2018; Canada et al., 2019) in 4-8-year-old children. For example, Ngo and colleagues (2018) found that 4-year-olds performed worse on a child-friendly version of the MST compared to 6-year-olds, who performed comparably to adults. This suggests that 4-6 years is an important period for pattern separation development and improvement. This set of findings aligns with alterations to hippocampal structure during aging and the protracted development of the hippocampal subfields into early childhood, respectively. This emphasizes the importance of examining brain-behavior relations in young children to better understand the differences in hippocampal structure/function in early childhood that may underlie this impaired mnemonic discrimination.

The role of the hippocampus in pattern separation and mnemonic discrimination

One neuroimaging study using an MST paradigm in children found a significant interaction between CA2-4/DG and age such that the relation between CA2-4/DG volume and lure discrimination, defined as the proportion of “old” responses to targets minus the proportion of “old” responses to lures, was positive in younger children (4-6 years) but negative in older children (6-8 years, Canada et al., 2019). Another study looking across middle childhood and adolescence (6-14 years) found that a bias towards pattern separation emerged with increasing hippocampal maturity (composite score derived from the structural maturity of the hippocampal subfields; Keresztes et al., 2017). Both studies highlight the importance of structural maturation of the hippocampus in supporting pattern separation, demonstrated by mnemonic discrimination improvements. However, to date, there are no studies investigating the role of ***functional*** maturation of the hippocampus in the development/improvement of mnemonic discrimination in children.

Methodological challenges of collecting MRI data in young children

Thus, despite extensive adult literature, an open question remains regarding the relation between developmental changes in hippocampal function during early childhood and mnemonic discrimination. However, this is a difficult question to address due to the methodological challenges associated with collecting functional MRI data while young children are in the scanner. For example, young children struggle to remain motionless during long functional runs, which may result in significant data loss and reduce power of subsequent analyses (Turesky, Vanderauwera, & Gaab, 2021). In addition, young children may find it too difficult to

respond to stimuli in the scanner via button response and, even if they are able to do so, the act of pressing the button itself may also result in head motion. This motion makes it difficult, sometimes impossible, to extract the hippocampal subfields during preprocessing. This is a significant problem because non-human primate neuroanatomical research demonstrates that early childhood is a period of protracted hippocampal development, particularly for the functional connections between DG and CA3 (Seress 2001; Lavenex and Lavenex 2013). Because DG/CA3 volume (Stark & Stark, 2017; Dillon et al., 2017; Doxey & Kirwan, 2015) and function (Reagh et al., 2018) have an established relation with mnemonic discrimination in adult humans, it is important to investigate how this relation differs in children whose hippocampi are not yet fully developed. However, no studies to date have investigated activation of the hippocampus in young children during a mnemonic discrimination task, leaving the precise window of pattern separation development unclear.

The current study

We based our fMRI MST task off an adult paradigm that used an event-related, incidental encoding design in order to leverage repetition suppression, the reduction in neural activity in response to a repeated stimulus (Henson, 2003). During the task, participants were shown a series of images and made a determination of whether the object belonged inside or outside via button press. On each trial, the object presented could be new (Foil), a repetition of a previously seen object (Target), or a similar object to one that was previously seen (Lure). Studies using this paradigm investigated activation differences between Targets, Lures, and Foils in voxels that

showed repetition sensitivity (differences in activation for repeated vs. novel stimuli) observed reduced activation for Targets relative to both Lures and Foils in CA3/DG, consistent with pattern separation, and reduced activation for both Targets and Lures relative to Foils in CA1, consistent with pattern completion (Bakker et al., 2008; Lacy et al., 2011).

However, because we are interested in using our paradigm for young children, we made several important changes from the adult paradigm. Therefore, for the current study, we developed a passive viewing, block design MST fMRI task that participants completed in two short functional runs after an outside of scanner encoding. A block design was selected because it has been shown to have higher statistical power than event-related designs, (Hay et al., 2022), which requires event-related designs to have longer functional runs to compensate. Because longer functional runs are not conducive to scanning child participants, we ran the task with the shorter functional runs in an adult sample initially to test out this paradigm before recruiting a preschool-aged child sample. Participants then completed an outside of scanner active retrieval. Because there was a delay of about 15 minutes between encoding and the in-scanner passive retrieval (the time it took to get participants into the scanner), our paradigm does not leverage repetition suppression like the one used by Bakker et al. (2008) and Lacy et al. (2011). Additionally, the stimuli participants viewed at encoding occur in a different context (sitting up in a chair, looking at a computer monitor) than the stimuli participants viewed during the in-scanner passive retrieval (lying down on the scanner bed, viewing stimuli through a mirror directed at the screen behind the scanner). This difference is particularly relevant for Targets, the

