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Memory-related hippocampal activation during sleep and temporal memory in toddlers

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ABSTRACT

Nonhuman research has implicated developmental processes within the hippocampus in the emergence and early development of episodic memory, but research in humans has been constrained by the difficulty of examining hippocampal function during early development. In the present study, we assessed 48 2-year-olds with a novel paradigm in which participants completed two games on a tablet that required remembering associations between unique characters, the places they visited, and the temporal order with which they did so. At the completion of each game, a unique, novel song played. Toddlers remembered spatial locations better than temporal order during an immediate test, after a 20-minute delay, and after a week delay. After the last behavioral session, toddlers underwent an fMRI task during natural nocturnal sleep evaluating hippocampal activation in response to learned and novel songs. We found that the extent of hippocampal activation for learned songs compared to novel songs during sleep was correlated with memory for temporal order across all time delays, but not with memory for spatial locations. The results confirm that the functional contribution of the hippocampus to early memory can be assessed during sleep and suggest that assessment of temporal aspects of memory in the current task best capture this contribution.

1. Introduction

Episodic memory, or the ability to remember past events in rich detail, requires that individuals retain information about the spatio-temporal context in which those events occurred (Tulving, 2002). This ability first emerges in infancy, but undergoes substantial improvement throughout the second and third years of life (Bauer, 2005; Bauer et al., 2000).

The hippocampus is critical for forming and retrieving episodic memories (Eichenbaum et al., 2007; Eichenbaum and Cohen, 2001), and developmental processes within this structure have been hypothesized to be responsible for behavioral changes in memory functioning during infancy and early childhood (Bauer, 2008; Gomez and Edgin, 2016; Lavenex and Banta Lavenex, 2013; Mullally and Maguire, 2014). For example, it has been argued based on non-human evidence that the full integration of the dentate gyrus and CA3 subfields within the hippocampal circuitry may promote the ability to form distinct memory representations that can be distinguished from those generated by similar events (Keresztes et al., 2018) and can be reinstated flexibly (Newcombe

et al., 2014). The timing of these developmental processes might coincide with sizeable volumetric increases in the hippocampus observed during the first few years of human life (Gilmore et al., 2012). To date, however, the examination of functional changes in young children has largely eluded research.

The function of the hippocampus has been primarily investigated with task-related functional Magnetic Resonance Imaging (fMRI), which is notoriously difficult to use with infants and toddlers. A previous study attempted to overcome these challenges by collecting task-related fMRI data during natural nocturnal sleep (Prabhakar et al., 2018). Specifically, Prabhakar and colleagues tagged a laboratory experience with a song, a stimulus that could be delivered through headphones during sleep. Presentation of auditory stimuli associated with past experiences during sleep has been shown to activate the network of brain regions involved in episodic memories (van Dongen et al., 2012) and studies of sleeping infants have confirmed processing of sensory properties of auditory stimuli during sleep (Dehaene-Lambertz et al., 2002), suggesting that memory-related activation would be observable in toddlers.

Consistent with this possibility, Prabhakar et al. (2018) found that

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hippocampal activation for a previously heard song was correlated with memory for the room in which the song had been heard; the association was even stronger when the memory measure additionally reflected whether toddlers remembered which of two puppets they experienced with the song and the room. These results indicate that the hippocampus can be reactivated in toddlers during sleep, that this activation may capture aspects of past episodic experiences and, for this reason, is associated with behavioral measures of recall. Several questions remain unanswered, however. First, in Prabhakar et al. (2018), songs were presented as background music in laboratory rooms, likely tagging overall contextual representations and not discrete aspects of the experience. Second, memory was assessed only with two questions at the end of a learning experience lasting 3 weeks and after an interval of several minutes from the last exposure. Therefore, it was difficult to fully evaluate memory retention and its associations with hippocampal function. The present study begins to address these limitations by promoting memory associations between songs and specific events including spatio-temporal information, and includes multiple assessment occasions, including immediate memory, 20-minute delay, and a 1-week delay.

1.1. Memory for spatio-temporal information in toddlers

Infants demonstrate remarkable memory abilities, including memory for the spatial and temporal context of past events. Memory for the association between events and their spatial context has been examined primarily with paradigms in which toddlers' memory is inferred from their searches for hidden objects. For example, Newcombe et al. (2014) asked toddlers to find two toys, each hidden in one of four boxes in two separate rooms. The same boxes were used in the two rooms, and the task required toddlers to recall the correct toy-box-room association. The authors found that 21- and 26-month-old toddlers could remember the correct box that was used to hide a toy in each of the two rooms, but only when the experimenters cued their memory for the box with a part of the hidden toy. Younger toddlers (15- to 20-month-olds) could remember which boxes were used in either room, but not the association with room context, and older toddlers (34-months and older) could recall the entire toy-box-room association correctly. Prior work has shown that retrieval support in the form of context clues or unique physical markings helps young children's spatial search abilities. Further evidence comes from Prabhakar et al.'s (2018) study wherein toddlers' hippocampal activation in response to a learned song was correlated with their memory for the specific room in which they had previously heard the song. Beginning around 25 months, toddlers develop the ability to recall objects or events with increasing specificity and without support (Ribordy et al., 2013). Overall, these studies suggest that the ability to recall spatial features can be observed early in the second year of life, but continues to improve throughout the third year. Based on Prabhakar et al. (2018) and other analyses of non-human animals (Lavenex and Banta Lavenex, 2013), these improvements may be supported by hippocampal development.

An episodic representation also includes retention of temporal information. A wealth of work using imitation paradigms demonstrates that infants retain temporal aspects of their experiences (e.g., Bauer and Leventon, 2013). However, the sequences of actions used with young infants were typically functionally enabling, such that an early step was required for the next step to be possible, which may have provided strong retrieval cues. Clear evidence of long-term retention of arbitrarily ordered, non-enabling actions was found in 28-month-olds who reproduced the sequences after a delay (Bauer et al., 1998).

