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Anatomo-functional changes in neural substrates of cognitive memory in developmental amnesia: Insights from automated and manual Magnetic Resonance Imaging examinations

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Abstract

Despite bilateral hippocampal damage dating to the perinatal or early childhood period and severely impaired episodic memory, patients with developmental amnesia continue to exhibit well-developed semantic memory across the developmental trajectory. Detailed information on the extent and focality of brain damage in these patients is needed to hypothesize about the neural substrate that supports their remarkable capacity for encoding and retrieval of semantic memory. In particular, we need to assess whether the residual hippocampal tissue is involved in this preservation, or whether the surrounding cortical areas reorganize to rescue aspects of these critical cognitive memory processes after early injury. We used voxel-based morphometry (VBM) analysis, automatic (FreeSurfer) and manual segmentation to characterize structural changes in the brain of an exceptionally large cohort of 23 patients with developmental amnesia in comparison with 32 control subjects. Both the VBM and the FreeSurfer analyses revealed severe structural alterations in the hippocampus and thalamus of patients with developmental amnesia. Milder damage was found in the amygdala, caudate, and parahippocampal gyrus. Manual segmentation demonstrated differences in the degree of atrophy of the hippocampal subregions in patients. The level of atrophy in CA-DG subregions and subicular complex was more than 40%, while the atrophy of the uncus was moderate (–24%). Anatomo-functional correlations were observed between the volumes of residual hippocampal subregions in patients and selective aspects of their cognitive performance, viz, intelligence, working memory, and verbal and visuospatial recall. Our findings suggest that in patients with developmental amnesia, cognitive processing is compromised as a function of the extent of atrophy in hippocampal subregions. More severe hippocampal damage may be more likely to promote structural and/or functional reorganization in areas connected to the hippocampus. In this hypothesis, different levels of hippocampal function may be rescued following this variable reorganization. Our findings document not only the extent, but also the limits of circuit reorganization occurring in the young brain after early bilateral hippocampal damage.

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KEYWORDS

developmental amnesia, FreeSurfer, hippocampus, memory, recall, VBM

1 | INTRODUCTION

In humans, hypoxic-ischemic events experienced early in life can damage specific subcortical brain structures such as the hippocampus, the basal ganglia, and the thalamus (Caine & Watson, 2000; de Vries & Groenendaal, 2010; Dzieciol et al., 2017; Gadian et al., 2000; Guderian et al., 2015; Sie et al., 2000). White matter (WM) abnormalities have also been found in newborns with hypoxic-ischemic encephalopathy (Azzopardi & Edwards, 2010; Gao et al., 2012; Porter et al., 2010), and these abnormalities can persist into adolescence (Nagy et al., 2005).

We previously identified a group of patients with hippocampal atrophy who had suffered hypoxic-ischemic episodes in infancy or childhood and later developed a memory disorder differing from that commonly described in patients with adult-onset amnesia of temporal lobe origin (Dzieciol et al., 2017; Vargha-Khadem et al., 1997). In the latter cases, the disorder most often takes the form of a global anterograde memory loss (i.e., one affecting both episodic and new post-injury semantic memory, thus severely restricting both recall and recognition processes) (Bayley & Squire, 2005; Manns et al., 2003; Scoville & Milner, 1957; Verfaellie et al., 2000). In patients with hippocampal damage of early onset, by contrast, the disorder is more limited, being characterized by markedly impaired episodic memory, recall/recollection, spatial processing, and navigation deficits, but relatively preserved semantic memory, working memory, and recognition performance. We have labeled this dissociated form of memory function “developmental amnesia” (Guderian et al., 2015; Patai et al., 2015; Picard et al., 2013; Rosenbaum et al., 2015; Vargha-Khadem et al., 1997). Given the early onset of hippocampal damage, the compensatory reorganization that has occurred in patients with developmental amnesia is likely to be distinct from what is observed in patients with hippocampal damage acquired in adulthood. The differential maturation of distinct hippocampal circuits during normal development might underlie the differential emergence of specific hippocampus-dependent memory processes (Lavenex & Banta Lavenex, 2013). In patients with adult-acquired hippocampal lesions, the damage has occurred to already-established and normally-functioning memory circuits, whereas in patients with developmental amnesia, the early bilateral lesions have probably led to the development of a differently organized memory system. For these reasons, it is difficult, and somewhat inappropriate, to compare memory function and cognitive profiles in patients with developmental amnesia to those of patients with adult-onset amnesia (Elward & Vargha-Khadem, 2018).

Among the many questions that have arisen from the study of patients with developmental amnesia, the foremost concerns the integrity of other regions of the brain, particularly the medial temporal lobe (MTL) and/or preserved hippocampal subregions that could be

involved in memory circuit reorganization following early hippocampal damage.

The degree of hippocampal atrophy in patients with developmental amnesia ranges from 28% to 62% compared to healthy controls (Dzieciol et al., 2017). This large range of hippocampal volume reduction in this cohort suggests that there may indeed be variability in the hippocampal response to hypoxia-ischemia at the level of hippocampal subregions. Hypoxia-ischemia is known to differentially affect the hippocampal fields and subdivisions. Studies of animal models of cerebral ischemia have reported that a brief episode results in selective neuronal death in the CA1 field of the hippocampus (Lavenex et al., 2011; Schmidt-Kastner & Freund, 1991) while the adjacent CA3 remains less vulnerable (Wang & Michaelis, 2010). In humans, while damage to CA1 is consistently reported following cerebral ischemia, damage to additional hippocampal regions is much more variable (Bartsch et al., 2015).