stimuli that participants viewed during both the outside of scanner encoding and in-scanner passive retrieval. Therefore, as will be seen in the next section, although our hypotheses align with Bakker et al. (2008) and Lacy et al. (2011) in that evidence of pattern separation will be consistent with different levels of activation for Targets relative to Lures and Foils (which will show comparable levels of activation), we anticipate greater, rather than smaller, activation for Targets as our design does not leverage repetition suppression. This prediction is in line with a study that used a study/test recognition paradigm in which in-scanner incidental encoding and active retrieval were separated by a long interval (Klappenstein et al., 2020). The study used a voxel-wise step function to test whether the hippocampus showed mnemonic discrimination (MD)-related activity such that activity for Lures was significantly different from Targets but comparable to Foils. Findings from this study revealed four clusters where the average activity to correct “old” responses to Targets differed from the average activity to correct “new” responses to foils and lures (Klappenstein et al., 2020) in the bilateral body, right head, and right body/head of the hippocampus. All of these clusters overlapped with DG/CA3. Additionally, voxel-wise correlations revealed that MD-related step function activity in right hippocampal body/head was positively related to the LDI. In the current study, we investigated whether the hippocampus, anterior, posterior, or total, showed differential activation to Targets, Lures, and Foils during passive viewing. Although adult work is able to image hippocampal subfields during functional tasks, because of the risk of motion in children, we acquired larger voxels, which allowed us to probe subregions, but not subfields.

Hypotheses

Adult studies investigating hippocampal subfield activation during mnemonic discrimination revealed that, in the DG/CA3, Lures showed significantly different activation from Targets, but not from Foils (Yassa & Stark, 2011; Lacy et al., 2011). Because the largest part of the DG is in the hippocampal body (Malykhin et al., 2010), which is in posterior hippocampus, we expect to see evidence of pattern separation in posterior hippocampus. Therefore, we hypothesize that the posterior hippocampus will show patterns of activation more consistent with *pattern separation* – less activation for Targets relative to both Lures and Foils, which will show comparable levels of activation, suggesting that Lures are being considered a novel stimulus (Foil) rather than a repetition of the original stimulus (Target).

Because both DG and CA3 have been implicated in pattern separation and CA3 is more prominent in the hippocampal head (anterior hippocampus) while the DG is more prominent in posterior hippocampus (Malykhin et al., 2010), we also expect these patterns to hold up when looking at the whole hippocampus. CA1, found primarily in the anterior hippocampus (Malykhin et al., 2010) has been associated with pattern completion processes - reconstructing memory traces from degraded signals (Bakker et al., 2008; Lacy et al., 2011). Therefore, in the current study, we expect the anterior hippocampus to show patterns of activation more consistent with *pattern completion* – comparable, higher activation levels for Targets and Lures relative to the activation for Foils - suggesting that the Lures are being considered a repetition of the original stimuli (Targets) rather than a novel stimulus (Foils).

Additionally, we will investigate whether the magnitude of the neural response relates to behavioral performance outside of the scanner. Several studies in adults have demonstrated greater hippocampal activity during successful retrieval (e.g., Cansino et al., 2002; Hannula & Ranganath, 2009; Hsieh et al., 2014). In a recent study with toddlers, behavioral memory for song-toy (remembering which toy they played with while a song was playing) and song-room (remembering which room they were in while a song was playing) associations were related to the strength of hippocampal activation while listening to that song during natural sleep (Prabakhar et al., 2018). However, these studies focused on the left and right hippocampus rather than dividing the hippocampus into subregions or subfields and also investigated source and recognition memory, which may rely on neural regions distinct from those engaged during pattern separation (Yassa & Stark, 2011; Stevenson et al., 2020). In order to investigate relations between activation and behavior, we calculated the accuracy of participants during an active retrieval phase of the MST task, which took place after the scan. We obtained scores for Lure correct rejections (LCRs) - correctly identifying a Lure as new; Foil correct rejections (FCRs) - correctly identifying a Foil as new; and Target Hits - correctly identifying a Target as old. Additionally, we calculated the Lure Discrimination Index (LDI) as the proportion of Target Hits minus the proportion of Lure False Alarms (incorrectly identifying a Lure as old). The LDI is considered a golden standard measure for mnemonic discrimination/pattern separation processes as it assesses a participant's ability to distinguish between similar stimuli (Targets and Lures). Values range from -1 to 1, with negative values indicating a tendency to overgeneralize (lump Lures in with

Targets as previously experienced stimuli), 0 indicates chance-level performance, and positive values indicate the ability to distinguish Lures from Targets.

In posterior hippocampus, we expect a positive association between behavioral accuracy and strength of hippocampal activation such that better LDI performance will be associated with greater differential activation for Targets relative to Lures. We also expect that both greater Target Hits will be associated with greater differential activation for Targets relative to Lures and Targets relative to Foils in posterior hippocampus, greater Lure Correct Rejections will be associated with greater differential activation for Targets relative to Lures but smaller differential activation for Lures relative to Foils in posterior hippocampus, and greater Foil Correct Rejections will be associated with greater differential activation for Targets relative to Foils in posterior hippocampus but smaller differential activation for Lures relative to Foils in posterior hippocampus.

