Received: 7 May 2021 | Revised: 30 June 2021 | Accepted: 24 July 2021

DOI: 10.1002/hipo.23385

RESEARCH ARTICLE

WILEY

Hippocampal subfield volumes and memory discrimination in the developing brain

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Funding information
Fondation de France, Grant/Award Number: 00070721; Fondation Mustela

Abstract

The ability to keep distinct memories of similar events is underpinned by a type of neural computation called pattern separation (PS). Children typically report coarse-grained memories narratives lacking specificity and detail. This lack of memory specificity is illustrative of an immature or impaired PS. Despite its importance for the ontogeny of memory, data regarding the maturation of PS during childhood is still scarce. PS is known to rely on the hippocampus, particularly on hippocampal subfields DG and CA3. In this study, we used a memory discrimination task, a behavioral proxy for PS, and manually segmented hippocampal subfields volumes in the hippocampal body in a cohort of 26 children aged from 5 to 12 years. We examined the association between subfields volumes and memory discrimination performance. The main results were: (1) we showed age-related differences of memory discrimination suggesting a continuous increase of memory performance during early to late childhood. (2) We evidenced distinct associations between age and the volumes of hippocampal subfield, suggesting distinct developmental trajectories. (3) We showed a relationship between memory discrimination performance and the volumes of CA3 and subiculum. Our results further confirm the role of CA3 in memory discrimination, and suggest to scrutinize more closely the role of the subiculum. Overall, we showed that hippocampal subfields contribute distinctively to PS during development.

KEYWORDS
development, episodic memory, hippocampus, pattern separation, segmentation, subfields

1 | INTRODUCTION

A key aspect of episodic memory (EM) is the formation of memory representations of events without these representations interfering with each other. This interference is more likely to occur if the represented events are highly similar. For example, two distinct but ordinary school days share a certain amount of common features. The resulting feature overlap could lead to memory interference, which would impair the quality and specificity of recall. A type of neural computation, called pattern separation (PS), was theorized decades ago as the putative mechanism by which similar representations could be discriminated in memory (Marr & Brindley, 1971); Complementary Learning Systems Theory: (Norman & O'Reilly, 2003). PS is the process by which distinct neural activation patterns that do not overlap are assigned to similar memory representations (Norman & O'Reilly, 2003; Yassa & Stark, 2011). In other words, orthogonal memory representations are created from similar inputs, reducing memory interference. Strong evidence now suggests that PS is indeed the mechanism by which similar memory representations are discriminated and that its neural substrate lies in the hippocampus, specifically hippocampal subfields dentate gyrus (DG) and *cornu Ammonis* area 3 (CA3; Bakker, Kirwan, et al., 2008; Mankin et al., 2015; Nakashiba et al., 2012; Yassa & Stark, 2011).

At the behavioral level, PS is usually assessed with the Mnemonic Similarity Task (MST; (Stark et al., 2019; Yassa, Mattfeld, et al., 2011). The MST was conceived as a behavioral proxy for PS by eliciting discrimination judgments between highly similar items. The ability to discriminate between identical and similar representations of previously presented items, memory discrimination, is thus thought to tap on PS-dependent processes. The direct involvement of DG and CA3 in memory discrimination, and by extension in PS, have been shown in humans by functional magnetic resonance imaging (fMRI) studies, as previously suggested by computational models of hippocampal function (Bakker, Kirwan, et al., 2008; Berron et al., 2016; Leutgeb et al., 2007; Myers & Scharfman, 2009; Neunuebel & Knierim, 2014; Schmidt et al., 2012); Yassa, Lacy, et al., 2011; Yassa, Mattfeld, et al., 2011). Structural magnetic resonance imaging (sMRI) studies also showed associations between in DG and CA3 volumes and memory discrimination performance (Doxey & Kirwan, 2015; Stark & Stark, 2017).

Memory narratives reported by young children are coarse-grained and lack specificity and detail; this could thus suggest that "immature" memory discrimination competence during childhood could play a key role in the ontogeny of EM (Canada et al., 2019; Ramsaran et al., 2019). Despite this, the development of PS during childhood and the relationship between PS development and hippocampal subfields maturation is poorly known. The scarcity of available data is mainly because this question emerged as an object of study only in recent years (e.g., Benear et al., 2020; Canada et al., 2019; Hassevoort et al., 2020; Keresztes et al., 2017; Ngo et al., 2018, 2019). The current study aims to contribute to our understanding of the relationship between memory discrimination and hippocampal subfields during childhood by examining the association between memory discrimination performance and the volumes of manually segmented subfields in children aged from 5 to 12 years. As the acquisition of fMRI data in young children is particularly challenging, this correlational sMRI approach is particularly suited to assess the relationship between memory competence and hippocampal subfields in children.

1.1 | Development of memory discrimination

To date, a few studies investigated the development of PS during childhood using the MST. These studies showed age-related differences in memory discrimination performance, but there are discrepancies between the suggested maturational timelines (Ngo et al., 2018; Rollins & Cloude, 2018). For example, Ngo et al. (2018) suggested an early maturation of memory discrimination, with adult-like performance reached around 6 years of age (Ngo et al., 2018), while Rollins and Cloude (2018) suggested a more protracted maturation, with age-related differences observed until 9–10 years of age. The development of PS early in life thus needs to be further investigated. An earlier or later maturation of PS would induce different interpretations regarding the relationship between the development of memory discrimination and the structural and functional maturation of its neural substrates (i.e., the hippocampal subfields).

1.2 | Maturation of hippocampal subfields

The maturation of hippocampal subfields during childhood is protracted. An initial phase of rapid maturational changes during the first 2–3 years of life (Lavenex & Banta Lavenex, 2013; Olson & Newcombe, 2013; Utsunomiya et al., 1999), is followed by a phase of more modest age-related changes (e.g., volumetric increases or decreases) which extends into adulthood (Krogsrud et al., 2014; Lee et al., 2014; Riggins et al., 2018; Tamnes et al., 2018). These age-related volumetric differences could be related to several causes, including neurogenesis, synaptogenesis, synaptic pruning, or myelination, among others (Lenroot & Giedd, 2006; Riggins et al., 2018). Importantly, age-differences in hippocampal subfields volumes during childhood and adolescence have been associated to age-differences in memory performance (e.g., Lee et al., 2014; Riggins et al., 2018; Tamnes et al., 2018), showing their functional significance.