Postmortem examinations have reported some neural cell loss in layers of entorhinal cortex in patients who suffered ischemic episodes in adulthood (Rempel-Clower et al., 1996). However, it was reported that the volume of the parahippocampal gyrus was not significantly reduced in patients with adult-onset amnesia presenting with bilateral hippocampal damage (Shrager et al., 2008). A cortical thickness analysis performed in a single patient with developmental amnesia did not find abnormality in the subhippocampal structures within the MTL, including the perirhinal and ventral entorhinal cortices (Jonin et al., 2018). Also, a recent study demonstrated that parahippocampal activity during scene reinstatement in patients with developmental amnesia was similar to controls (Elward et al., 2021). However, the structural integrity of the perihippocampal gyrus, which likely supports semantic memory and other preserved mnemonic processes, remains to be assessed quantitatively in patients with developmental amnesia.

Here, we studied the largest cohort of patients with the rare condition of developmental amnesia ever assembled to document the extent of structural brain damage and hypothesize possible circuit reorganizations that may be involved in compensating hippocampal function. We used voxel-based morphometry (VBM) and FreeSurfer automated segmentation on MRI scans to estimate the extent of tissue changes in cortical and subcortical areas, including the entire hippocampus. We also used manual segmentation to estimate the volume of three hippocampal subregions (uncus, CA-DG, and subicular complex) and three surrounding cortical areas (entorhinal, perirhinal, and parahippocampal cortices) in patients with developmental amnesia and healthy controls. Controls and patients were assessed with neuropsychological tests of intelligence (Wechsler Adult Intelligence Scale, 3rd Ed. [WAIS-III] or Wechsler Intelligence Scale for Children, 4th Ed. [WISC-IV]) and recall/recognition for verbal and visual material (Doors and People Test). Finally, we

investigated the relationships between the degree of atrophy of hippocampal subregions and cognitive deficits.

2 | MATERIALS AND METHODS

2.1 | Participants

A total of 32 control participants and 23 patients with developmental amnesia were included in this study. All participants were part of a long-term study. The first patients with developmental amnesia (DA) were described in 1997 (Vargha-Khadem et al., 1997). Developmental amnesia is a rare condition, and recruitment of the 23 patients has taken almost three decades. The patients with developmental amnesia were characterized by (i) a history of episodes of hypoxia-ischemia in early life, (ii) quantified hippocampal volume reduction above ~25% relative to a group of controls, and (iii) severely impaired episodic memory (Dzieciol et al., 2017). Bilateral hippocampal atrophy in the order of 20%–30% may be necessary (but not sufficient) for the syndrome of developmental amnesia to appear (Isaacs et al., 2003). The most common etiology was perinatal hypoxic-ischemic encephalopathy (Table S1). While long-term neurodevelopmental outcome depends on the severity of the hypoxic-ischemic episode, subtle cognitive deficits and behavioral alterations have been revealed through long-term evaluations even in mild forms of hypoxia-ischemia (de Vries & Jongmans, 2010).

When all the manual volume estimates were completed, one of the patients, who presented with moderate memory deficits and only 17.7% hippocampal volume reduction associated with two unconfirmed episodes of prolonged seizures at age 4, was excluded from the developmental amnesia group.

Also, we excluded from the developmental amnesia group a patient with temporal lobe epilepsy presenting with a 24.2% hippocampal volume reduction but without a documented episode of early hypoxia-ischemia and/or status epilepticus. Additionally, blinded neuroradiological examination carried out independently by one of the authors (WKKC) revealed that this patient's MRI scan was entirely normal. The hippocampus, fornix, and mammillary bodies were noted to have a normal appearance in contrast to all other patients with developmental amnesia.

The developmental amnesia group included three patients (DA05, DA06, and DA10) who had sustained hypoxic-ischemic episodes between the ages of 9 and 12 years in contrast to other patients who had suffered such episodes perinatally or within the first 3 months of life. However, it has been previously demonstrated that the early (below age 1) and late (between 6 and 14 years) groups exhibit similar profiles and thus concluded that the effective age at injury for developmental amnesia extends from birth to puberty (Vargha-Khadem et al., 2003). We report volume and performance comparisons between later-onset and other patients with DA in Table S2.

VBM, automatic (FreeSurfer), and manual segmentations were performed on 32 control participants (16 females; mean age: 17.7 years, standard deviation [SD] 7.7, range 8–38) and 23 patients

with developmental amnesia (11 females; mean age: 20.3 years, SD 9.1, range 8–40).

The study was approved by the London-Bentham Research Ethics Committee (REC Reference No. 05/Q0502/88), and all participants and their carers read an age-appropriate information sheet and gave written informed consent according to the Declaration of Helsinki before commencing the study.

2.2 | Structural MRI

Participants were either scanned with a 1.5T-MRI scanner (24 control participants, 16 patients with developmental amnesia) or with a 3T-MRI scanner (eight control participants, seven patients with developmental amnesia).

Whole brain structural 1.5T-MRI scans were obtained using a Siemens AVANTO scanner, with a T1-weighted 3D FLASH sequence with the following parameters: repetition time 11 ms, echo time 4.94 ms; in-plane resolution 1 mm × 1 mm; slice thickness of 1 mm (Cooper et al., 2011).

Whole brain structural 3T-MRI scans were obtained using a 3T Siemens PRISMA scanner with a 20 channel head coil. A T1-weighted magnetization-prepared rapid gradient-echo (MPRAGE) scan was acquired with the following parameters: in-plane resolution of 1 mm × 1 mm; slice thickness of 1 mm; repetition time of 2300 ms; echo time of 2.74 ms (Buck et al., 2019).