In anterior hippocampus, we expect that smaller differences in activation for Targets relative to Lures will be associated with greater Target Hits, which is more in line with pattern completion processes of treating a Lure more like a repeated stimulus (Target) than a novel one (Foil). Additionally, we anticipate that greater activation differences between Targets and Foils as well as between Lures and Foils will predict both greater Target Hits and greater Foil Correct Rejections.

Chapter 2: Methods

Participants

A total of 34 adult participants (18-28 years; $M_{age} = 23.30 \pm 3.07$ years; 27 females) participated in the current study. Participants were recruited through the University of Maryland campus. Information about the study was sent to the University of Maryland Graduate Student Government (GSG) listserv, in an announcement to students taking PSYC355: Developmental Psychology, and was disseminated by the Neurocognitive Development Lab's lab manager to other psychology labs at UMD. All participants had no history of head or brain injury and no contraindications for MRI per self-report.

Data from two additional participants were collected but ultimately excluded due to quality issues. One participant responded “yes” to all stimuli during the out-of-scanner retrieval, suggesting that they either did not understand the task or did not attend to the pictures during the initial encoding phase. The other participant was excluded due to an imaging artifact that rendered the data unusable.

Materials

The mnemonic similarity task (MST) was adapted from Ngo et al.'s (2018) child-friendly version of the task originally designed for adults. The stimuli were drawn from an online repository of stimuli used for an adult version of the task (<http://faculty.sites.uci.edu/starklab/mnemonic-similaritytask-mst/>) as well as the internet. A subset of pictures was chosen from the repository based on how interesting the objects are to children (e.g., toys) and how likely it is that children are

familiar with them (e.g., hats). Although the current study only included adult participants, this decision was made because the ultimate goal of this study is to pilot this fMRI MST task prior to recruiting child participants. Participants also filled out a demographic questionnaire, which included questions on biological sex and age (which were used as covariates in subsequent analyses).

Procedure

All methods used in the current study were approved by the University of Maryland Institutional Review Board. Participants were sent an electronic copy of the consent form and MRI screening form prior to the study visit.

MST fMRI task design

Outside of the MR scanner, participants encoded 60 pictures in two blocks of 30 (infinite duration; 0.5 interstimulus interval (ISI)). Participants were shown a series of pictures and were asked to decide whether they thought the object pictured belonged inside or outside. Participants gave verbal responses, and the experimenter recorded the response on the keyboard. In the scanner (approximately 15 minutes later), participants completed two 3-minute runs of passive retrieval where they were asked to attend to pictures presented. Each run consisted of 15 seconds of a flashing smiley face stimulus at the beginning, six 15-second task blocks (2 blocks of each condition: Target, Lure, Foil), 5 rest blocks where the participants saw a smiley face, and 15 seconds of the flashing smiley face stimuli at the end. The smiley face was used instead of fixation to keep future child participants engaged. To vary presentation order, participants completed one of two orders: Target, Lure, Foil,

Target, Lure, Foil, or Foil, Lure, Target, Lure, Target, Foil. Stimuli within each block were randomized. Each stimulus (picture or smiley face) was presented for 2 seconds with a 1 second ISI. The inter-block intervals were jittered, varying from 9 to 15 seconds with a mean of 12 seconds (see Figure 1 for a diagram of the task design). After the scan, participants completed an active retrieval in which they were shown 30 pictures (10 Targets, 10 Lures, 10 Foils) and asked whether they saw this picture before (during encoding) in order to obtain a behavioral measure of retrieval. Participants responded verbally with “Yes” or “No” and their responses were recorded by the experimenter. The in-scanner and outside of scanner tasks were run via Eprime 2.0 (Psychology Software Tools, Pittsburgh, PA).

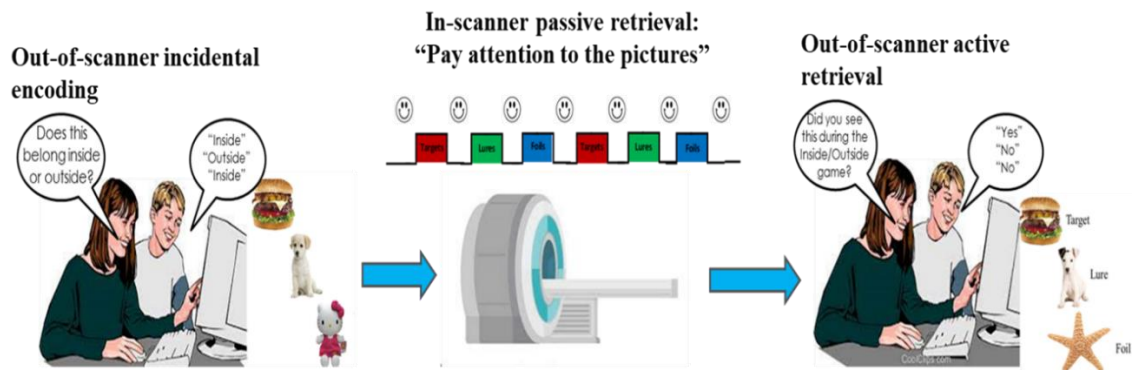


Figure 1. MST fMRI task design

MRI Acquisition

Adult participants were shown the mock MRI and told what the actual scan would entail prior to MRI acquisition. 16 of the total 34 participants were scanned in a Siemens 3.0-Tesla MAGNETOM TrioTim scanner with a 32-channel phased array head coil and 18 of the total 34 participants were scanned in a Siemens 3.0-Tesla Prisma scanner. Scanner type and counterbalancing were confounded such that all