Overall, these results suggest that the ability to retain arbitrary relations between events and their spatio-temporal context is reliable during the third year of life. However, very few studies have examined retention of spatio-temporal information within the same paradigm, limiting our ability to directly compare memory for these types of information in early childhood. Studies conducted with preschoolers

(Ribordy Lambert et al., 2016) and older children (Lee et al., 2016; Picard et al., 2012) have suggested that memory for temporal order may lag behind that of memory for spatial location, despite the development of both being linked to changes in hippocampal structure (e.g., Lee et al., 2020). We examined memory for spatial and temporal features within the same paradigm and predict that toddlers might retain memory for the former better than the latter.

1.2. Memory retention

Infants and toddlers forget event details at a faster rate than their older counterparts (e.g., Bauer, 2005). For example, Bauer (2005) matched groups of 16- and 20-month-olds for immediate memory and showed that 16-month-olds forgot more information than 20-month-olds after 1-month and 6-month delays. Moreover, 22-month-olds could imitate sequences of arbitrary actions immediately, but not after a delay; only at 28-months could infants do so both immediately and after a two-week delay (Bauer et al., 1998). Overall, time delays result in significant information loss in infants and young children. In this study, we asked whether the predicted difference between retention of spatial and temporal features persisted across delays or whether memory for temporal information is lost at a faster rate.

1.3. Study overview

The goal of the present study was to examine the association between hippocampal function and memory for specific events, including spatio-temporal information, and whether this association differed as a function of type of information and persisted across multiple testing intervals. We taught a sample of 2-year-olds to play games which required them to remember where and in what order to place 3 characters. The completion of the game activated a novel song. Toddlers' memory for the game was tested immediately after learning, after a 20-minute delay, and after 1-week delay.

We expected that toddlers would remember better the unique locations visited by each character compared to the order with which the characters were moved. In addition, we predicted that memory would decline as a function of time delay. However, we also considered the alternative hypothesis that memory declines would be limited due to repeated opportunities to learn the game prior to the delay; this procedural choice was motivated by our interest in ensuring that there would be sufficient retention by the time toddlers participated in the fMRI session.

Our fMRI paradigm took place during natural nocturnal sleep after the completion of the behavioral sessions. It included one of the learned songs, one reversed song (which was either the same learned song played backward, or the other learned song played backward). The reversed song was included so as to examine whether associations between memory performance and hippocampal activation depended on the presentation of the exact song or whether pitch, tone, timber, tempo, of the song without the exact melody were sufficient to reactivate the memory. We expected that behavioral performance would be generally associated with hippocampal activation in response to the learned songs, especially the songs played as they were learned (i.e., forward). Based on Prabhakar et al. (2018), associations were expected to be stronger in the right hippocampus compared to the left hippocampus.

Although the current study focuses on hippocampal activation because the literature has largely focused on changes in this structure to explain early memory development (e.g. Bauer, 2008; Gomez and Edgin, 2016; Lavenex and Banta Lavenex, 2013; Mullally and Maguire, 2014), we recognize that episodic memory emerges from the additional contribution of a network of cortical regions, including the parahippocampal and angular gyri (e.g., Moscovitch et al., 2016; Ranganath and Ritchey, 2012). Thus, we explored whether the predicted associations between memory and activation extended to these cortical regions associated with episodic retrieval.

2. Methods

2.1. Participants

A total sample of 87 2-year-old toddlers participated. Neuroimaging data were collected from 48 of them ($M = 28.36$ months; $SD = 22$ months, $range = 25.22$ – 32.15 months; 20 males), although two of the 48 failed to provide any behavioral measures of memory. The other 39 toddlers provided behavioral data but did not provide neuroimaging data because they were either unable to fall asleep ($n = 32$), stay asleep ($n = 6$) during fMRI data collection, or there was an error during fMRI acquisition ($n = 1$).

2.2. Procedure

Our procedure included three laboratory visits which were, on average, one week apart ($M = 5.92$ days, $SD = 3.03$ days). In addition, there was a nighttime visit to the Imaging Research Center, which occurred as soon as possible after the second session.

2.2.1. Preparatory session

An initial session was held to acquaint the participant with the experimenters, obtain consent, and prepare families for the neuroimaging aspect of the study. After consent, parents or guardians completed questionnaires about their child's demographics, verbal ability via the MacArthur-Bates Communicative Development Inventories (Fenson et al., 2007), temperament via the Early Child Behavior Questionnaire (ECBQ; Putnam et al., 2006), and an in house questionnaire designed to assess toddlers' sleep habits for use during collection of neuroimaging data. Sleep habits included whether children primarily slept on their backs, were sensitive to noise while sleeping, and slept through the night; each of these questions was scored as either 0 for no, 1 for yes, 0.5 for sometimes. While parents completed these assessments, experimenters played with their toddlers. In preparation for the neuroimaging session, parents were sent home with a practice kit that consisted of earplugs and headphones, as well as information about the online location of audio files of sample scanner sounds. Parents were instructed to insert the earplugs and have children wear headphones while listening to the scanner sounds for approximately 1 h at the beginning of each night for at least 1 week before the scanning session. This allowed parents and toddlers to become familiar with the MR environment. Experimenters were in frequent contact with parents during this time to assess their child's comfort and preparation for the actual scanning procedure.

2.2.2. Behavioral session 1

During Session 1, participants were exposed to two songs. Three songs were created for use in this study and were counterbalanced across participants and conditions. We used 20-second clips that included unique rhythms, tempos, and keys with vocalizations consistent with English phonotactics (e.g., Bodu). Two of the songs were each uniquely associated with the completion of one of two versions of the **Tablet Song Game**. The third song was used as novel song in the fMRI paradigm. Each game version was played in a consistent laboratory room for all sessions. Characters, locations and order were always the same in each of the games across time intervals. A unique puppet animal accompanied the toddler and experimenter throughout the room in order to keep the toddler engaged. Thus, toddlers met a total of two puppets (e.g., an elephant and a lion), which were identified by name. Game versions and room order were counterbalanced across participants but were consistent across sessions for each individual participant.