2.2.1 | Voxel-based morphometric analysis

Processing of the structural MRI scans was carried out using Statistical Parametric Mapping 12 (SPM12 (Ashburner, 2009); version 7771, downloaded from <https://www.fil.ion.ucl.ac.uk/spm/>) running on MATLAB 2020b (The Mathworks, Natick, MA, USA). Using the segmentation procedure implemented in the CAT12 toolbox (<https://neuro-jena.github.io/cat/index.html>), the images were segmented into gray matter (GM), WM, and cerebrospinal fluid (CSF). For each participant, this resulted in a set of three images in the same space as the original T1-weighted image, in which each voxel was assigned a probability of it being GM, WM, and CSF. The CAT12 toolbox was also used to ensure the quality of the segmentation, which was either “good” (“B,” controls $n = 2$; patients $n = 1$), “satisfactory” (“C,” controls $n = 25$; patients $n = 17$), or “sufficient” (“D,” controls $n = 5$; patients $n = 5$). The images were smoothed using 8 mm kernels. “Modulated normalized” parameter in CAT12 was used to create tissue class images in alignment with the template. This parameter multiplies (“modulates”) the voxel values with the Jacobian determinant (i.e., linear and non-linear components) derived from the spatial normalization. The structural MRI data were analyzed using the smoothed, modulated GM segments from 23 patients and 32 controls. A general linear model with factors group (control and patients) and covariates of no interest (age at scan and intracranial volume [ICV]) was used to identify the group-wise pattern of GM atrophy in patients

with developmental amnesia. Statistical maps of volume change were displayed using a voxel-wise threshold of $p < .001$. The Anatomy toolbox for CAT12 was used to determine the probability of the voxels being located in particular structures (e.g., hippocampus).

2.2.2 | FreeSurfer analysis

Cortical reconstruction and volumetric segmentation were performed with the FreeSurfer software v7.3.2 (downloaded from <https://surfer.nmr.mgh.harvard.edu/>). Briefly, this processing includes motion correction and averaging of multiple volumetric T1 weighted images, removal of non-brain tissue, segmentation of the subcortical WM and deep GM volumetric structures, intensity normalization, and parcellation of the cerebral cortex into units with respect to gyral and sulcal structure producing representations of cortical thickness (Dale et al., 1999; Fischl et al., 1999; Fischl & Dale, 2000). We also used a FreeSurfer tool that produces an automated segmentation of the anterior hippocampus (head) and the posterior hippocampus (body and tail) (Iglesias et al., 2015).

2.2.3 | Manual segmentation

For the manual measurement of regions of interest (ROI) volumes, the data were reformatted into 1 mm-thick contiguous slices in the coronal plane. ROI cross-sectional areas were measured in all slices along the entire length of the hippocampus, entorhinal, perirhinal, and parahippocampal cortices using ITK-SNAP (version 3.8.0; www.itksnap.org) (Yushkevich et al., 2006). Manual tracing is still the gold standard for measuring hippocampal volume and is particularly appropriate for samples of relatively small size (Akudjedu et al., 2018), presenting with various levels of hippocampal atrophy (Schmidt et al., 2018), or including children and adolescents (Herten et al., 2019). All manual measurements of the ROIs were carried out by one of the authors (LJC), who remained blind to participant identity (Figures S1 and S2). We estimated the inter-rater reliability of the manual segmentation method by comparing our hippocampal volume estimates with those obtained by David G. Gadian in smaller cohorts and published in previous articles (Cooper et al., 2011; Dzieciol et al., 2017). The correlations between the volumetric estimates were strong in patients with DA ($r_{(17)} = 0.65$; $p = .004$) and controls ($r_{(20)} = 0.55$; $p = .01$).

The hippocampus comprises the CA fields (CA3, CA2, and CA1), the dentate gyrus (DG), subiculum, presubiculum, and parasubiculum (Amaral & Lavenex, 2007). The human uncus [also termed the “uncal portion of the hippocampal formation”] (Amaral et al., 1984) is situated antero-medially and consists of slightly modified DG, CA3, CA2, CA1, and subiculum (Ding & Van Hoesen, 2015). For the segmentation of the hippocampus and its subregions, we followed the guide provided by Dalton et al. (2017). Given the difficulty to distinguish hippocampal CA fields on 1.5T and 3T-MRI acquisitions, we restricted our volumetric analyses to three ROIs: uncus (defined according to Ding and Van Hoesen) (Ding & Van Hoesen, 2015), CA-DG (CA fields

and DG), and subicular complex (subiculum, presubiculum, and parasubiculum). The segmentation of the entorhinal, perirhinal and parahippocampal cortices was based on structural descriptions of human MTL and segmentations protocols (Blaizot et al., 2010; Ding & Van Hoesen, 2010; Frankó et al., 2014; Insausti et al., 1998; Kivisaari et al., 2020). See [Supporting Information](#) for more details.

The volumes in cubic millimeters were calculated by summing the number of voxels ($1 \times 1 \times 1$ mm) for each ROI. The volume of the hippocampus as a whole was calculated as the sum of hippocampal subregions' volumes (uncus, CA-DG, and subicular complex). We then used parametric tests as volumetric estimates of the hippocampal subregions and cortical areas were normally distributed (Shapiro-Wilk normality test; control: all $p > .07$; patients: all $p > .05$). The volume of all the ROIs was calculated as the mean of the left and right hemisphere measurements.

ICV was manually measured on the sagittal data set with a 1-in-10 random and systematic sampling strategy (Van Paesschen et al., 1997). Landmarks for ICV were the dura mater (easily visible over the convexities of the cerebrum and cerebellum) or the inside of the skull if the dura was not visible. The pontomedullary junction was used as a ventral landmark. The ICV was normally distributed (Shapiro-Wilk normality test; control: $p = .05$; patients: $p = .23$). The ICV was 6.8% smaller in the developmental amnesia group than in the control group ($t_{(53)} = -2.70$; $p = .009$). The total ICV and age at scan/test were used as covariates to correct ROI volumes. Corrections, derived from the multiple regression line of control ROI volume (V) versus ICV and age at scan/test (AGE), were applied based on the formula $[\text{corrected}_V = \text{raw}_V + a \times (\Delta\text{ICV}) + b \times (\Delta\text{AGE})]$ where “ a ” and “ b ” are the regression coefficients.