To date, two studies have directly examined the association between differences in hippocampal subfields volumes and differences in memory discrimination performance in the developing brain. Canada et al. (2019) examined the individual contribution of hippocampal subfields' volumes to memory discrimination performance in 4–8 years old children. They showed an age-mediated association between combined DG/CA3 volume and memory discrimination, highlighting the pivotal role of these subfields in PS. However, as these two subfields were combined in a single ROI in the aforementioned study, a separate assessment of the roles of DG and CA3 is still lacking. Another study, Keresztes et al. (2017), used a multivariate approach describing the shared variance between age and all hippocampal subfields' volume in a single latent variable, which was positively correlated to memory discrimination performance in 6–14 years old children, and young adults. This suggested that hippocampal subfield maturation as a whole is related to memory discrimination performance, suggesting inter-dependency in the maturational processes of each subfield. Indeed, while most of the literature points to the privileged role of DG and CA3 in PS, there is also data suggesting the contribution of other subfields, for example, the subiculum (Potvin et al., 2009) or CA1 (Hanert et al., 2019). Therefore, more investigations are necessary to disentangle the association between hippocampal subfields and PS in the developing brain.

1.3 | Current study

Here, we aimed to contribute to the understanding of the relationship between hippocampal maturation and PS during development. We assessed memory discrimination performance as a proxy for PS and manually segmented hippocampal subfields on the MRI images of 26 children aged from 5 to 12 years old. This allowed us to examine the association between hippocampal subfields' volumes and memory discrimination performance to investigate how PS is related to hippocampal subfields in the developing brain. Our hypotheses were the following: (1) we expected to observe a positive correlation between age and memory discrimination performance. (2) We expected to

observe associations between age and hippocampal subfields volumes, with specific associations for each subfield, suggesting developmental trajectories specific to each subfield. (3) We hypothesized that differences in memory discrimination performance would be associated with differences in hippocampal subfields volumes, particularly for DG and/or CA2-3, which are known to be the main neural correlates of PS, but not necessarily restricted to them (see Keresztes et al., 2017).

2 | METHODS

2.1 | Participants

Fifty children aged from 4–12 years old (mean: 8.27 years, standard deviation: 2.3 years) participated in this study as part of a larger study on the neural correlates of EM during development. Fifty-five percent of the participants were males and 45% females. Among our 50 participants, 11 children had no or incomplete data, resulting a sample of 39 children with neuroimaging data. Data acquisition was performed under the regulations of an appropriate Ethical Committee board (CPP 2011-A00058-33).

2.2 | MRI acquisition

Imaging data were collected at the NeuroSpin research center, CEA, Gif-sur-Yvette, France. Children first followed an MRI training session on a mock scanner set in a children-friendly environment. They were told a compelling story, making them astronauts on a mission to understand the brain, taking aboard a spaceship (the scanner), and wearing a space helmet (the head coil). For the mission to succeed, children were told to try staying still as much as possible, for the scanner to take accurate pictures of their brains. Once the children were familiarized with the sonic and visual environment of the scanner, the acquisition begun. Images were acquired on a Siemens PRISMA 3T scanner (Siemens Medical Solutions, Erlangen, Germany) with a 64-channel head coil. The animation movie *Wall-E* (Pixar Animation Studios) was shown to children during the scanning sessions to bolster engagement and reduce head motion caused by intolerance to noise and sensation of boredom.

We first acquired a T1-weighted MPRAGE volume (TR = 300 ms, TE = 2.98 ms, 0.9 mm isotropic resolution, 175 slices, acceleration factor GRAPPA2). The resulting image was used to localize the hippocampus in a subsequent oblique coronal T2-weighted structural sequence, which was acquired perpendicular to the main axis of the hippocampus (interleaved TR = 3970 ms, TE = 89 ms, FOV 173 mm, 0.45 × 0.45 mm in-plane resolution, 2.1 mm through-plane resolution, 46 slices). Two T2w images were acquired for each subject and interleaved to produce the full T2w scan.

2.3 | MRI preprocessing

T1w data was corrected for B1 bias and skull-stripped, using the fsl anat pipeline (fsl.fmrib.ox.ac.uk/fsl/fslwiki/fsl_anat). Each of the two T2w sequences were 2D aligned using fsl FLIRT (3 degrees of freedom). This ensures that the images are correctly aligned on the *x* and *y*-axis (in-plane resolution), but remain at their respective through-plane location. The co-registered images were then interleaved to obtain a single T2w sequence for each participant and skull-striped. The skull-stripped T1 image was registered to the skull-stripped T2 image using freesurfer's (Zöllei et al., 2020) MRI robust register command with the following parameters: 6 degrees of freedom (rigid body alignment), normalized mutual information cost function, and no prior initialization. After visual inspection of the quality of registration, the orientation of the registered T1 image was swapped to match that of the T2 image, that is, to have an oblique orientation.

2.4 | Segmentation of hippocampal subfields

Visual inspection of T2w data prior to segmentation showed that several subjects had poor data quality due to excessive head motion. This was mainly due to the fact that the T2w sequence acquisition was performed at the end of a 45 min-long neuroimaging protocol. Thus, among the 39 subjects with neuroimaging data, 11 were excluded because of insufficient data quality to perform a reliable segmentation. Exclusion of poor data was made by experimenters with expertise in structural segmentation of hippocampal subfields, based on the careful visual inspection of each MR image. Images where identification of subfields boundaries was compromised by motion, resulting in blurred data, were thus excluded from our sample. Overall, this resulted in a final segmentation sample of 28 subjects, giving 56 data points (2 per hemisphere) for each subfield.

We manually segmented the 28 retained images using ITK-SNAP (Yushkevich et al., 2006). Only subfields inside the hippocampal body were segmented, as subfields in the hippocampal body have particularly identifiable anatomical landmarks. This ensured a reliable segmentation given our resolution (for similar approaches, see (Lee et al., 2014; Mueller et al., 2011; Neylan et al., 2010; Yushkevich et al., 2010). The anterior limit of the body was identified based on the presence of the uncal apex: the body section began one slice posterior to the uncal apex (Bernasconi et al., 2003). The posterior limit of the body was identified one slice anterior to the coronal slice at which the colliculi disappeared (Bernasconi et al., 2003).

Hippocampal subfields were then manually segmented in the hippocampal body following relevant anatomical landmarks following the protocol of Dalton et al. (2017). This protocol was chosen because of its precision and exhaustivity in terms of segmentation procedure details, because it allows to segment separately the hippocampal body from the hippocampal head and tail, and because it was conceived as a synthesis of several widely used segmentation protocols (see Dalton et al., 2017). Each subfield per slice of the hippocampal body was segmented following the methodology described by Dalton et al. (2017) in this order: DG/CA4, CA2-3, CA1, and subiculum. Table 1 shows the boundary landmarks used for manually segmenting the hippocampal subfields. As CA4 is often considered as a part of the DG (often called the hilar region), DG/CA4 will be referred to as the DG in the manuscript for simplicity.