participants scanned on the Trio received the first counterbalancing order (Targets, Lures, Foils, Targets, Lures, Foils) and all participants scanned on the Prisma received the second counterbalancing order (Foils, Lures, Targets, Lures, Targets, Foils). Therefore, we collapsed across all stimuli condition types and built a Stimuli > Rest contrast to assess whether there were any differences in simple activation in each hippocampal ROI based on scanner type. No significant differences were observed. Structural images were acquired using a T1 magnetization-prepared rapid gradient-echo (MPRAGE) sequence (192 slices; 0.9 mm isotropic for Trio and 0.4×0.4×0.9 mm for Prisma; TR = 1900 ms; TE = 2.32 ms; TI = 900 ms; flip angle = 9°; pixel matrix = 256 X 256). During the same scanning session, functional data were collected in two three-minute runs (see description of task above in the *MST fMRI task design* subsection of the *Procedure* section). The functional runs had the following parameters: 144 EPI volumes with a 60-slice interleaved acquisition; voxel size = 2.2 mm isometric; TR = 1250 ms; TE = 39.4 ms; slice thickness = 2.2 mm; flip angle = 90°; FoV = 210 mm.

Data Analysis

MRI Preprocessing

Images were preprocessed in SPM12 (<https://www.fil.ion.ucl.ac.uk/spm/software/spm12/>), based on Matlab (Mathworks). First, functional images were realigned to correct for motion. Then, the structural images were co-registered to the mean functional image. The structural images were then segmented into gray matter (GM), white matter (WM), and cerebrospinal fluid

(CSF) prior to normalizing the functional images from native space to Montreal Neurological Institute (MNI) space. Finally, functional images were smoothed using a 6-mm full width at half maximum (FWHM) Gaussian kernel. Additionally, motion artifacts were identified using the Artifact Detection Tools software (http://www.nitrc.org/projects/artifact_detect). Movement parameters generated during this step were entered into the first level GLM as nuisance regressors. Movement regressors were identified using a movement threshold of 3 mm and a rotation threshold of 0.05 mm.

After preprocessing, the images were entered into a first-level general linear model (GLM) to model Targets, Lures, and Foils during the time series and then were convolved with a hemodynamic response function to build contrasts to compare the neural activation for the different task conditions (Targets > Lures, Targets > Foils, Lures > Foils). Because our hypotheses were specific to the role of the hippocampus in pattern separation, we used structural ROI masks of the left and right anterior hippocampus, posterior hippocampus, and whole hippocampus. Follow-up analyses collapsed across left and right, resulting in bilateral anterior and bilateral posterior hippocampal ROIs as well. All ROIs used in the current study are group-level masks derived from a separate adult sample.

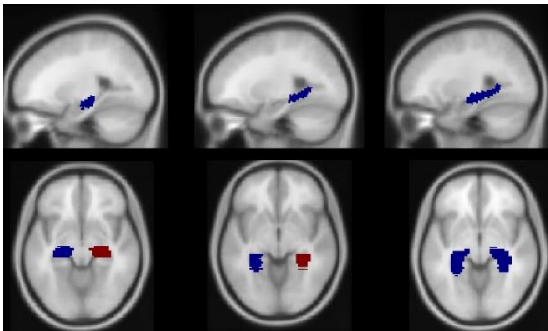


Figure 2. Hippocampal ROIs used in the current study. The left images show left (blue) and right (red) anterior hippocampus, the middle images show left (blue) and right (red) posterior hippocampus, and the right images show bilateral whole hippocampus.

Statistical Analyses

All statistical analyses were run in RStudio (www.rstudio.com). Bivariate Pearson correlations were run to determine the relations between age, functional activation in the hippocampal ROIs for each contrast, and behavioral performance outside of the scanner. After running the bivariate correlations, we next investigated whether participants showed differential activation for the Targets relative to Lures (Targets > Lures), Targets relative to Foils (Target > Foils), and Lures relative to Foils (Lures > Foils). Contrast estimates for Targets > Lures, Targets > Foils, and Lures > Foils were extracted from each hippocampal ROI using the MarsBaR toolbox in SPM12 (<https://marsbar-toolbox.github.io/index.html>). After parameter and contrast estimate extraction, ROI analyses were run in MarsBaR by taking the mean of the voxels extracted for each ROI, creating a summary value that represented all the voxels in each ROI. Then, for each contrast (Target > Lure, Target > Foil, Lure > Foil), Bonferroni-corrected (for number of regions in analysis) t-tests were run to compare the effect of Targets relative to Lures, Targets relative to Foils, and Lures relative to Foils on each of the hippocampal ROIs. Therefore, the corrected threshold for analyses looking at left/right anterior and posterior hippocampus was 0.0125 (0.05/4). Then, in subsequent analyses we collapsed across left and right anterior and posterior hippocampus to assess these differences. The corrected threshold for these

subsequent analyses looking at bilateral anterior, bilateral posterior and whole hippocampus was 0.017 (0.05/3).