The **Tablet Song Game** (adapted from Prabhakar and Ghetti, 2020) involved turning on a song by inputting a sequence of actions on a touchscreen tablet by placing characters in locations where they belonged. The game started with a screen showing 3 characters (e.g. Astronaut, Doctor, etc.) and 3 arbitrary locations (e.g., School, Slide,

etc.; Fig. 1a). Toddlers were shown that each of the three characters ought to be placed in one of the three locations in a certain order (Fig. 1b), resulting in the final display (Fig. 1c). Although characters and locations were meaningful, the verbal labels for the locations were not used, and they were indicated to the participants in vague terms (e.g., "First, she goes there, then he goes there, last she goes there") to reduce the possibility of facilitating toddlers with better vocabulary skills. Once the sequence was completed accurately, a novel song played, and a new character appeared to dance on the screen (see Fig. 1d). During the first demonstration, toddlers were instructed to "help turn on "Puppet's name" song." The experimenter then performed the matching procedure slowly, indicating the characters' chosen order using order signifiers (i. e., first, next, last) and verbally acknowledging their locations (e.g., here, there, etc.). When the song began to play, experimenters said "And that's how you turn on the song! Now it's your turn." Accuracy for spatial location was calculated as the number of correctly placed characters out of three. More than one character could be placed in the same location, which toddlers did occasionally (26 % of total trials across all participants and testing times). Thus, chance performance for the spatial details was 0.33 (i.e., calculated as the average of 0.33 chance of being correct in 3 trials, each associated with the same chance level). Accuracy for temporal order was calculated as the number of characters chosen in the correct order. For temporal order, chance performance levels also amounted to 0.33, but for different reasons. Determination of chance accounts for dependency in temporal order trials and the fact that chance levels depend on which choice toddlers make. If toddlers select the first character correctly, then chance for them was 0.415 (i.e., the mean of 1/3 and 1/2). If toddlers first wrongly selected the second character, then their second choice could never be correct and chance can be calculated as 0.167 (i.e., the mean of 1/3 and 0). Finally, if toddlers wrongly select the third character at start, then the second choice can still be correct and chance corresponds to 0.415 (i.e., the mean of 1/3 and 1/2). Overall the average chance level across participants is the average of 0.415, 0.167, and 0.415, which corresponds to the average expected value (i.e., 0.33).

In each room, toddlers were first shown the procedure of the **Tablet Song Game**. As soon as the experimenter completed the sequence, the song specific to that room played for 30 s. Then, toddlers were asked to imitate the experimenter and recreate the sequence to play the song (practice trial). Regardless of the toddlers' success at reproducing the correct sequence, the experimenter showed the sequence again resulting in the song playing. At this point, toddlers' initial memory was tested (Immediate Test) to assess whether they could correctly position the characters in their location and whether they moved them in the correct temporal order.

Based on extensive piloting that suggested difficulty with retention of temporal order, we decided that placing the characters in the correct location was sufficient to trigger the song to play in an attempt to increase the probability that toddlers would cause the song to play on their own and maintain motivation. In other words, if toddlers made incorrect spatial placements, but selected the characters in the correct order, the song would not play. However, this happened in only 5.4% of trials over the total number of trials across time interval and room. We elected not to give corrective feedback following mistakes so as to not discourage toddlers and make the task more demanding. Instead, we gave multiple opportunities to learn through the experimenter's demonstrations. We elected not to let the song play regardless of performance level, because we told the toddlers that the song would be triggered by performing well.

Participants and experimenters completed the game together before ending the task, in order to strengthen their memory for the game. The song continued to play throughout the remainder of the session in a given room, while toddlers engaged in other activities, and then toddlers reengaged with the song when they were asked to play the **Tablet Song Game** again (20-Minute Delay). After attempting to recall, all toddlers were shown how to play the game again regardless of their success to

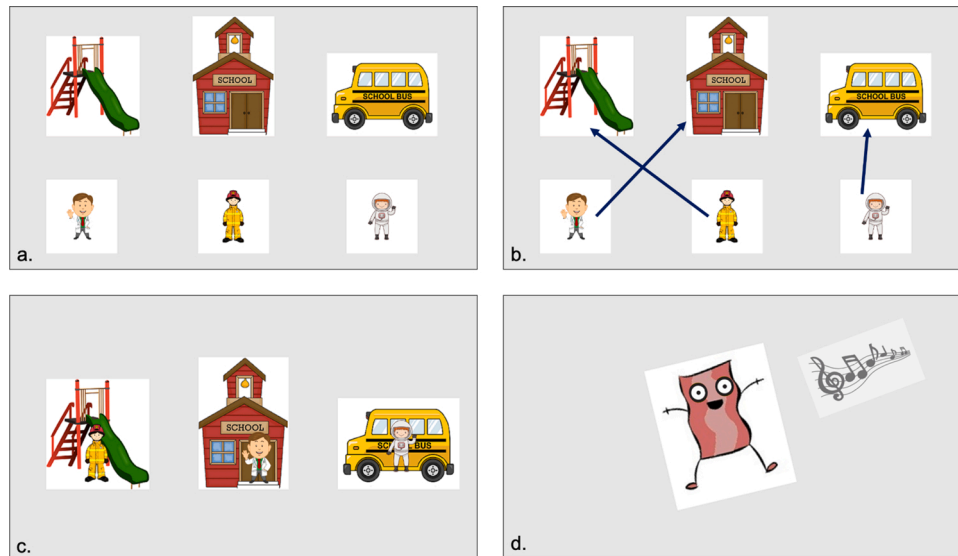


Fig. 1. Character-location matching tablet game. In each of the two rooms at both sessions, the Tablet Song Game began with two rows of arbitrary characters and locations. Toddlers were shown that the characters on the bottom row moved to specific locations (a-c) in the top row in a specific temporal order. If the characters were properly matched to their spatial locations (regardless of temporal order) a unique character (d) appeared to dance to a novel song.

ensure equal exposure to the song.