The reliability of the obtained manual segmentations was assessed by computing an inter-rater reliability index between two independent tracers. Of the 28 subjects with usable data manually segmented by one rater (S.P.), 10 subjects have been re-segmented by another rater (D.I.) using the same segmentation protocol to assess inter-rater reliability. Each rater was blind to age, sex, and memory performance of participants. According to Bartko (1991), it has been agreed that an inter-rater reliability (as measured through Dice's index [Dice, 1949]) ≥0.7 represents good to excellent spatial agreement. For the left hippocampus, inter-rater reliability was 0.83 for CA1, 0.68 for CA2-3, 0.88 for DG, and 0.77 for subiculum. For the right hippocampus, inter-rater reliability was 0.79 for CA1, 0.67 for CA2-3, 0.84 for DG, and 0.77 for the subiculum. With mean inter-reliability of 0.79 and 0.77 for the left and right hippocampus, our results are consistent with inter-rater reliability found in previous studies (e.g., Palombo et al., 2013), and deemed satisfactory.

The obtained ROI (CA1, CA2-3, DG, and subiculum) volumes (Figure 1) were then corrected for intracranial volume (ICV) using a covariance approach (Raz et al., 2005). Correcting for ICV is necessary to account for the fact that differences in ROI volumes are related to differences in head size, as estimated by ICV. ICV was computed as the volume of a mask representing the whole brain, which was estimated by combining three brain extraction methods: Freesurfer "recon-all" (Desikan et al., 2006), ANTs "BrainExtraction" (Avants et al., 2009) with OASIS template and SPM8 (Ashburner & Friston, 2005). The brain masks resulting from these 3 methods were averaged, and manually corrected when necessary (for similar approaches, see Bender et al., 2018; Canada et al., 2019; Keresztes et al., 2017; Riggins et al., 2018). To adjust ROI volumes for ICV, we computed the slope of the linear regression between each ROI volume (including the total hippocampal body volume) and ICV (βICV) to determine the statistical relationship between ICV and ROI volume. Then, we multiplied each βICV slope by each subject's mean-centered ICV and subtracted this product from raw ROI volumes (see Schlichting et al., 2019, for a similar approach). This removes the statistical relationship between ROI volumes and ICV volume. Thus, the corrected subfields volumes were obtained as follow:

$$Volume_{\text{corrected}} = Volume_{\text{Raw}\,i} - \beta(\text{ICV}_{\text{Raw}\,i} * ICV_{\text{Mean}\,i})$$

To verify that the reported statistical effects described in this study were not the sole product of this adjustment procedure, we conducted analyses on raw volumes first and then on corrected volumes. Only the latter analyses are reported. The age-related trajectories of raw (unadjusted) volumes are presented in Figure S1.

TABLE 1 Landmarks used for segmentation of hippocampal subfields

Subfield	Location	Landmark
Cornu Ammonis 1 (CA1)	Lateral to CA2-3 and the DG	Lateral border—started at the inferior point of the dorsomedial border and drew the ventromedial border of the CA1 mask by following the VHS until we reached the center of the DG/CA4 mask. Dorsolateral border—we create a straight line as the inferior border and draw a line following the dorsolateral wall of the hippocampus until the starting point.
Cornu Ammonis 2-3 (CA2-3)	Dorsal to the DG	Lateral border with CA1—straight diagonal line from the dorsal portion of the VHS where it begins to turns ventrally to the dorsolateral corner of the superior wall of the hippocampus. Medial border—follow the anatomical limit of the superior wall in a medial direction toward the medial extent of the lateral external digitation until reached to the point where we started.
Dentate Gyrus (DG)/CA4	Center portion of the hippocampus	Ventral, lateral, and dorsal border—traced the dark line of the VHS by beginning on the lateral extent of the uncal sulcus until we reached the point above at which we started. Medial border—draw a line from the dorsal limit of the VHS to the ventral direction until we reach the point where we started.
Subiculum	Ventral portion of the hippocampus, medial to CA1	The inferior boundary of the subiculum from the parahippocampal cortex was demarcated at the nadir of the concavity in the medial wall between the collateral sulcus and hippocampus. The boundary between the CA1 and subiculum was based on the CA1 mask. Indeed, the lateral border of the subiculum is the ventromedial border of the previously created CA1 mask.

Note: These landmarks are adapted from the segmentation protocol described in Dalton et al. (2017).

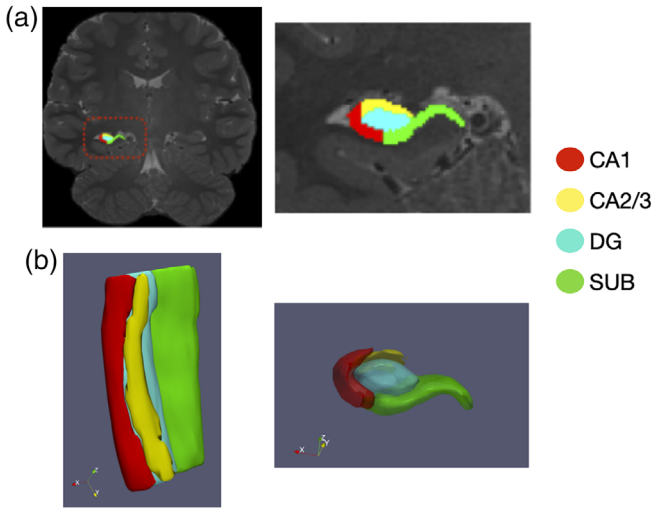

FIGURE 1 (a) Manually segmented subfields of one subject, superimposed on its T2w scan. (b) Three-dimensional surface reconstruction of the hippocampus of another subject, in dorsal and coronal views. CA, cornu ammonis; DG, dentate gyrus; SUB, subiculum

2.5 | Behavioral assessments

After MRI acquisitions, children were given a battery of cognitive tests. This included the MST (Stark et al., 2019), and the children's version of Raven's Colored Progressive Matrices task (PM47; Raven et al., 2003), a measurement of fluid intelligence.

An incidental encoding version of the MST, as described in Ngo et al. (Ngo et al., 2018), was used to assess memory discrimination as a behavioral proxy for PS. One hundred images of objects were selected from Craig Stark's Database specifically designed for the MST task (http://faculty.sites.uci.edu/starklab/mnemonic-similarity-task-mst/). Images were chosen for their appeal and familiarity to children (e.g., toys and food). The MST consisted in an incidental encoding phase where the participant had to perform indoors/outdoors judgments, followed by a test phase evaluating memory discrimination. In an initial incidental encoding phase, 60 pictures of objects were displayed one by one in a randomized order. The participant looked at each picture for 3 s. The picture then disappeared in order to control for duration of stimuli exposure. From that moment, the participant had to state whether the object seen in the picture was something used outdoors or indoors. The participant had 3 s to provide orally it's answer, which was recorded by the experimenter, after which the experiment proceeded automatically to the next trial. In the subsequent test phase, 60 pictures were displayed one by one in a randomized order. Out of these 60 pictures, 20 were already presented during the incidental encoding phase ("target" trials); 20 were similar, but not identical, to the pictures presented during the incidental encoding phase ("lure" trials); and 20 were totally new ("foil" trials). For each picture, the participant had to make "old," "new," or "similar" judgments, in order to correctly identify the target, lure, or foil trials, respectively. The discrimination phase was preceded by six training trials (two training trials per type of response). The responses were given orally by the participant and recorded by the examiner.