Then, we assessed whether the magnitude of differences in activation between the conditions (Target > Lure, Target > Foil, Lure > Foil) predicted out-of-scanner accuracy during retrieval using multiple regression analyses. Behavioral performance from the outside of scanner retrieval was calculated for Targets (Target Hits - number of “yes” responses to Targets), Lures (Lure Correct Rejections - number of “no” responses to Lures), and Foils (Foil Correct Rejections – number of “no” responses to Foils). Additionally, in order to represent pattern separation processes specifically, we calculated a Lure Discrimination Index (LDI) using the following formula: $LDI = \text{Target Hits} - \text{Lure False Alarms}$ (“yes” response to Lures).

Chapter 3: Results

Preliminary Analyses

Behavioral performance during outside of scanner retrieval

Table 1. shows behavioral performance on Targets, Lures, and Foils, as well as the ability to distinguish between Targets and Lures (measured via the LDI).

Table 1. Behavioral performance on Targets, Lures, Foils and the Lure Discrimination Index (LDI)

	Mean	SD	Range
Target Hits	0.95	0.11	0.5 - 1
Lure Correct Rejections	0.47	0.2	0.1 - 0.9
Foil Correct Rejections	0.98	0.04	0.9 - 1
LDI	0.43	0.21	0 - 0.9

Note: Target Hits are the proportion of “Yes” responses to Targets, Lure Correct rejections are the number of “No” responses to Lures, and Foil Correct Rejections are the number of “No” responses to Foils.

The majority of participants were at or near ceiling for performance on Targets and Foils, with 25 of the 34 participants (75%) correctly identifying all 10 Targets as something they did previously see and 26 of 34 participants (76%) correctly identifying all 10 Foils as something they did not previously see. Performance on Lures was more variable, with half of the participants (17 of 34) correctly identifying less than half of the Lures as something they did not previously see. Figure 3 shows the distribution of behavioral performance for Targets, Lures, the Lure Discrimination

Index, and Foils. shows the distribution of behavioral performance for Targets, Lures, the Lure Discrimination Index, and Foils. The high performance on both Targets and Foils suggests that participants understood the task but the variable performance on lures suggests that there was variability in the “precision” of their memories for item details.



Figure 3. Histograms showing distribution of proportion scores for Targets Hits (blue), Lure Correct Rejections (yellow), the Lure Discrimination Index (green), and Foil Correct Rejections (red).

Does the anterior or posterior hippocampus respond differentially to Targets vs. Foils, Targets vs. Lures, and Lures vs. Foils?

Prior to assessing differences in activation for Targets, Lures, and Foils, mean activation for Targets, Lures, and Foils were plotted (see Figure 4).

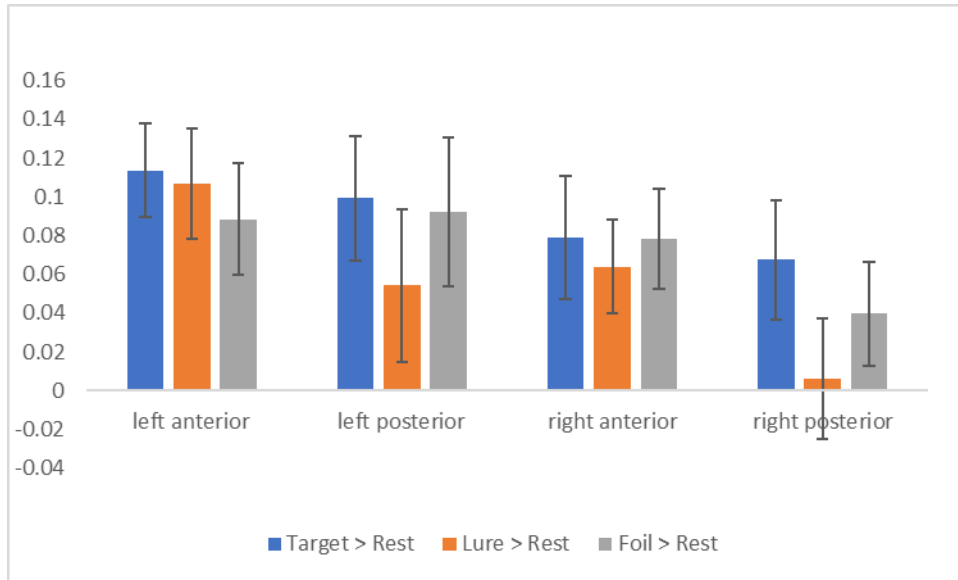


Figure 4. Differential activation for Targets relative to Rest (blue bars), Lures relative to Rest (orange bars), and Foils relative to Rest (silver bars) for the left and right anterior and posterior hippocampus.