2.3 | Behavioral analyses

2.3.1 | WISC-IV/WAIS-III

The WAIS-III and WISC-IV provide four index scores: Verbal Comprehension Index, measuring understanding and expression of verbal concepts; Perceptual Reasoning Index, reflecting visuospatial perception and perceptuomotor manipulation; Working Memory Index, tracking online immediate memory and executive control; and Processing Speed Index, measuring speed of visuospatial discrimination, and copying of number-symbol associations. The four index scores are expressed as standard scores with a mean of 100 and a SD of 15.

Scoring

The WISC-IV or WAIS-III were administered to all patients with developmental amnesia (11 females, mean age: 20.3 years, SD: 9.1, range: 8–40, WISC-IV: $n = 7$, WAIS-III: $n = 16$) and to 23 controls (13 females, mean age: 18.0 years, SD: 8.4, range: 8.2–38, WISC-IV: $n = 4$, WAIS-III: $n = 19$). For the analysis of the data, we then used parametric tests as the data were normally distributed in all four indices (Shapiro-Wilk test of normality; control: all $p > .36$; patients: all $p > .10$).

2.3.2 | The Doors and People Test

The Doors and People Test was administered according to the instructions in the published manual (Baddeley et al., 1994), as described in detail in previous reports (Adlam et al., 2009; Patai et al., 2015). Briefly, for the verbal recall subtest ("People"), participants were presented with four pictures of people and, after three learning trials, asked to recall their names cued by their profession. For the visual recall subtest ("Shapes"), participants first copied, and drew the shapes from memory after three learning trials. For verbal recognition ("Names"), participants were presented with a list of names and then asked to recognize each one from a list of four alternatives. Finally, in the visual recognition subtest ("Doors"), participants viewed a list of doors and then identified each one from a list of four alternatives. See [Supporting Information](#) for more details.

Scoring

The Doors and People Test was administered to all patients with developmental amnesia ($N = 23$, 11 females, mean age: 20.3 years, SD: 9.1, range: 8–40) and to 21 controls (11 females, mean age: 17.6 years, SD: 8.6, range: 8.2–38). One of the patients performed all but the "Names" subtest ("People," "Doors," "Shapes": $N = 23$; "Names": $n = 22$). Given that the developmental amnesia group included individuals under the age of 16, which is the first age band at which standard scores are available on the Doors and People Test, we used standard scores based on the scores of our control group; raw scores (SD): People, 28.2 (6.9); Doors, 18.9 (3.8); Shapes, 34.6 (2.7); Names, 18.6 (3.7). For the verbal and visual recall subtests ("People" and "Shapes"), the maximum score was 36. For the verbal and visual recognition subtests ("Names" and "Doors"), the maximum score was 24. We converted patients' and controls' raw scores to z-scores relative to the control group's scores. For the analysis of the data, we then used nonparametric tests as the data were not normally distributed in all four subtests (Shapiro–Wilk test of normality; control: $p < .001$; patients: $p = .044$).

3 | RESULTS

3.1 | Neuroradiological assessment

Neuroradiological ratings based on visual inspection of the MR images provided independently by one of the authors (WKKC) revealed abnormally small fornix and mammillary bodies in all but two patients with developmental amnesia (Table S1). No abnormalities were detected in the parahippocampal gyrus (perirhinal, entorhinal, and parahippocampal cortices), or the thalamus, and the basal ganglia. Additional visible abnormality was observed in some cases in the WM and the cerebellum. The pattern of visible abnormality detected within the hippocampal circuit, and the notable absence thereof in other cortical and subcortical structures, was consistent across individual patients irrespective of their varying etiology, and age at hypoxic-ischemic-induced hippocampal damage.

3.2 | Voxel-based morphometry

CAT12/SPM12 VBM analysis provided estimates of GM volumes in patients with developmental amnesia and controls (Figures 1 and 2). GM volume was significantly reduced bilaterally in the hippocampus (left: -24.1% ; right: -24.3% ; both $p < .001$), thalamus (left: -17.1% ; right: -17.0% ; both $p < .001$), and amygdala (left: -11.6% ; right: -10.1% ; both $p < .001$) in patients with developmental amnesia compared to controls. Milder GM volume reductions were observed in patients with developmental amnesia in the caudate nucleus (left: -9.8% ; right: -7.6% ; both $p < .02$), entorhinal area (left: -5.6% ; right: -4.7% ; both $p < .05$), parahippocampal gyrus (left: -5.5% ; right: -5.3% ; both $p < .05$) and in the right putamen (-6.9% ; $p < .05$). Other significant differences are shown in Table S3. CAT12/SPM12 also provided estimates of cortical surfaces (thickness). Analysis based on the gyral-based atlas "Desikan-Killiany-Tourville" (Desikan et al., 2006) revealed a mild reduction in the parahippocampal gyrus thickness (left: -9.3% ; right: -7.2% ; both $p < .01$) in patients with developmental amnesia. Other significant differences are shown in Table S4.

3.3 | FreeSurfer automatic segmentation

FreeSurfer provided volume estimates of subcortical areas in patients with developmental amnesia and controls (Figure 2). Significant volume reductions were observed bilaterally in patients with developmental amnesia in the hippocampus (left: -30.4% ; right: -33.8% ; both $p < .001$), thalamus (left: -11.6% ; right: -10.9% ; both $p < .001$), caudate (left: -11.1% ; right: -9.2% ; both $p < .01$), putamen (left: -10.3% ; right: -8.4% ; both $p < .01$), and ventral diencephalon (left: -8.6% ; right: -7.6% ; both $p < .001$). Volume reductions were also observed in the left pallidum (-7.2% ; $p < .01$) and right amygdala (-9.4% ; $p < .01$). FreeSurfer identified a reduction in the cerebral WM (-6.2% ; $p < .01$) and corpus callosum (-11.9% ; $p < .01$) volume in patients with developmental amnesia. FreeSurfer also provided estimates of cortical GM volumes. Significant cortical GM volume reduction was observed in patients with developmental amnesia in the bilateral parahippocampal cortex (left: -10.3% ; right: -11.9% ; $p < .05$) and in the right medial orbitofrontal cortex (-6.5% ; $p < .01$).