Following previous studies (e.g., Ngo et al., 2018), PS was assessed through memory discrimination, which is the percentage of correct "old" responses from which was subtracted the percentage of responses were subjects incorrectly gave "old" responses to "lure" items. Additionally, we also computed a measurement of item memory as the percentage of correct "old" responses from which was subtracted the percentage of responses were subjects incorrectly gave "new" answers to "target" items. While memory discrimination is a proxy for PS, using item memory as an additional measurement of a different memory function allowed us to control for the specificity of our findings, following previous studies (Canada et al., 2019; Ngo et al., 2018).

2.6 | Statistical analyses

Out of the 28 subjects with usable segmentation data, 2 were excluded from the analyses because of lack of compliance during the behavioral assessments, resulting in lacking or unusable MST data. Therefore, 26 subjects were included in our final sample (mean age: 7.95, median age: 7.45, age standard deviation: 2.25, 16 males). Because we had no hypotheses regarding hemispherical differences between subfields, data points were collapsed across hemispheres, resulting in total bilateral subfield volume of each subfield (for a similar approach, see Canada et al., 2019).

2.6.1 | Age-related differences of memory discrimination and item memory

We examined potential age-related differences in memory discrimination and item memory by conducting regressions models predicting item memory and memory discrimination with age. To look for potential nonlinear relations, we also tested models included quadratic and cubic age terms. The best fitting model was chosen with a hierarchical linear regression approach: we used an ANOVA test to assess if the model including more variables predicted memory discrimination or item memory above and beyond the contribution of a single age predictor. We controlled for multiple comparisons by adjusting raw *p*-values with an FDR procedure (Benjamini & Hochberg, 1995).

2.6.2 | Age-related differences of hippocampal subfields' volumes

We examined age-related differences in hippocampal subfields' volumes by conducting regressions models predicting the volume of each hippocampal subfields with age. Because the development of hippocampal subfields is heterogeneous (Østby et al., 2009), we do not necessarily

expect a linear relation between subfields' volume and age. Therefore, we also tested models including quadratic and cubic age terms. Model selection was performed with a hierarchical regression approach similarly to the previous section. Sex was added as a covariate in a second step to control for potential sex-related differences of hippocampal subfields volumes. We controlled for multiple comparisons by adjusting raw *p*-values with an FDR procedure across models (Benjamini & Hochberg, 1995).

2.6.3 | Association between hippocampal subfields' volumes and memory discrimination

Finally, we examined the association between memory discrimination performance and the volumes of hippocampal subfields. We used a multilinear regression model per subfield ($N = 4$), predicting memory discrimination with the volume of each subfield. Age, sex, and Raven's matrix standard scores, were added in the models as covariates to control for their potential confounding effects. To assess the significance of the association between memory discrimination performance and hippocampal subfields, we used a hierarchical linear regression approach. In the first step, we used an ANOVA test to assess if the model including the tested hippocampal subfield volume predicted memory discrimination above and beyond the contribution of the control variables (age, sex, and Raven's matrix standard scores). The significance of the model comparison ANOVA was deemed to express the significant contribution of hippocampal subfields' volumes for explaining the variance of memory discrimination performance. In the second step, we added an interaction term between the tested subfield's volume and age, to test for potential interactions between age and subfields volumes in relation to memory discrimination performance (see Canada et al., 2019, for a similar approach). We used an ANOVA test to assess if the model including the interaction term predicted memory discrimination above and beyond the contribution of the model without the interaction term.

These analyses were also performed with item memory and Raven's matrix standard scores as the dependent variables, in order to assess the specificity of our findings. The correlogram showing correlations between memory measures and subfields volumes is presented in Figure S2.

The *p*-values of all tested models were adjusted with FDR to adjust for multiple comparisons. Moreover, *p*-values of the predictive variables inside each model were corrected with FDR separately for each model. An alpha value of .05 was used for all analyses.

3 | RESULTS

3.1 | Age-related differences of memory discrimination and item memory

Memory discrimination was positively associated to age using a simple linear model ($F = 9.18$, $R2 = 0.28$, $p = .011$). Models including quadratic and cubic age terms did not explained memory discrimination variance above and beyond the variance explained by the linear model (quadratic model vs. linear model: $F = 0.58$, $p = .45$; cubic vs. linear model: $F = 1.14$, $p = .33$). Item memory was not correlated to age, in all tested models (linear model: $F = 0.06$, $R2 = 0.003$, $p = .79$). Figure 2 illustrates the association between age and these two behavioral measurements.

Memory discrimination and item memory performances were not correlated, when controlling for sex ($r = -.08$, $p = .71$) or sex and age ($r = -.11$, $p = .58$).

Memory discrimination and Raven's matrix standard scores were not correlated, when controlling for sex ($r = -0.10$, $p = .59$), or sex and age ($r = -0.01$, $p = .94$). Similarly, item memory and Raven's matrix standard scores were not correlated, controlling for sex ($r = -0.18$, $p = .37$), or sex and age ($r = -0.16$, $p = .41$).

3.2 | Age-related differences of hippocampal subfields' volumes

We examined age-related differences of hippocampal subfields volumes using regressions models, which were compared with a hierarchical regression approach. The plots illustrating the fitting models for each subfield are shown in Figure 3.

The linear model predicting CA1 with a simple age term was significant ($F = 8.32$, $R2 = 0.26$, $p = .02$). Adding sex as a covariate in the model, sex was not a significant predictor of CA1 volume, while age was still significant ($t = 2.8$, $p = .01$). The model with a quadratic age term did not predict the variance of CA1 volume above and beyond than the variance predicted by the linear model ($F = 0.29$, $p = .59$), as well as the model including a cubic age term ($F = 0.30$, $p = .73$).

For CA2-3, the linear model was not significant ($F = 1.34$, $R2 = 0.05$, $p = .33$). Adding quadratic and cubic terms did not explain the variance of CA2-3 volume above and beyond that explained by the linear model (quadratic vs. linear: $F = 1.24$, $p = .27$; cubic vs. linear: $F = 0.62$, $p = .54$). Sex was not a significant predictor of CA2-3 volume and adding sex as a covariate did not change the nonsignificance of age to predict CA2-3 volume.