Mean activation for Targets, Lures, and Foils in the right posterior hippocampus trended towards patterns observed in previous studies (e.g., Klippenstein et al., 2020) in which mean activation for correct “old” responses to Targets differed from the mean activation for correct “new” responses to Lures and Foils in right body of the hippocampus. However, Klippenstein et al. (2020) also showed this pattern in right hippocampal head (anterior hippocampus), which was not observed in the current study.

ROI analyses in MarsBaR revealed that activation for Targets was marginally greater than activation for Lures in right posterior hippocampus ($t = 2.05$, $p_{corrected} = 0.094$) (Figure 4). No significant differences were observed for the Target > Lure contrast for any other ROI ($ps > .05$). No significant differences were observed

between Targets and Foils for any of the ROIs ($ps > .05$) or between Lures and Foils for any of the ROIs ($ps > .05$).

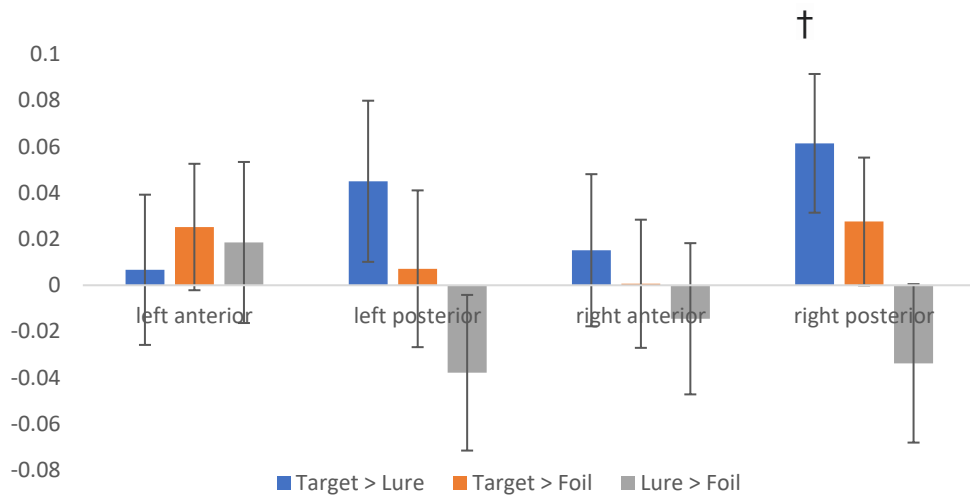


Figure 5. Results of ROI analysis showing differential activation (contrast estimates) for Targets, Lures, and Foils in each of the hippocampal ROIs. Note: † $< .10$.

There were no significant differences in activation for Targets relative to Lures, Targets relative to Foils, and Lures relative to Foils in bilateral anterior, posterior, or whole hippocampus ($ps_{corrected} > .05$).

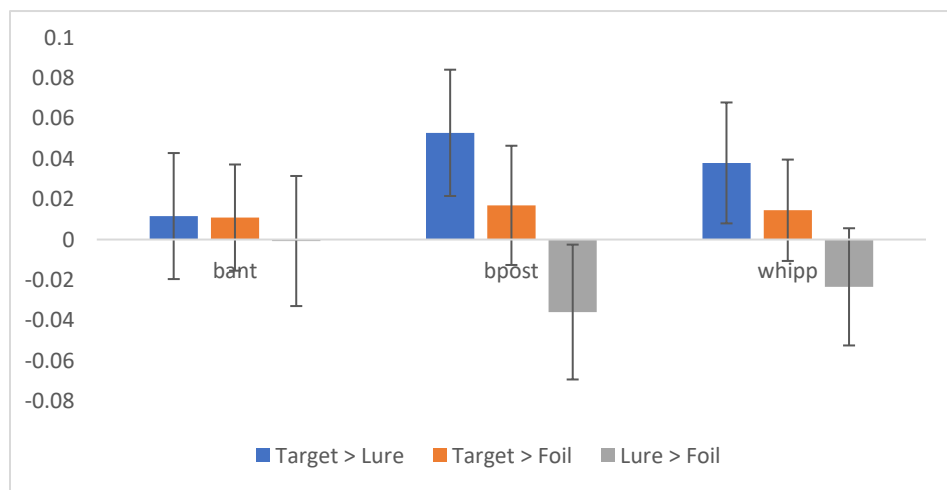


Figure 6. Results of ROI analysis showing differential activation (contrast estimates) for Targets, Lures, and Foils in each of the bilateral hippocampal ROIs.

Does the magnitude of activation during ‘passive memory retrieval’ predict behavioral retrieval performance outside the scanner?