Each time the song started playing, the experimenter demonstrated a simple dance action (e.g., shake your head; reach for the sky). We reasoned that this procedure would facilitate further attention to the song. Immediately after finishing the games in the first room, toddlers moved to the second room, where the other version of the game was played with a different song.

2.2.3. Behavioral session 2

During this session approximately one week after *Behavioral Session 1*, the toddlers returned to the lab and were asked to demonstrate how to play the **Tablet Song Game** (One –Week Delay). Although entering the same room where the sequence was previously learned may have cued toddlers’ memories, no reminder demonstration or practice sequence was given to toddlers before completing the one-week delay test. After completing the one-week delay test, participants viewed the experimenter playing the game correctly once and, finally, participants and experimenters completed the game together again to ensure exposure to the song regardless of performance and to promote retention prior to the nighttime neuroimaging session (Fig. 2).

2.3. Nocturnal neuroimaging session

Toddlers underwent their neuroimaging session during natural nocturnal sleep within 3 days after the second laboratory visit ($M = 1.80$ days, $SD = 2.88$ days). During the night visit, families arrived between 7 PM and 10 PM depending on their toddler’s typical sleeping schedule and the session lasted approximately 2 h. The scanner bed was outfitted with a memory foam mattress pad and pillows, as well as several

blankets and stuffed animals for the child’s comfort. Parents could bring comfort items for their child, which were properly screened for safety ahead of time. Earplugs and headphones were placed on the toddlers for sound protection and auditory stimulus delivery, approximately 10–15 min after they had fallen asleep on the scanner bed. We confirmed children were asleep if they had been lying on their back with earplugs and headphones on the scanner bed and had not moved for 10 min. At this point, the parent and experimenter attempted to move the child’s arm to determine whether they would wake up with the movement. If the child continued to sleep through this disruption, the scan proceeded. Using this procedure, the scan generally began at least 30 min after sleep onset and was completed within the first 50 min after sleep onset (1 typical infant sleep cycle) to increase the chances that children were in slow-wave sleep during the functional scans (e.g., Anders and Taylor, 1994; Mitra et al., 2017). Although the examination of the effects of slow-wave sleep falls beyond the scope of the current research, we sought to maximize our chances of observing reliable hippocampal activation, given previous studies identifying memory reactivation during slow-wave sleep (Rudoy et al., 2009; van Dongen et al., 2012). A parent and a researcher were present inside the scanner room within arm’s reach of the child for the duration of the scan. Lights in the back of the scanner allowed the parent and experimenter to have full view of the child’s face and body, and monitor for signs of waking up (e.g., any body, face, or eye movements). When the child showed such signs, it was determined that the child was waking, and the experimenter stopped the scan.

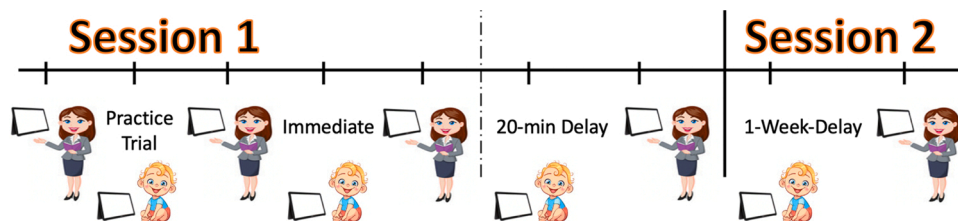


Fig. 2. Sequence of Events in Tablet Matching Game. Toddlers’ memory was assessed across two sessions with an Immediate test, a 20-Minute-Delay test, and One –Week-Delay Test.

2.4. fMRI acquisition and design

Images were acquired via a 3T Siemens TIM Trio MRI System at the University of California, Davis, Imaging Research Center using a 32-channel coil. Functional images were acquired using a gradient echo-planar imaging pulse sequence [repetition time (TR), 1500 ms; echo time (TE), 24 ms; field of view (FOV), 216 mm; number of slices, 46; voxel size, 3 mm isotropic; 250 volumes acquired]. During the functional scan, children heard three 20-second blocks of three different stimuli: one of the songs heard during the laboratory visits (Target), a song novel to the child (Novel), and either the target song or the other song presented in the laboratory sessions played in reverse (Reverse). Approximately half of the participants were exposed to the reversed version of the target song (R_T) while the other half were exposed to the reversed version of the non-target song (R_{NT}). Twenty-second blocks of silence separated the song blocks. In total, there were nine song blocks, three blocks of Target, Reverse, and Novel respectively, interspersed by silence, with each 20-second song block modeled as a distinct Target, Reverse, or Novel event block. We used a randomized sequence to present the order of Target, Reverse, and Novel blocks for the remaining eight blocks for each participant. This functional protocol lasted 6:23 min. A T1-weighted high-resolution magnetization-prepared rapid-acquisition gradient echo (MPRAGE) scan in the sagittal plane was also obtained (TR, 2500 ms; TE, 3.23 ms; FOV, 226 mm; voxel size, 0.70 mm isotropic) prior to the functional scan (7:08 min). Overall, with the localizers (00:22 min), the complete scanning protocol took 13:53 min to complete.

2.5. fMRI data processing and analysis

Data were preprocessed and analyzed using FEAT in FSL5.0.8. (<https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/>). Preprocessing included slice timing and motion correction. FSL's motion outliers function (<https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLMotionOutliers>) identified motion outliers greater than 0.9 mm by measuring relative intensity differences and defining outliers using the upper threshold for creating boxplots. We excluded scans with more than 20 % of the volumes with motion outliers as defined by this function. This resulted in 2 scans being excluded for excessive motion because of an average of 30 % volumes affected in these participants. A total of 227 volumes were rejected across 23 participants (average = 9.87 volumes per participant, range = 1–41 volumes) and they were corrected by including a confound matrix of outliers in the general linear model. The sample included in these analyses showed an average relative framewise displacement of 0.16 mm ($SD = 0.12$ mm, range = 0.04–0.64 mm) and an average absolute displacement of 0.39 mm ($SD = 0.70$ mm, range = 0.07–1.48 mm).