For DG, the linear model was not significant ($F = 0.09$, $R2 = 0.004$, $p = .75$). Neither adding a quadratic age term ($F = 1.36$, $p = .25$), nor a cubic age term ($F = 1.59$, $p = .22$) explained DG variance above and beyond that explained by the linear model. Sex was not a significant predictor of CA2-3 volume and adding sex as a covariate did not change the nonsignificance of age.

For the subiculum, the linear model was significant ($F = 6.37$, $R2 = 0.21$, $p = .031$). Adding sex as a covariate in the model, sex was not a significant predictor of CA1 volume, while age was still significant ($t = 2.43$, $p = .02$). Neither adding a quadratic age term ($F = 0.65$, $p = .41$), nor a cubic age term ($F = 0.33$, $p = .72$) explained subiculum variance above and beyond that explained by the linear model.

Finally, we examined the association between total volume of the hippocampal body with age, controlling for sex. We observed a positive relationship between age and hippocampal body volume in the linear model ($F = 9.95$, $R2 = 0.29$, $p = .02$). Adding quadratic ($F = 0.03$, $p = .84$) or cubic ($F = 0.16$, $p = .84$) age terms did not

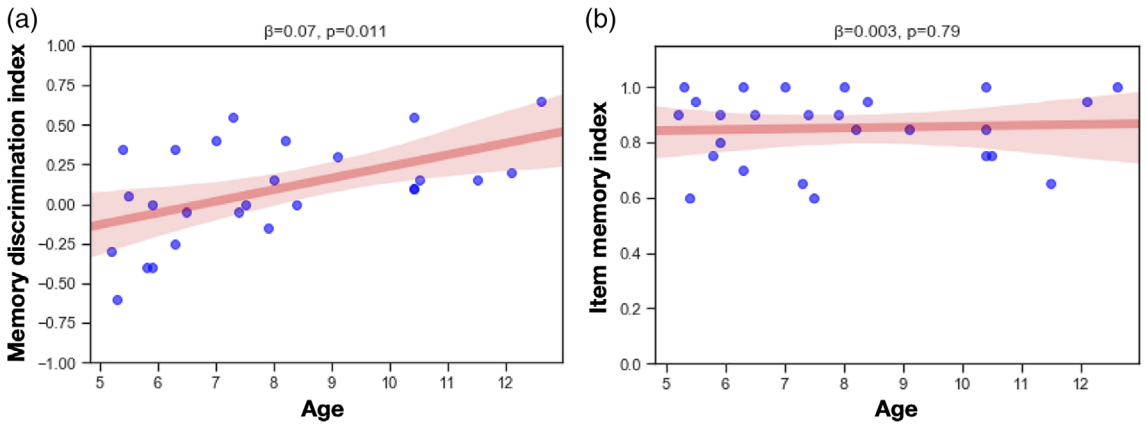

FIGURE 2 (a) Regression between age and memory discrimination; (b) regression between age and item memory

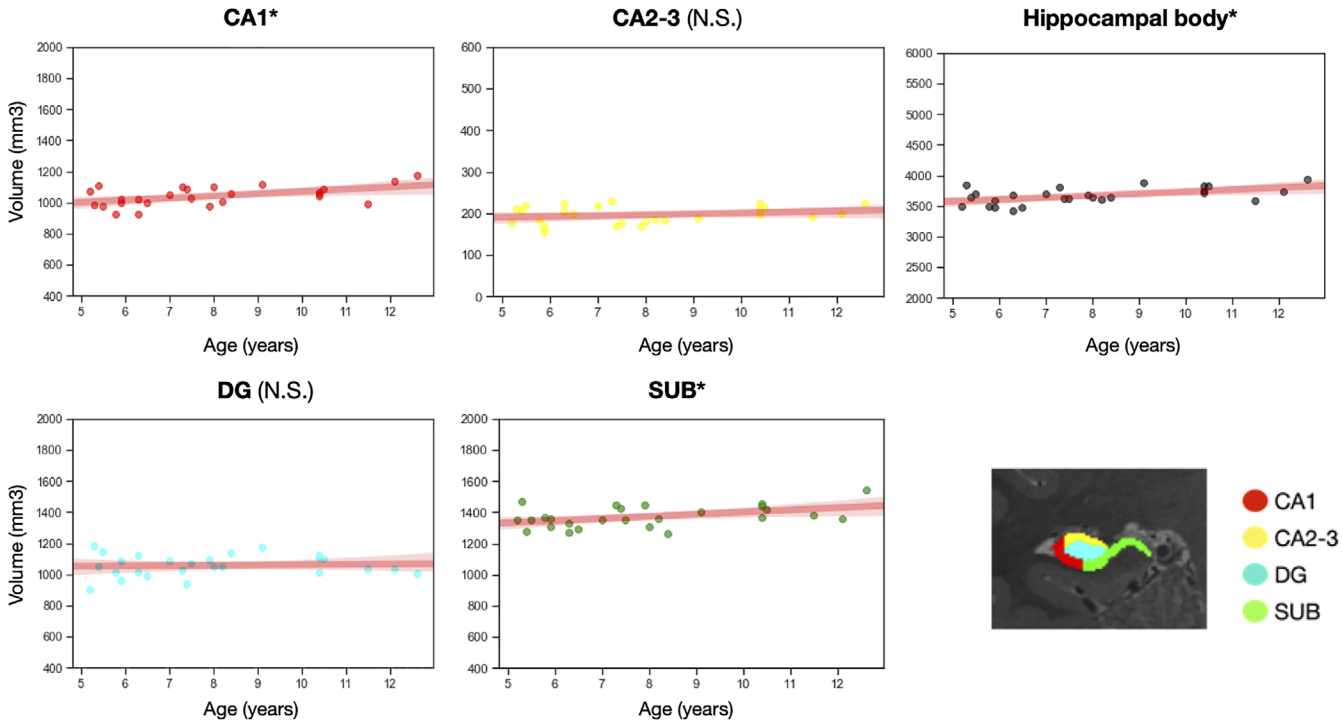

FIGURE 3 Plots of the regressions between adjusted bilateral hippocampal subfields' volumes and adjusted total hippocampal body volume, with age. CA, cornu ammonis; DG, dentate gyrus; SUB, subiculum. Subfields are shown on a coronal slice of the hippocampus on the bottom right. *, corrected p <.05, N.S, not significant

explain hippocampal body volume variance above and beyond the linear model. Sex was not a significant predictor of CA2-3 volume and adding sex as a covariate did not change the nonsignificance of age.