Given the restricted range and limited variability in participant responses to Targets and Correct Rejections, only relations with LDI and LCR were explored. Linear regression analyses predicting outside of scanner behavioral performance from hippocampal activation were run to assess whether the magnitude of differential activation to Targets, Lures, and Foils predicted the ability to correctly identify a Lure as something novel (measured via LCR) and the ability to distinguish between Targets and Lures (measured via LDI). Each model included one of the contrast estimates in one of the hippocampal ROIs predicting one behavioral outcome (e.g., the contrast estimate for Targets relative to Lures in left anterior hippocampus predicting the LDI). These analyses revealed that, in left anterior hippocampus, mean activation for Targets, $B = 0.47$, $t = 1.86$, $p = .0718$, as well as the differential activation for Targets relative to Lures, $B = 0.34$, $t = 1.86$, $p = .0728$, was marginally predictive of LDI. This indicates that the greater the activation to Targets and the greater the differences in activation between Targets and Lures, the better participants were at distinguishing between Targets and Lures during the outside of scanner retrieval (identifying Targets as something previously seen and Lures as something not previously seen).

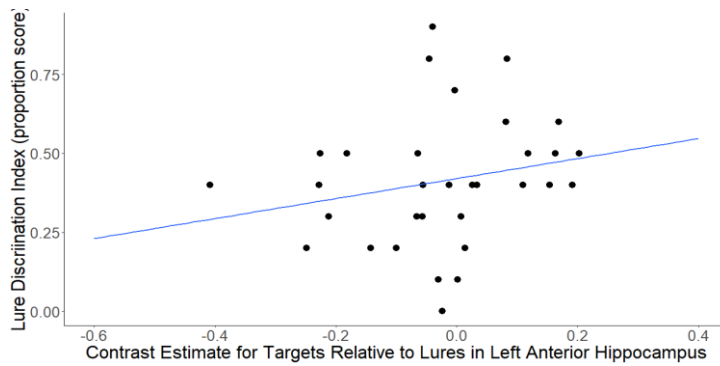


Figure 7. Associations between differential activation for Targets relative to Lures and LDI in left anterior hippocampal ROI.

Additionally, in left anterior hippocampus, the mean activation for Targets, $B = 0.47$, $t = 1.98$, $p = .0568$ as well as differential activation for Targets relative to Lures, $B = 0.35$, $t = 1.99$, $p = .0554$ was marginally predictive of LCR. Therefore, the greater the activation for Targets and the greater the difference in activation between Targets and Lures, the better participants were at identifying a Lure as something novel during the outside of scanner retrieval.

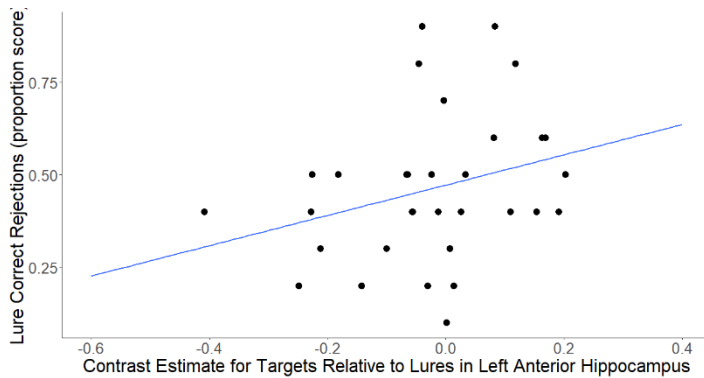


Figure 8. Associations between differential activation for Targets relative to Lures and LCR in left anterior hippocampal ROI Mean activation for Lures and Foils as well as the difference in activation for Targets relative to Foils and Lures relative to Foils did not significantly predict LDI or LCR ($ps > .05$).

Chapter 4: Discussion

This study assessed whether a novel block design, passive viewing fMRI MST task with two short functional runs could elicit and detect pattern separation processes in adult participants. Results revealed some evidence of pattern separation processes in posterior hippocampus.

Differential activation for Targets, Lures, and Foils

There was marginally greater activation for Targets relative to Lures in right posterior hippocampus. This is in line with pattern separation processes (greater distinction between neural response to Targets and Lures). However, we also expected greater activation for Targets relative to Foils. The lack of significant differences in activation between Targets and Foils may be due to the large variability in neural activation across participants. This may reflect differences in attention levels of the participants throughout the scanning session. Although participant alertness was monitored, it is possible that some participants experienced lapses in attention during the task.