Automated segmentation of hippocampal substructures using the FreeSurfer tool revealed more pronounced atrophy of the posterior hippocampus (body + tail) than the hippocampal head in patients with developmental amnesia (-36% and -26% , respectively; paired t test, $t_{(22)} = -5.64$; $p < .001$).

3.4 | Manual segmentation estimates

Three hippocampal subregions (uncus, CA-DG, and subicular complex) and three surrounding cortical areas (entorhinal, perirhinal, and parahippocampal cortices) were manually segmented in healthy controls ($N = 32$) and developmental amnesia patients ($N = 23$) (Figures S1 and S2). The volume of the hippocampus as a whole was 40% smaller

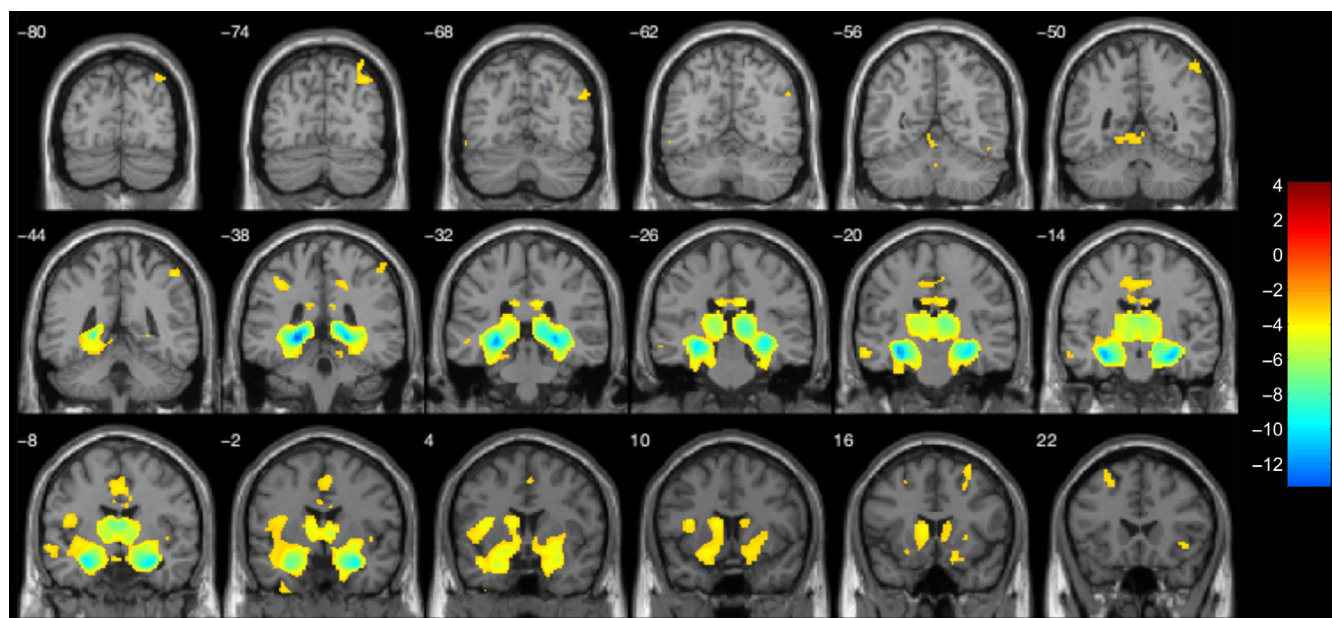


FIGURE 1 Results of CAT12/SPM12 voxel-based morphometry analysis comparing patients with developmental amnesia to healthy controls. Differences between a group of controls ($N = 32$) and a group of patients with developmental amnesia ($N = 23$). Main differences were observed in the bilateral hippocampus, thalamus, and amygdala ($p < .001$).