3.3 | Association between hippocampal subfields' volumes and memory discrimination

We used a two-stepped hierarchical linear regression approach to assess the association between subfield's volumes and memory discrimination. In a first step, we used four regression models (one per subfield) including control variables and the tested subfield's volumes to assess if they predicted the variance of memory discrimination performance above and beyond a model including only control variables (age, sex, and Raven's matrix scores). In a second step, we added an interaction term between age and the tested subfield's volume in all models to assess if this model predicted the variance of memory discrimination performance above and beyond the model of the first step. p-values were adjusted for multiple comparisons by correcting the p-values of all models with a FDR procedure. Moreover, p-values of the predictive variables inside each model were corrected with FDR separately for each model. To verify that our results were not

impacted by collinearity, we computed variance inflation factors (VIFs) for all models. VIFs ranged from 1.03 to 1.49, which was lower than the traditionally retained thresholds of 5 or 10 (James et al., 2017; Vittinghoff et al., 2012).

TABLE 2 Summary of the full model predicting memory discrimination with control variables and CA2-3 volume

Variable	β	*t*-value	Corrected *p*-value
Intercept	**−1.56**	**−2.72**	**.048**
Sex	−0.03	−0.29	.91
Age	**0.059**	**2.50**	**.048**
Raven's matrix score	−0.003	−0.11	.91
CA2-3	**0.006**	**2.34**	**.048**

Note: Dependent variable: Memory discrimination. Bold shows significance at $p<0.05$ (corrected). Full model: $F = 4.29$, R2 = 0.45, corrected *p*-value = .04.
Abbreviation: CA, cornu ammonis.

TABLE 3 Summary of the full model predicting memory discrimination with control variables, subiculum volume, and subiculum volume*age interaction

Variable	β	*t*-value	Corrected *p*-value
Intercept	**11.35**	**2.80**	**.022**
Sex	**−0.24**	**−2.18**	**.049**
Age	−0.6633	−2.66	.022
Raven's matrix score	0.026	0.861	.4
SUB	**−0.008**	**−2.91**	**.01**
SUB*age	**0.001**	**2.83**	**.022**

Note: Dependent variable: Memory discrimination. Bold shows significance at $p < 0.05$ (corrected). Full model: $F = 4.21$, R2 = 0.51, corrected *p*-value = .04.
Abbreviation: SUB, subiculum.

The model with CA1 volume did not explain the variance of memory performance above and beyond the model comprising only control variables (model comparison: $F = 1.87$, $p = .18$). The model including an interaction term did not explain the variance of memory discrimination above and beyond the variance explained by the model without the interaction term (model comparison: $F = 0.06$, $p = .80$).

The model with CA2-3 volume explained the variance of memory performance above and beyond the model comprising only control variables (model comparison: $F = 5.5$, $p = .029$) and explained 45% of the variance of memory discrimination ($F = 4.29$, R2 = 0.45, $p = .04$; Table 2). CA2-3 was a significant predictor of memory discrimination performance ($t = 2.34$, $p = .04$). Adding an interaction term did not explain the variance of memory discrimination above and beyond the variance explained by the model without the interaction term (model comparison: $F = 0.02$, $p = .88$).

The model with DG volume did not explain the variance of memory performance above and beyond the model comprising only control variables (model comparison: $F = 0.41$, $p = .52$). The model including an interaction term did not explain the variance of memory discrimination above and beyond the variance explained by the model without the interaction term (model comparison: $F = 0.11$, $p = .73$).

The model with subiculum volume did not explain the variance of memory performance above and beyond the model comprising only control variables (model comparison: $F = 0.36$, $p = .55$). However, the model including an interaction term explained the variance of memory discrimination above and beyond the variance explained by the model without the interaction term (model comparison: $F = 8.01$, $p = .01$). The model with the interaction term explained 51% of the variance of memory discrimination ($F = 4.21$, R2 = 0.51, $p = .04$) (Table 3). In this model, subiculum volume, and the interaction term between subiculum volume and age were significant predictors of memory

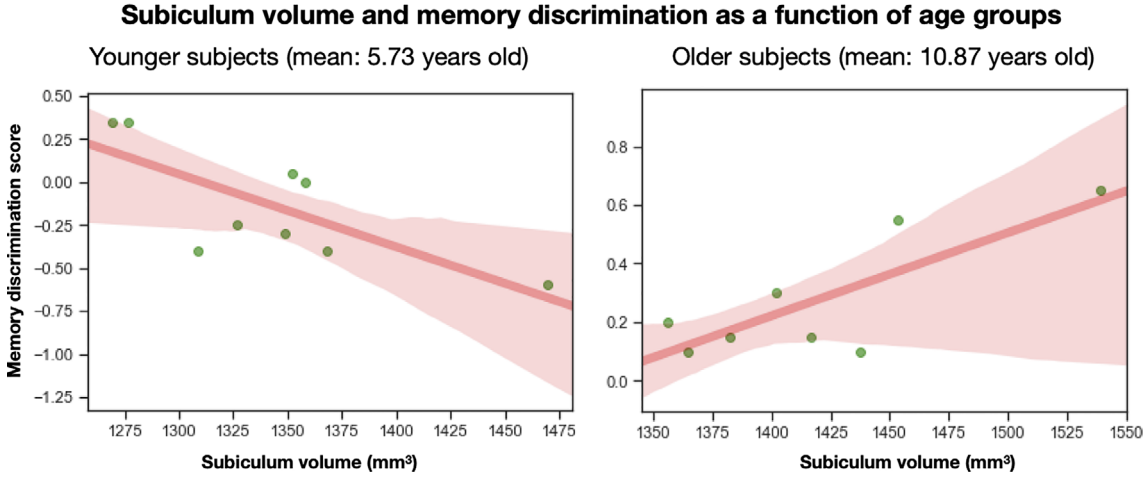

FIGURE 4 Association between memory discrimination and subiculum volume as a function of age. Left: for younger subjects (younger than the median age minus half of its standard deviation), the correlation between memory discrimination and subiculum volume is negative. Right: for older subjects (older than the median age plus half of its standard deviation), the correlation between memory discrimination and subiculum volume is positive

discrimination performance (subiculum volume: $t = -2.91$, $p = .01$; interaction term: $t = 2.83$, $p = .022$).

The significance of the interaction term between subiculum and age for predicting memory discrimination suggests an age-moderated association between subiculum and memory discrimination. To illustrate the moderating effect of age, we plotted memory discrimination scores in relation to subiculum volumes separately for younger subjects (younger than 0.5 standard deviation below the median age: i.e., from the youngest subject to 6.33 years old) and for older subjects (older than 0.5 standard deviation above the median age: i.e., from 8.57 years old to the oldest subject; Figure 4). These separate subiculum-memory discrimination plots as a function of age showed that for younger subjects, the relation between subiculum volume and memory discrimination is negative, while for older subjects, the relation between subiculum volume and memory discrimination is positive.