Functional and structural data were all registered to a standard toddler template created by the University of North Carolina (26) from a sample of 95 toddlers ($M = 33.65$ months) (bric.unc.edu/ideagroup/free-software/). Each registration was visually inspected by investigators to ensure it was successful. We confirmed visually that all were successfully registered to the template.

General linear models were conducted using FEAT in FSL to model Target, Novel, and Reverse song types during the time series and were convolved with a double-gamma hemodynamic response function to yield two main contrasts of interests (e.g., Target > Novel and Reversed > Novel) to examine whether increased activation for the exact reproduction of the song or a changed representation via reversing was associated with memory. Our hypotheses centered on hippocampal function, and thus we focused our analyses to the right and left hippocampal masks, which were obtained from parcellation maps provided by the University of North Carolina 2-year-old template (right: 5538 voxels, 50 % probability; left: 5785 voxels, 50 % probability; see Fig. 3a). Parameter estimates were extracted from these structurally defined hippocampal masks. We also investigated activation in the left and right parahippocampal gyrus (right: 8542 voxels, 50 % probability; left: 7585 voxels, 50 % probability; see Fig. 3b) and angular gyrus (right: 17,988 voxels, 50 % probability; left: 12,992 voxels, 50 % probability; see Fig. 3c) obtained via parcellation maps from the University of North Carolina 2-year-old template.

3. Results

3.1. Behavioral results

We first conducted preliminary analyses to examine whether there were any differences between toddlers who successfully completed the neuroimaging sessions and those who did not in terms of background variables (e.g., age, language, temperament, etc.) and memory performance. Results showed that there were no significant differences between those scanned and not scanned in age, inhibition, attention shifting, attention focusing, vocabulary, sleep behavior, temporal memory, or spatial memory (see Table 1).

We then conducted a 2 (Information type: Spatial or Temporal) X 3 (Test occasion: Immediate, 20-minutes, 1-week) within-subjects ANOVA investigating memory accuracy. This ANOVA revealed a significant effect of information type ($F(1, 40) = 5.33, p = .03, \eta_p^2 = .02$), such that memory for the spatial location the characters visited was significantly higher ($M = 0.53, SD = 0.28$) than memory for the temporal order with which characters were moved ($M = 0.46, SD = 0.31$). There was no significant main effect of test occasion (immediate, $M = 0.48, SD = 0.32$; 20-minute interval, $M = 0.50, SD = 0.29$, 1-week interval, $M = 0.51, SD$

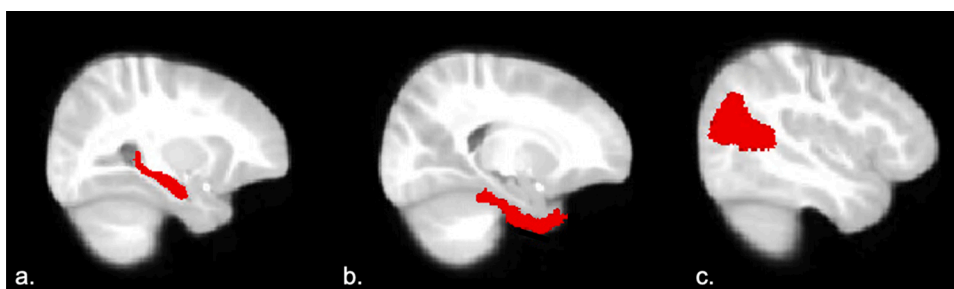


Fig. 3. Masks Utilized for Structurally defined Regions-of-Interest Analysis. **a. Right and Left Hippocampal Masks.** Group analyses were constrained to the right (5538 voxels, 50 % probability) and left (5785 voxels, 50 % probability) hippocampal masks using age-appropriate hippocampal templates from the University of North Carolina 2-year template. Shown at $X = 25, Y = -11, Z = -12$. **b. Right and Left Parahippocampal Gyrus Masks.** Right (8542 voxels, 50 % probability) and left (7585 voxels, 50 % probability) parahippocampal gyrus masks taken from University of North Carolina 2-year template. Shown at $X = 18, Y = -9, Z = -31$. **c. Right and Left Angular Gyrus Masks.** Right (17,988 voxels, 50 % probability) and left (12,992 voxels, 50 % probability) angular gyrus masks taken from University of North Carolina 2-year template. Shown at $X = 38, Y = -55, Z = 15$.

Table 1
Comparison of toddlers who completed the fMRI session and toddlers who, for various reasons, did not complete the fMRI session.

	Scanned <i>n</i> = 48	Non Scanned <i>n</i> = 39	
Age	<i>M</i> = 28.42; <i>SD</i> = 1.99	<i>M</i> = 28.02; <i>SD</i> = 2.25	<i>t</i> (83) = -0.70, <i>p</i> = .49
Sex	21 male; 27 female	16 male; 23 female	
ECBQ Inhibition	<i>M</i> = 3.06; <i>SD</i> = 0.66	<i>M</i> = 2.82; <i>SD</i> = 0.82	<i>t</i> (74) = -1.42, <i>p</i> = .16
ECBQ Attention Shifting	<i>M</i> = 5.31; <i>SD</i> = 0.65	<i>M</i> = 5.28; <i>SD</i> = 0.67	<i>t</i> (74) = -0.20, <i>p</i> = .84
ECBQ Attention Focusing	<i>M</i> = 4.72; <i>SD</i> = 0.85	<i>M</i> = 4.84; <i>SD</i> = 0.54	<i>t</i> (75) = 0.68, <i>p</i> = .50
MacArthur Words Known	<i>M</i> = 32.9%; <i>SD</i> = 20.6%	<i>M</i> = 33.0%; <i>SD</i> = 22.2%	<i>t</i> (78) = 0.04, <i>p</i> = .97
Back Sleeping *	<i>M</i> = 0.94; <i>SD</i> = 0.29	<i>M</i> = 0.97; <i>SD</i> = 0.12	<i>t</i> (68.07) = 0.70, <i>p</i> = .49
Sleeping Through Night †	<i>M</i> = 0.85; <i>SD</i> = 0.34	<i>M</i> = 0.86; <i>SD</i> = 0.34	<i>t</i> (69.51) = 0.12, <i>p</i> = .90
Noise Sensitivity **	<i>M</i> = 0.25; <i>SD</i> = 0.41	<i>M</i> = 0.17; <i>SD</i> = 0.37	<i>t</i> (73.72) = -0.95, <i>p</i> = .34
Temporal Memory	<i>M</i> = 0.46; <i>SD</i> = 0.23	<i>M</i> = 0.44; <i>SD</i> = 0.27	<i>t</i> (74) = 0.03, <i>p</i> = .97
Spatial Memory	<i>M</i> = 0.52; <i>SD</i> = 0.23	<i>M</i> = 0.56; <i>SD</i> = 0.31	<i>t</i> (74) = 0.82, <i>p</i> = .42