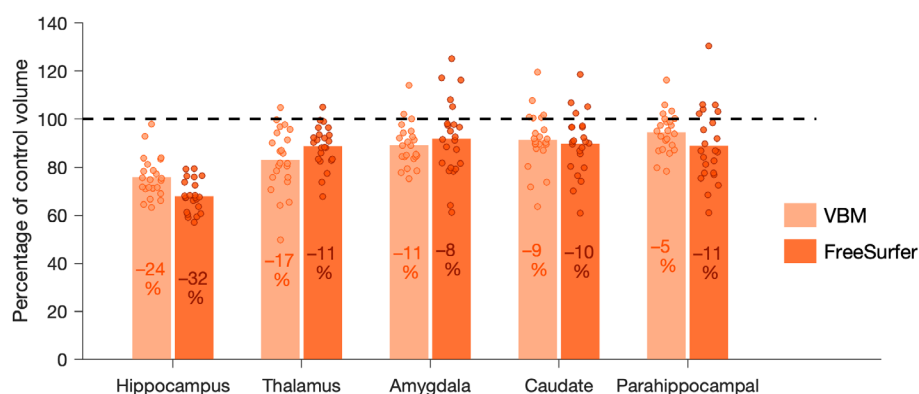


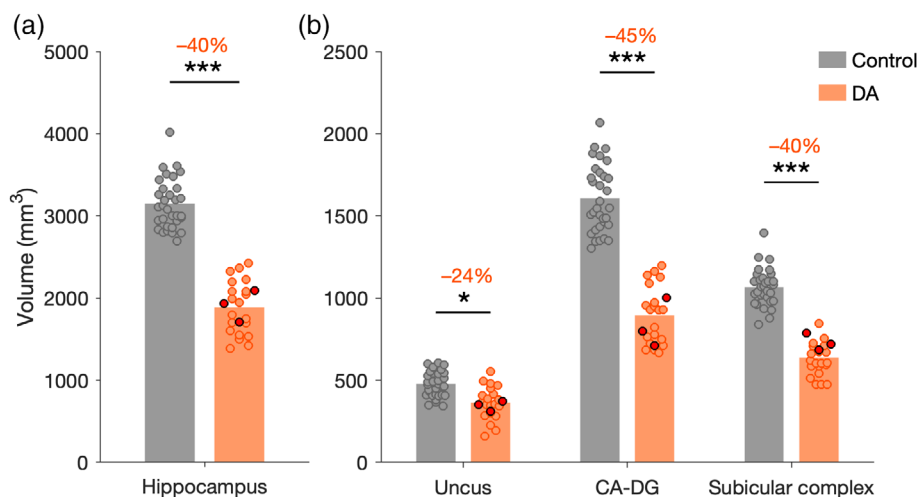
FIGURE 2 Brain areas with significant volume reduction in patients with developmental amnesia according to both voxel-based morphometry (VBM) and FreeSurfer analysis. Volumes of regions of interest in patients with developmental amnesia ($N = 23$) are shown as a percentage of the mean control volume ($N = 32$). Percentage values refer to the mean difference to control group. Volumes are calculated as the average of left and right hemisphere volumes. All volumes are corrected for intracranial volume and age.

in the patients than in the control group (range: -23% to -56% ; $t_{(53)} = -14.9$; $p < .001$) (Figure 3; Table S5). The volume of the hippocampal subregions was also significantly smaller in the patients than in the control group (two-way analysis of variance [ANOVA], $F_{(1,159)} = 382.0$, $p < .001$). The uncus was 24% smaller (range: $+16\%$ to -67% ; Tukey's honestly significant difference (HSD) post hoc test: $p = .024$), the CA-DG subregions were 45% smaller (range: -25% to -58% ; $p < .001$), and the subicular complex was 40% smaller (range: -21% to -55% ; $p < .001$). The level of atrophy of the patients' hippocampal subregions differed significantly from each other ($F_{(2,66)} = 12.9$, $p < .001$). Tukey's HSD post hoc test indicated that the CA-DG and subicular complex showed greater atrophy than the uncus (both $p < .001$).

The volume of the subicular complex and CA-DG subregions were correlated in both control and patient groups (Figure S3; control, $r_{(31)} = 0.46$; $p = .009$; DA, $r_{(22)} = 0.65$; $p < .001$). The volume of the uncus was not significantly correlated with other hippocampal subregions in controls (both $p > .1$) and only with the CA-DG subregion in patients with DA ($r_{(22)} = 0.6$; $p = .003$).

Atrophy of the hippocampus in the patients group was significantly lower in its anterior (-41%) than its posterior (-49%) segment (using the uncus apex as a landmark; paired t test, $t_{(22)} = 2.2$; $p = .036$). Because no differences were observed between the anterior and the posterior segment of the CA-DG (paired t test, $t_{(22)} = 1.2$; $p = .26$) or subicular complex ($t_{(22)} = 1.2$; $p = .25$) subregions, the lower level of atrophy observed in the anterior part of

FIGURE 3 Volume of the hippocampus and its subregions in developmental amnesia. Volume of the hippocampus (a) and its subregions (b, uncus, CA-DG, and subicular complex) in control (gray; $N = 32$) and developmental amnesia (orange; $N = 23$) groups. The three patients with DA who were older at onset are shown in darker color. Volumes are calculated as the average of left and right hemisphere volumes. Percentage values refer to the mean difference to control group. All volumes are corrected for intracranial volume and age. $*p < .05$; $***p < .001$.



the whole hippocampus can be attributed to the relatively more preserved uncus.

There was a global difference in the volume of the entorhinal, perirhinal, and parahippocampal cortices between the control and patient groups (Table S5; two-way ANOVA, $F_{(1,159)} = 7.8$, $p = .006$), but no statistical differences in pairwise comparisons when perirhinal, parahippocampal, and entorhinal cortex were examined separately (Tukey's HSD, all $p > .26$).

3.5 | Comparison between segmentation methods

Hippocampal volume estimates obtained with the VBM, FreeSurfer, and manual segmentation protocols were compared. While the automated methods reported reliable group differences, VBM and FreeSurfer overestimated the hippocampal volume compared to manual segmentation. In the VBM analysis, hippocampal volume was overestimated by 5% in the control group and by 33% in the DA group compared to our manual estimates. In the FreeSurfer analysis, hippocampal volume was overestimated by 33% in the control group and by 51% in the DA group. The correlations between corrected hippocampal volume estimates obtained by the automatic and manual segmentation methods were strong in the control group but weak in the group of patients with developmental amnesia (Figure S4).

3.6 | Doors and People Test

All patients with developmental amnesia ($N = 23$) and 21 of the control participants were assessed on the Doors and People Test, which provides equated measures of recognition and recall in the visual and verbal domains. All patients' subtest scores were significantly below zero (Wilcoxon signed rank test: all $Z < -2.4$, all $p < .016$), indicating that patients were impaired relative to controls (who represent zero, as their scores were used to convert raw scores into z-scores). The patients' scores for the four Doors and People subtests differed significantly from each other (Friedman's test: $\chi^2_{(3,n=22)} = 43.7$, $p < .001$).