Raven's matrix standard scores were not a significant predictor of memory discrimination in all models described above. Performing the analyses without Raven's matrix standard scores did not significantly change the results. Moreover, hippocampal subfields volumes were not significant predictors of Raven's matrix standard scores (Table S1).

To verify for a possible confounding effect of the variance of total hippocampal body size, we also performed the same regression analyses with hippocampal body volume as a covariate, which did not significantly change the results. Combining the volumes of CA2-3 and DG in a single ROI, combined DG/CA2-3 was not a significant predictor of memory performance in a model without the interaction term (model comparison: $F = 0.001$, $p = .96$) and with the interaction term (model comparison: $F = 0.22$, $p = .63$).

Last, to examine the specificity of the association between hippocampal subfields and memory discrimination, we also ran models predicting item memory with control variables and subfields' volumes. None of the model predicting item memory with hippocampal subfields' volumes were significant.

4 | DISCUSSION

We aimed to assess the association between hippocampal subfields' volumes and memory discrimination, a behavioral proxy for PS, during development. Our main results were: (1) we observed age-related differences of memory discrimination performance in our age span; (2) we highlighted distinct age-related differences of hippocampal subfields' volumes, suggesting distinct developmental trajectories for each subfield; and (3) we showed an association between hippocampal subfields' volumes and memory discrimination performance. CA2-3 and subiculum were significant predictors of memory discrimination. Furthermore, the association between memory discrimination and subiculum was moderated by age. Subfields' volumes were not predictors of item memory, showing that the reported association between memory and subfields' volumes is specific to memory discrimination.

4.1 | Memory discrimination, but not item memory, is subject to age-related differences

Memory discrimination was positively correlated with age, suggesting memory discrimination could continue to improve continuously until late childhood. This result is in agreement with the results reported by Rollins and Cloude (2018). The authors found that 8–9 years old children memory discrimination performance was worse than adults, while 11–12 years old children performed similarly to adults. Combined with ours, these results suggest that memory discrimination performance could continue to improve during childhood until approximately 10 years of age. However, as our study did not include adult subjects, we cannot test this hypothesis directly. This contradicts the finding that memory discrimination performance of 6 years old children at a MST task was similar to that of adults' by Ngo et al. (2018). Task difficulty, relative to children's familiarity to the presented stimuli, has been shown to influence memory discrimination performance (Benear et al., 2020). Thus, these differences might be explained by the possibility that some items included in our study or the study of Rollins and Cloude were too unfamiliar to elicit a plateau of children's performance, compared to the items used by Ngo and colleagues. Still, the reasons explaining these disagreements remain elusive. Further studies will have to examine the precise developmental trajectory of memory discrimination from early childhood to adulthood while considering variables that might impact performance (e.g., item familiarity). Knowing the precise developmental timeline of memory discrimination is essential to understand how memory discrimination relates to EM development as a whole.

By contrast to memory discrimination, item memory performance was not associated with age, as previously reported (e.g., Ngo et al., 2018). We also did not find an association between memory discrimination performance and item memory performance. Hence, we further highlight that memory discrimination and item memory are two independent memory processes, as they likely rely on distinct neural correlates. While memory discrimination is mainly associated with the hippocampus, item memory has been shown to rely on medial temporal lobe regions, such as the perirhinal cortex (e.g., Davachi, 2006).

4.2 | Age-related differences of hippocampal subfields volumes suggest distinct developmental trajectories

We observed age-related differences of hippocampal subfields volumes from early to late childhood. Specifically, we found that CA1 and subiculum volumes were linearly and positively associated with age, suggesting continuous volumetric increases of these two subfields during childhood. CA2/3 and DG volumes were not associated with age. These findings echo the results of studies that previously examined the developmental trajectories of hippocampal subfields in the hippocampal body (Lee et al., 2014; Riggins et al., 2018). Lee et al. (2014) reported positive associations of CA1 of and

CA3/DG volumes with age, but not of the subiculum, in an 8–14 years old cohort. Riggins et al. (2018) reported age-related differences of subfields volumes in the hippocampal head, but not in the hippocampal body, in a 4–9 years old cohort. Our results are thus partly in agreement with theirs, which are also only in partial mutual agreement. Several factors, such as differences in segmentation protocols, sample size, or studied age span, could contribute to study-specific findings. Besides the hippocampal body, several studies have described the developmental trajectories of hippocampal subfields in the whole hippocampus, with differing results. Canada et al. (2019) found a positive association between age and subiculum volume in a 4–9 years old cohort, as well as a nonlinear association for CA1. Krogsrud et al. (2014) found positive associations between age and the volumes of the subiculum, CA1, DG, and CA2-3, in a 4–22 years old cohort. In a longitudinal study including subjects from 8 to 28 years old, Tamnes et al. (2018) found linear increases of CA1 and the subiculum, and linear CA2-3 and DG decreases. Overall, most of the aforementioned studies reported linear positive associations between age and CA1 and subiculum volumes, as we did in the present work.

We thus suggest that CA1 and the subiculum volumes likely undergo age-related volumetric increases during childhood in the hippocampal body, as it might be the case in the hippocampus as a whole. Myelination processes in the subiculum, occurring until adulthood (Krogsrud et al., 2014; van Praag et al., 2005), could explain the positive association between age and subiculum volume reported here. Age-related differences of CA1 volume could be related to increased connectivity and synaptogenesis between the pyramidal cells of the CA1 and the other subfields, or the entorhinal cortex. The size growth of CA1 and the subiculum in the hippocampal body suggested here could be the contributors of the larger hippocampal body size in adults, compared to children (DeMaster et al., 2014).

4.3 | Association between hippocampal subfields' volumes and memory discrimination

PS plays a crucial role in forming episodic memories by ensuring that similar representations are kept distinct from each other, reducing memory interference (see Keresztes et al., 2018 for a discussion). We hypothesized that the DG and/or CA3 volume would be associated with memory discrimination performance, a behavioral proxy for PS (Canada et al., 2019; Yassa & Stark, 2011). Partly in accordance with this hypothesis, we found that CA2-3 but not DG volume was associated with memory discrimination performance. We hence further confirm the association between CA2-3 and memory discrimination (e.g., Yassa & Stark, 2011). The positive correlation between memory discrimination suggests that, at a given age, larger CA2-3 in the hippocampal body is associated to better memory discrimination performance. Specifically, as we controlled for the volumes of other subfields, a relative larger CA2-3 size than the size of other hippocampal subfields could contribute to better memory discrimination. Similar relations between CA2-3 size in the body and memory performance (using other tasks than memory discrimination) were found by former studies (Daugherty et al., 2016; Lee et al., 2014; Riggins et al., 2018; Tamnes et al., 2014). A larger CA3 could be related to several factors, such as increasing connectivity and synaptogenesis between CA3 pyramidal cells and DG granule cells.