* Do toddlers sleep primarily on their back? 0–1 score for no/yes responses.
 † Do toddlers sleep through the night? 0–1 score for no/yes responses.
 ** Are toddlers sensitive to noise while sleeping? 0–1 score for no/yes responses.

= 0.29; *F*(1, 80) = 0.42, *p* = .66) or trial by type interaction (*F*(1, 80) = 0.08, *p* = .92; Fig. 4).

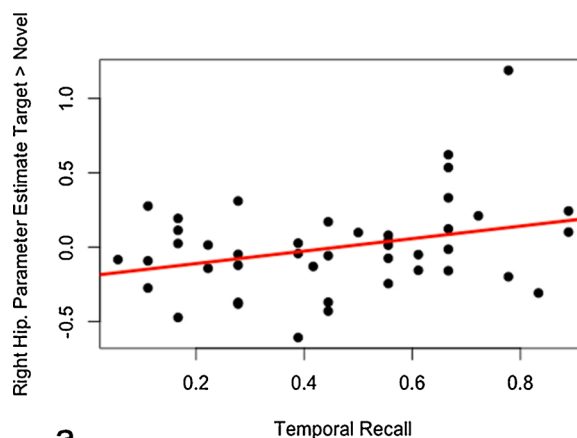
Participants were significantly above chance (0.33) on all spatial (*t*s(42) ≤ 5.07, *p* < .001) and temporal trials (*t*s(42) ≤ 3.01, *p* ≤ .002). There were no differences between first and second room performance for either spatial memory (*t*s(41) ≤ -0.72, *p* = .47) or temporal memory (*t*s(41) ≤ 0.68, *p* = .50) in any of the intervals.

3.2. fMRI results

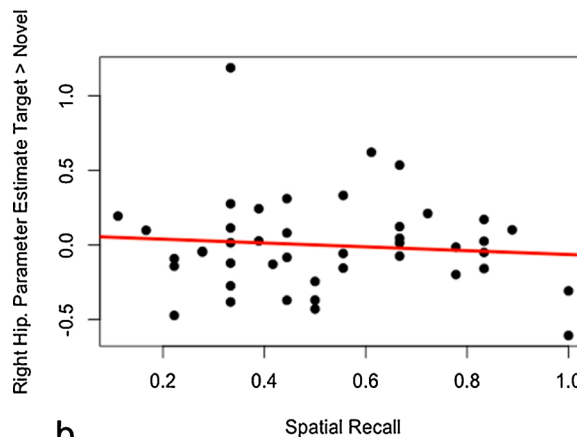
Given that the behavioral results indicated no performance difference as a function of testing occasion, and in order to accurately capture memory ability as a whole, we calculated the average memory performance across all testing occasions separately for spatial and temporal memory and correlated these averages with hippocampal activation. We found a significant correlation between activation for the Target compared to Novel (Target > Novel) contrast in the right hippocampus

for temporal order memory (*r*(41) = 0.31, *p* = .04; Fig. 5a). However, we did not find a correlation between activation in this contrast and spatial location (*r*(41) = -0.095, *p* = .55; Fig. 5b). The difference between these two correlations was significant (Steiger’s *z* = 2.88, *p* = .004).

Additionally, when we correlated activation in the Reversed > Novel



a.



b.

Fig. 5. a) Association between activation in the right hippocampus and memory for temporal order (*r*(41) = 0.31, *p* < .05). b) Association between activation in the right hippocampus and memory for spatial location (*r*(41) = -0.09, *p* = .54).

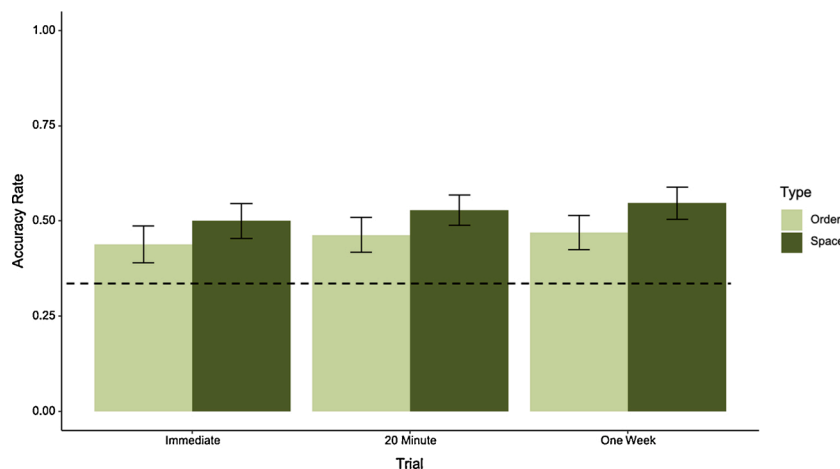


Fig. 4. Behavioral Performance Results from ANOVA on behavioral data. Toddlers performed better on the spatial aspect of the task than the temporal aspect. Chance level is marked at 0.33.

contrast in the right hippocampus, we found the same pattern of results, such that there was a significant correlation with memory for temporal order ($r(41) = 0.43, p = .004$), but not for spatial location ($r(41) = 0.01, p = .94$). The difference between these two correlations was also significant (Steiger's $z = 2.43, p = .015$).