The visual recall ("Shapes") subtest yielded a significantly greater deficit than all of the other subtests (all $p < .001$). The degree of deficit on the verbal recall ("People") subtest was greater than on the two recognition subtests (both $p < .02$). The degree of deficit was greater on the visual recognition ("Doors") subtest than on the verbal recognition ("Names") subtest ($p = .001$). Collapsing across subtests, we found a greater deficit in recall compared with recognition ($Z = -4.04$; $p < .001$) and a greater deficit in memory for visual compared with memory for verbal material ($Z = -4.11$; $p < .001$).

We observed significant negative correlations between the two recall subtest scores and the volume of the uncus in the developmental amnesia group (verbal recall ["People"]: Pearson's $r_{(22)} = -0.50$; $p = .015$; visual recall ["Shapes"]: $r_{(22)} = -0.42$; $p = .047$; Figure 4a,b). No other correlations for other subtests or other ROI in the developmental amnesia group were significant (all $p > .15$; Table S6). Collapsing across test material confirmed that scores on recall were inversely correlated with the volume of the uncus in the developmental amnesia group ($r_{(22)} = -0.49$; $p = .016$; Figure 4c). In the control group, no correlations for any subtests or ROI were significant (all $p > .18$; Table S6).

3.7 | WISC-IV/WAIS-III

All patients with developmental amnesia ($N = 23$) and 23 of the control participants were assessed on the WISC-IV or WAIS-III. Patients were impaired relative to our group of controls only for the Perceptual Reasoning Index scores (two-way ANOVA, $F_{(1,176)} = 10.61$, $p = .001$; Tukey's HSD post hoc test, $p = .04$; all other $p > .25$). There were significant inverse correlations between the volume of the uncus and patients' scores for the Verbal Comprehension Index, the Perceptual Reasoning Index, the Working Memory Index, and the Processing Speed Index (all $r_{(22)} < -0.42$; all $p < .05$; Figure 5; Table S7). The Processing Speed Index scores were also negatively associated with the volume of the subicular complex in patients ($r_{(22)} = -0.43$; $p = .04$). In controls, the Working Memory Index scores were positively associated with the volume of the subicular complex ($r_{(22)} = 0.46$; $p = .026$).

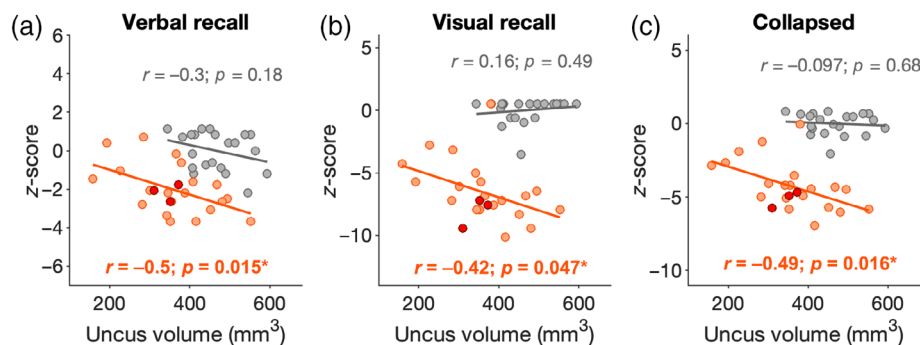


FIGURE 4 Doors and People recall scores correlations with the volume of the uncus. The patients' scores (orange; $N = 23$) on recall subtests of the Doors and People Test correlated negatively with the volume of the uncus. (a) Verbal recall ("People") subtest. (b) Visual recall ("Shapes") subtest. (c) Collapsed scores. The controls' scores (gray; $n = 21$) did not correlate with the volume of the uncus. The three patients with DA who were older at onset are shown in darker color. Pearson's correlation coefficient. All volumes are corrected for intracranial volume and age. * $p < .05$.

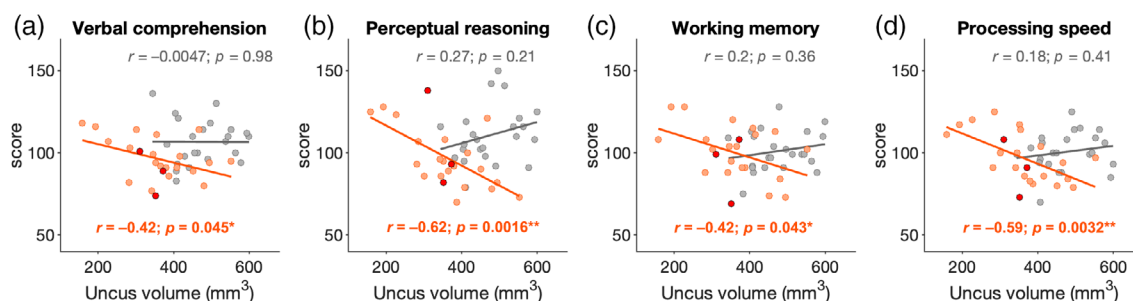


FIGURE 5 Wechsler Intelligence Scale for Children, 4th Ed. (WISC-IV)/Wechsler Adult Intelligence Scale, 3rd Ed. (WAIS-III) indices scores correlations with the volume of the uncus. The patients' scores (orange; $N = 23$) on Wechsler Intelligence Scales WISC-IV or WAIS-III correlated negatively with the volume of the uncus. (a) Verbal Comprehension Index. (b) Perceptual Reasoning Index. (c) Working Memory Index. (d) Processing Speed Index. The controls' scores (gray; $n = 23$) did not correlate with the volume of the uncus. The three patients with DA who were older at onset are shown in darker color. Pearson's correlation coefficient. All volumes are corrected for intracranial volume and age. ** $p < .01$; * $p < .05$.