As the DG is frequently highlighted as the main neural correlate of PS (e.g., Berron et al., 2017; Yassa & Stark, 2011) we would have expected to observe an association between memory discrimination and the volume of this subfield. This absence of relation is thus somewhat surprising. As we limited our study to the hippocampal body, it is possible that this relation is not observed, or less important, in the hippocampal body compared to the whole hippocampus. Indeed, a relationship between memory discrimination performance and the combined volumes of DG and CA2-4 (total hippocampus) during development was found by a previous study (Canada et al., 2019). However, the study from Canada and colleagues combined DG and CA2-4 in a single region of interest. This approach prevented assessing if the association between subfields volumes and memory discrimination was shared by both subfields, or only driven by one. Future studies will have to more precisely assess associations during development between PS, CA3, and DG, in the whole hippocampus and separately for the hippocampal head, body, and tail.

We found an association between the volume of the subiculum and memory discrimination. The subiculum is not classically associated with PS, but instead with pattern completion (e.g., Bakker, Kirwan, et al., 2008). However, some previous findings suggested that the subiculum takes part, in some cases, in PS. A study conducted in rats found that impairments of the dorsal subiculum were associated with impaired PS performance (Potvin et al., 2009). An ultra-high-field MRI study in adults found subiculum's role in scene discrimination (Hodgetts et al., 2017). A study from Lee et al. (2014), while not directly using a measurement of memory discrimination, showed an association in children and adolescents between subiculum volume and item false alarm rates, which could rely on discrimination processes partly dependent on PS. Therefore, the subiculum can also be involved in, or related to, PS, which we also suggest here. The subiculum is not part of the trisynaptic circuit, a loop connecting CA1 to the DG and to CA2-3 classically associated with PS. However, the subiculum is a major output of the trisynaptic circuit through connections via the fornix. A possible explanation for the relation between subiculum volume and memory discrimination performance could be that the subiculum volume partly expresses the efficacy at which information is transmitted between the bilateral hippocampi or to other cortical or subcortical regions through the fornix. It is possible that, to some extent, the subiculum behaves similarly to CA3, in the sense that it can take part in both PS and completion processes.

The relationship between subiculum volume and memory discrimination was moderated by age. Visualization of the relationship between subiculum volume and memory discrimination (Figure 4) as a function of age showed that for younger subjects, the association between subiculum and memory discrimination was negative, and positive for older subjects. A similar age-moderated relation between subiculum size and memory performance was found by Riggins

et al. (2018) in the hippocampal head, albeit in the opposite direction (positive correlation for younger children, negative correlation for older children). The head and body of the hippocampus are subjects to distinct maturational trajectories during childhood (e.g., DeMaster et al., 2014; Riggins et al., 2018). Distinct types of age-moderated associations, as a function of hippocampal subregions (head or body) and memory function, are thus likely to be observed. Here, the age-moderated relationship between memory discrimination and subiculum volume could suggest that the subiculum is differently related to memory discrimination as children approach puberty. For example, increased myelination processes in the subiculum in later childhood and adolescence could explain the positive association found in older children. This increased myelination could conduct information from the DG and CA3 subfields to cortical output regions through the subiculum and the fornix, contributing to PS performance. Even if the nature of this age-moderated association should be interpreted with caution, this nevertheless shows the overall relation between subiculum volume and memory discrimination performance during development.

Overall, we further confirm an association between CA2-3 and memory discrimination (Yassa & Stark, 2011), and suggest an association between memory discrimination and the subiculum. We provided evidence regarding the specificity of these findings as hippocampal subfields volumes were not correlated to item memory or to Raven's matrix standard scores.

4.4 | Limitations and future directions

Our study is subject to several limitations. First, although our initial sample comprised 50 subjects, which can be deemed reasonable in a developmental study, our final sample was limited to 26 data points. This important loss of data was mainly caused by the sensitivity to motion of the high-resolution T2w sequence used for the segmentation of the hippocampal subfields. A relatively low sample size thus limits the reach of our conclusions, despite satisfactory statistical effect size and correction for multiple comparisons. Low sample size was the consequence of our choice to keep only totally satisfying data to perform segmentation in order to maintain high accuracy. Second, another caveat of our study is that our design was cross-sectional rather than longitudinal. Longitudinal studies are better endowed to capture developmental trajectories by examining intra-subject rather than inter-subject variability. Third, the approach used here is indirect and correlational, only suggesting an association between subfields and memory discrimination by using subfields volumes as a proxy for hippocampal function. This type of approach could be completed by investigations of the role of hippocampal subfields in memory discrimination through more direct means, for example, using functional activation studies (e.g., Benear et al., 2020). Finally, we restricted our segmentation to the hippocampus' body to ensure reliable segmentations, but this limits our conclusion to this subregion rather than to the hippocampus as a whole. As subfields' developmental trajectories vary along the anteroposterior axis (e.g., Riggins et al., 2018), it is relevant to assess subfields separately for the hippocampal head and body. Segmenting the head of the hippocampus is more complex than segmenting the body, but several protocols allow to do so (e.g., Joie et al., 2020). Still, we provide the first examination of the relation between memory discrimination and the main hippocampal subfields (separating DG and CA2-3) in the context of development. Future directions could include extending this investigation to the hippocampus' head, to verify if the relationship between memory discrimination and the subiculum is also found in the hippocampal head. Our results also invite, more generally, to scrutinize more closely the putative role of the subiculum in PS.

5 | CONCLUSION

We showed that memory discrimination performance is associated to age from early to late childhood. We highlighted distinct age-related association between age and hippocampal subfields in the hippocampal body, and showed that volumes of CA2-3 and subiculum were associated with memory discrimination performance. Our results confirm the role of CA2-3 in PS during childhood, and suggest an involvement of the subiculum (at least in the hippocampus' body) in memory discrimination. These results stress the need to further investigate the different contributions of hippocampal subfields to memory discrimination, and thus to PS, during development.

ACKNOWLEDGMENTS

This work was supported by Fondation de France (grant n°00070721, P.I. Marion Noulhiane), Fondation Mustela (Bourses de Recherche 2017 to Antoine Bouyeure), and Paris University (Bourse ministérielle de doctorat to Antoine Bouyeure). The authors would like to thank the nurses and radio manipulators for their help in this study. Special thanks to Chantal Ginisty.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Bouyeure, A., Patil, S., Mauconduit, F., Poiret, C., Isai, D., & Noulhiane, M. (2021). Hippocampal subfield volumes and memory discrimination in the developing brain. *Hippocampus*, *31*(11), 1202–1214. https://doi.org/10.1002/hipo.23385