Relation between magnitude of functional activation and outside of scanner behavioral performance

Greater differences in activation for Targets relative to Lures in left anterior hippocampus predicted a higher LDI and LCR. This was in line with predictions, but the region was surprising as we anticipated to see relations between *posterior* hippocampal activation and the LDI, as the LDI is a measure of mnemonic discrimination, a behavioral index of pattern separation. However, this prediction was

based on the distribution of subfields along the longitudinal axis as we did not have the resolution to investigate hippocampal subfields in the current study. Given that the anterior hippocampus is implicated in encoding, whereas the posterior hippocampus is implicated in retrieval (Poppenk et al., 2013), these findings may be explained by the task design. In the scanner, participants completed a passive retrieval where they were asked to pay attention to the stimuli and were not told that some of the pictures would be repeated stimuli they saw at encoding. Therefore, participants may have been engaging in encoding processes during this part of the tasks.

Also, it is important to note that the majority of the participants in this study were at or near ceiling for Target Hits and Foil Correct Rejections during the outside of scanner retrieval but were more variable in their performance on Lures. Therefore, the Lures may have been too difficult for some participants, resulting in overgeneralizing (i.e., pattern completion) during both passive retrieval and the outside of scanner retrieval (indicating that Lures were objects they previously saw during encoding).

Limitations and Future Research

This study offers important information regarding the functional neural mechanisms underlying pattern separation processes. Additionally, it lays the foundation for future studies to assess the relation between functional development of the hippocampus and development of pattern separation in young children through the development of a novel, block design, passive retrieval, MST fMRI task with two short functional runs. However, there were several limitations of the current study.

First, although this study heavily drew upon the hippocampal subfield

literature, the current analyses investigated anterior and posterior hippocampus, with hypotheses taking into account the distribution of subfields along the longitudinal axis. Thus, the current study offered a less fine-grained investigation of the neural mechanisms underlying pattern separation than the existing adult literature (e.g., Lacy et al., 2011). Future studies should use high-resolution functional magnetic resonance imaging sequences to allow researchers to investigate functional activation in hippocampal subfields during this block design MST fMRI task and how it relates to outside of scanner behavioral performance. This would require increasing the resolution of the scan by decreasing the voxel size to 1.5 mm isotropic. Technological advances have allowed for the scanning time of such high-resolution sequences to be reduced significantly and participants are able to watch a movie during acquisition of this scan. Therefore, although there are still concerns regarding motion, it is worth attempting to collect this data.

Second, this study only investigated mean activation in the hippocampal ROIs for each condition contrast. As a result, our findings were dependent on sensitivity to detect differences across conditions. One way to improve on the method from the current study is to use the lure-similarity approach described Klippenstein et al. (2020). In this method, regions sensitive to the differences between Targets and Lures are first identified by identifying the voxels for which activation for Lures is significantly different from Targets but not from Foils. Then, within those lure-similarity regions, differences in activation for Targets, Lures, and Foils are assessed. Moreover, differences in mean activation across conditions (e.g., lower activation for Targets relative to Lures and Foils) do not speak to how different stimuli are being

represented in the hippocampus. Future analyses could address this limitation by using representational similarity analysis (RSA), a form of multivoxel pattern analysis which would allow researchers to extract information about the patterns of representations for Targets, Lures, and Foils across the voxels of the hippocampus. Local heterogeneity regression (Local-Hreg; Purcell & Rapp, 2018) is a relatively recent method that, similar to RSA, allows researchers to investigate the neural similarities (or differences) in response to our contrasts of interest across the voxels of the hippocampus independently of mean activation. However, whereas RSA calculates the mean activation in each voxel and then looks at cross-voxel patterns, Local-Hreg keeps the time series intact by first calculating the similarity of each voxel with its neighbors and then using these values for each voxel (Purcell & Rapp, 2018). In this way, Local-Hreg can assess the degree of learning/differentiation in local neural representations, with the idea that well-learned representations (e.g., Targets) may show greater differentiation than less well-learned representations (e.g., Lures and Foils). Therefore, our immediate next step will be to employ the lure-similarity approach described above in order to assess pattern separation processes without being constrained to repetition sensitivity. After this step, we will utilize a multivariate approach in order to assess the heterogeneity in how Targets, Lures, and Foils are being represented in both anterior and posterior hippocampus. This will allow us to better understand the role of the hippocampus in pattern separation processes than the univariate approach taken in the current study.

Finally, our ultimate goal in developing this fMRI MST paradigm is to investigate whether children show differential hippocampal activation for Targets,

Lures, and Foils as well as different relations between magnitude of neural activation and behavioral performance outside of the scanner when compared to an adult sample. Therefore, one future direction will be to recruit a sample of 3-4-year-old children. Additionally, we will be interested to apply the multivariate approaches outlined in our next steps in the adult sample above to the child sample as well. Such findings will help elucidate the neural mechanisms underlying pattern separation development in early childhood.

Conclusions

The current study provides some preliminary evidence of pattern separation processes in posterior hippocampus and relations to a behavioral index of pattern separation using a novel, block design, passive retrieval task. These findings are important in understanding how functional characteristics of the hippocampus underly the development of pattern separation processes, which are essential for recollection of episodic memories. Additionally, the development of this child-friendly fMRI task sets the stage for investigating the role of functional maturation of the hippocampus in the development/improvement of mnemonic discrimination in children through pattern separation processes.

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