In the left hippocampus, the correlation between the Target > Novel contrast and temporal memory was not statistically significant ($r(41) = 0.22, p = .16$), and it was smaller than that in the right hippocampus (Steiger's $z = 1.66, p = .04$ one-tailed). In contrast, we found a significant correlation between temporal memory and Reversed > Novel contrast activation ($r(41) = 0.36, p = .02$), which was not significantly greater than that found in the right hippocampus (Steiger's $z = 1.26, p = .10$). As in the right hippocampus, no significant association was found for spatial memory in the left hippocampus for either the Target > Novel contrast ($r(41) = -0.12, p = .44$) or the Reversed > Novel contrast ($r(41) = 0.09, p = .59$).

Finally, we conducted exploratory analyses in two additional cortical regions that are consistently found to be active during episodic retrieval, the parahippocampal gyrus and the angular gyrus. We found that memory for temporal order was significantly associated with activation in the right parahippocampal gyrus ($r(41) = 0.35, p = .02$) and right angular gyrus ($r(41) = 0.33, p = .03$) for the Target > Novel contrast. This was not the case for spatial memory (right parahippocampal: $r(41) = -0.17, p = .29$; right angular gyrus: $r(41) = 0.08, p = .60$). Correlations with memory for temporal order and Target > Novel activation were marginal in both the left parahippocampal gyrus ($r(41) = 0.30, p = .051$) and left angular gyrus ($r(41) = 0.29, p = .06$); spatial memory was not significantly correlated with activation in the left parahippocampal gyrus ($r(41) = -0.15, p = .34$) or left angular gyrus ($r(41) = 0.07, p = .67$). In the Reversed > Novel contrast, bilateral activation in the angular gyrus was significantly correlated with temporal memory (right: $r(41) = 0.35, p = .02$; left: $r(41) = 0.31, p = .04$), but not activation in the parahippocampal gyrus (right: $r(41) = 0.23, p = .14$; left: $r(41) = 0.13, p = .41$). No aspect of spatial memory was correlated with Reversed > Novel contrast activation in the parahippocampal gyrus (right: $r(41) = -0.02, p = .91$; left: $r(41) = -0.05, p = .75$) or angular gyrus (right: $r(41) = -0.00, p = .96$; left: $r(41) = 0.002, p = .99$).

4. Discussion

The present study was designed to examine the association between memory for spatio-temporal information and hippocampal function in toddlers. In a previous study, hippocampal activation for a song was correlated with memory for aspects of an event that occurred while the song was playing (Prabhakar et al., 2018). The present study was designed to extend these previous findings in two ways. First, we were interested in establishing whether songs could be used to tag specific aspects of a past episode, as opposed to capturing the broader context as was the case in Prabhakar et al. (2018). For this reason, we tested toddlers' memory for specific spatio-temporal features of a discrete event associated with a unique song. Second, memory assessments occurred at multiple time points including immediate memory, 20-minute delay, and a 1-week delay. Previous methods for assessing memory in this age group have not systematically examined retention of spatial and temporal features of an event within the same paradigm. The Tablet Song Game begins to overcome this limitation, while additionally forming associations with novel songs.

We first determined that toddlers' memory for spatial features was significantly better than their memory for temporal features, regardless of time delay. We cannot exclude the possibility that reinforcement of spatial locations, but not temporal order, with the song may have preferentially supported spatial recall. However, toddlers played the game by placing the characters in a spatial location in a certain order. Therefore, they could not have known that it was spatial location alone that triggered the song. Furthermore, the full spatio-temporal sequence was shown again after toddlers completed their attempt regardless of

their success. Better retention of spatial details is consistent with previous research showing clear evidence that infants notice the location of objects and retain information about it. For example, Richmond et al. (2015) demonstrated that 18- and 27-month-olds exhibited a visual preference for objects that had switched on a screen indicating that they had encoded their location. Just after their second birthday, however, toddlers experience significant difficulty at retaining unique associations between objects and their location, particularly if the locations are similar and toddlers are not provided with object cues to orient them in their search (Newcombe et al., 2014). Development during early childhood brings about the ability to remember more specific spatial associations enabling the ability to minimize interference from having learned associations between objects and similar locations (e.g., Newcombe et al., 2014; Ribordy Lambert et al., 2016).

Previous research has also demonstrated that infants and young children retain information about temporal aspects of their experiences. Even young infants demonstrate tracking of temporal order rules in statistical learning paradigms (Tummeltshammer et al., 2017), and utilize temporal order information to track object locations presented on a screen (Kirkham et al., 2007). Moreover, in the domain of declarative memory, infants have demonstrated retention of temporal information with their imitation behavior and, although abilities to retain ordered actions are detected at the end of the first year (e.g., Carver and Bauer, 2001), the utilization of enabling actions in these young infants suggest that memory for temporal order requires substantial cueing and scaffolding. Development into the third year affords more independent recall of ordered actions of arbitrary, not enabling actions (Bauer et al., 1998).

Despite these remarkable abilities and early development, these studies have not compared memory for spatial and temporal features within the same paradigm, raising the questions of whether we might find the same advantage for memory for spatial location compared to memory for temporal order in toddlers that is found in older children (Lee et al., 2016). Our results are consistent with these earlier findings and confirm that retaining temporal order is more challenging. Nevertheless, we cannot exclude that some aspects of our paradigm may have facilitated retention of spatial locations. Locations on the screen in our tablet game were marked by meaningful images (e.g., school, doctor, etc.). Although the use of these locations was advantageous for ecological validity, it is possible that memory for the association between characters and location was facilitated by the overlap between the physical location on the screen and the meaningful place appearing in that location. The fact that similar age toddlers have been found to have a difficult time retaining arbitrary associations between co-occurring objects (as pictures of characters and pictures of locations are co-occurring; Johnson et al., 2020) suggests that physical location may be the primary reason for stronger performance.

The difference between spatial and temporal memory was retained across delays, and no decline in performance was observed. Although declines during the one week delay were expected, previous literature has consistently showed that repeated exposure and opportunity to imitate supports retention even in infancy (Bauer and Leventon, 2013). Future studies may include longer delays in order to probe the neural substrates of retention and forgetting. Our paradigm was designed to provide repeated opportunity for the toddlers to learn the association between the game and the song used to tag the experience to be delivered during sleep to probe hippocampal function. However, it could be modified to include behavioral assessments after the neuroimaging session to examine how hippocampal activation during sleep may predict long-term retention.

Our fMRI results revealed that toddlers' ability to recall the temporal, but not spatial, features of the game was significantly correlated with hippocampal activation in the right hippocampus. This supports the claim that songs can be successfully used, not only to tag the context of children's experiences (Prabhakar et al., 2018), but also more specific events or features of events, underscoring that this experimental

approach can be used to probe various aspects of children's memories. Moreover, not only was memory for temporal features associated with activation in the right hippocampus for the target song presented in the identical form as during study, but also when it was played backward. When played backward, the correlation with performance was significant bilaterally. In Prabhakar et al. (2018), only the correlation between behavioral performance and activation for Target > Novel was statistically significant; the correlation with Reversed > Novel was in the same direction but not reliable, leaving open the question of whether the song ought to be presented in its exact form in order to reactivate aspects of the original memory. The current findings provide evidence that hippocampal activation can also be triggered by the highly similar reversed song, suggesting some degree of flexibility in memory reactivation and, possibly, retrieval. Nevertheless, we recognize that the level of similarity is high between target and reversed songs given that the elements of the original song (e.g., pitch, tone, timber, tempo, etc.) are maintained in the reversed versions of the songs and only the song's melody differs. Future research should confirm whether bilateral hippocampal recruitment is more likely under increased flexibility demands. Finally, given the presence of a song heard exactly as it was previously heard in our fMRI task, additional research should investigate whether reinstatement of a memory must first occur exactly as it was previously experienced in younger infants before it can be reinstated flexibly.

It is not clear why only memory for temporal order was associated with hippocampal activation in this study. Associations with retrieval of spatial features of episodic memory have been reported previously in fMRI studies with adults (Burgess et al., 2002; Moscovitch et al., 2005) and children (DeMaster et al., 2013), and were hypothesized in toddlers (Sluzenski et al., 2004). It is possible that the high level of performance obtained here, matched with restricted range and given that only two games were played, reduced the chances to identify associations. The association with temporal order is interesting in its own right for at least two reasons. First, temporal order in imitation paradigms with infants and young children has been long considered a signature of an emerging episodic memory (Bauer, 2008). Second, the current results provide the first evidence of a link between the hippocampus and temporal memory in very young children, as it has been hypothesized for years (Bauer, 2005, 2008; Pathman and Bauer, 2012).

We had predicted that activations would be stronger in the right compared to the left hippocampus, based on previous findings by Prabhakar et al. (2018) and knowledge that changes in hippocampal structure may occur in the right hippocampus earlier than those in the left hippocampus (Uematsu et al., 2012). The stronger associations between activation of the right hippocampus and temporal memory are consistent with this prediction. On the other hand, associations between activation in both the left and right hippocampus for the song played backward and temporal memory underscores bilateral functionality. Previous research has found that the hippocampus undergoes substantial volumetric increases in the first few years of life, particularly in the second and third years (Gilmore et al., 2012; Uematsu et al., 2012). This is about the same time that episodic memory emerges, particularly spatio-temporal contextual memory (Gomez and Edgin, 2016; Mullally and Maguire, 2014). Although all of the subregions of the hippocampus are active when encoding or recalling both spatial and temporal features, the CA2 subfield may have a greater pattern of activity in response to temporal features than to spatial features (Mankin et al., 2015). These findings, coupled with knowledge from animal studies, indicate that hippocampally-dependent learning and memory emerge at timepoints consistent with the second and third years of human life (Dumas and Rudy, 2009; Raineki et al., 2010), but questions remain about the specificity of the link between temporal memory and functional lateralization of the hippocampus.

Finally, we investigated two additional cortical regions, the parahippocampal and angular gyri, which are consistently found to be associated with episodic memory retrieval (Smith et al., 2004). In these regions, we found associations with temporal memory in both the Target

> Novel and Reversed > Novel contrasts. These findings underscore that hippocampal development does not operate in isolation to support the emergence of episodic memory abilities in early childhood. Future studies ought to investigate the contribution of structural and functional connectivity of the hippocampus to cortical regions to the emergence of episodic memory.

There are several limitations in the present study. First, it is possible that children who slept easily represent a unique subgroup of participants and, therefore, it is possible that these results do not generalize to all children. However, there were no obvious differences between toddlers who did or did not successfully complete the neuroimaging session on many relevant variables, including levels of cognitive performance, language, temperament and sleeping habits. Second, our lack of electroencephalography data prevents us from linking our results to specific sleep stages. Although we did not advance any prediction that requires the examination of sleep stages, future research would benefit from this characterization. Third, the task required toddlers to attend to both spatial and temporal information; it is possible that this may have interfered with the more demanding task, if this is the case, temporal order may be underestimated in this task, even though toddlers performed above chance across tasks.

Taken together, our findings reveal new links between hippocampal function and memory for temporal order, as assessed with a unique game event. These results contribute to a nascent literature on hippocampal and cortical contributions to early memory functioning and confirm that songs can be used to tag discrete episodes.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.dcn.2020.100908>.

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