4 | DISCUSSION

In this study, we documented the extent of brain damage in patients who had suffered hypoxic-ischemic episodes in infancy or childhood and later developed the syndrome of developmental amnesia. While the hippocampus exhibited the greatest degree of atrophy, we show that damage also occurs in the thalamus and to a lesser extent, in the amygdala, caudate, and parahippocampal gyrus in patients with developmental amnesia. These findings replicate and extend previous reports in the same cohort of patients (Dzieciol et al., 2017; Gadian et al., 2000). We also addressed the question of whether the volumes of residual hippocampal subregions are associated with cognitive memory performance in these patients. Using a combination of neuropsychological test results, we showed several inverse relationships between the volume of the residual uncus and patients' performance on recall memory, Verbal Comprehension Index, Perceptual Reasoning Index, Working Memory Index, and Processing Speed Index. The effects reported here suggest that in patients with developmental amnesia, the remaining hippocampal tissue, depending on its extent of damage, provides signals that may inhibit compensatory mnemonic

development by the relatively preserved surrounding cortical areas. This process could occur because the absence of hippocampal inputs promotes structural and/or functional reorganization in areas connected to the hippocampus (Chareyron et al., 2016; Villard et al., 2023). This extent of the anatomical or functional reorganization may depend on the extent of hippocampal damage and the level of remaining hippocampal signals. However, whatever the extent of hippocampal damage in developmental amnesia, and despite these compensatory reorganizations, hippocampal-dependent episodic memory retrieval remains irreversibly compromised.

4.1 | Methodological considerations

Although manual tracing is still the gold standard for measuring the volumes of hippocampal subregions and cortical areas on MRI acquisitions, especially in the case of patients, manual segmentation is subjective and susceptible to measurement errors. Also, the precision of the measure is limited by the resolution of the MRI scans. However, analyses of magnetic resonance (MR) images for estimating the extent

of hippocampal damage in amnesic patients have been validated by postmortem examinations (Rempel-Clower et al., 1996). In particular, a clear concordance has been reported in the appearance of the damaged hippocampus on the MRI and in the histological sections (Rempel-Clower et al., 1996). Here, we used in addition a combination of automated and manual approaches, all of which showed the same pattern of damage in patients, particularly along the antero-posterior axis of the hippocampus and the parahippocampal gyrus. The present study shows that although hippocampal volume estimates obtained with automated methods are overestimated (Schmidt et al., 2018), particularly in the hippocampal-lesioned population, automated methods can reliably detect differences between experimental groups. Volumetric estimates obtained by automated methods in control subjects can be correlated with those obtained by manual methods, but this is not the case for volume estimates in patients with hippocampal damage, highlighting the contribution of manual segmentation and the need for a combination of approaches.

4.2 | Differential effect of early hypoxia-ischemia on hippocampal subregions

Our observation that the cornu ammonis - dentate gyrus (CA-DG) were the most affected hippocampal subregions in patients with developmental amnesia is congruent with documented reports of greater sensitivity of this subregion to hypoxia-ischemia. It has long been known that hypoxia and ischemia result in selective neuronal death in the CA1 field (Schmidt-Kastner & Freund, 1991), although the reason for this selectivity is still debated (Wang & Michaelis, 2010). Neurohistological studies of patients who suffered ischemic episodes in adulthood have reported cases with neural cell loss restricted to the CA1 region bilaterally, whilst the CA1' region of the uncus, the subiculum, CA3, and surrounding cortices were all preserved (Rempel-Clower et al., 1996; Zola-Morgan et al., 1986). High-resolution magnetic resonance imaging showed that CA1 was always affected in patients with hippocampal damage (Bartsch et al., 2015).

In contrast, the uncus showed a low sensitivity to hypoxia in our patient cohort, which could be a reflection of the distinct vascularization of this hippocampal subregion. The branches of the posterior cerebral artery (PCA) coming from the vertebral artery irrigate the posterior part of the hippocampus, while the branches of the anterior choroidal artery (AchA) originating from the internal carotid artery irrigate the uncus portion of the hippocampus (Erdem et al., 1993; Huther et al., 1998; Marinković et al., 1992). Hippocampal blood supply shows great individual variability. High-resolution angiography and anatomical studies have highlighted that the anterior hippocampal region (including the uncus) could receive a mixed blood supply (from both the PCA and the AchA) in about half of individuals studied, whereas in the other half a single supply (from the PCA only) is observed (Erdem et al., 1993; Perosa et al., 2020; Spallazzi et al., 2019). A mixed blood supply in the anterior hippocampal region could provide more vascular reserve and lower vulnerability to

neuronal injury and atrophy (Liebeskind, 2003). Thus, in a proportion of individuals with a mixed blood supply, the uncus might exhibit greater resistance to the adverse effects of hypoxic-ischemic events than the other hippocampal regions.

4.3 | Uncus, recall, and working memory

The residual uncus could be partly functional in patients with developmental amnesia and could be recruited for recall and working memory. Connectivity studies in nonhuman primates have shown that the uncus is less connected to other regions of the hippocampus, and that it has its own associational system of connections (Kondo et al., 2009). Notably, the uncus is also the only hippocampal region reciprocally connected to its contralateral counterpart (Amaral et al., 1984). The uncus' unique connectivity could allow this region to support some information processing despite severe damage to the other hippocampal areas. We reported here that the volume of the uncus correlated negatively with recall scores as well as working memory performance in patients with developmental amnesia. In the WAIS-III/WISC-IV test, Working Memory Index is made up of two subtests (Digit Span and Letter Number Sequencing) both requiring immediate verbal recall. The function of the uncus is not well understood mainly because its structure-function mapping remains to be determined in rodents (Ding, 2013), but in humans, the uncus has been proposed to be involved in the long-term recall of scenes (Zeidman et al., 2015). With regard to working memory, the more established view is that the hippocampus does not contribute significantly to working memory (Eichenbaum, 2006; Eichenbaum et al., 1994). However, an alternative view suggests that the hippocampus can contribute to any memory task, including working memory (Hannula & Ranganath, 2008; Libby et al., 2014), in particular in supporting high-precision binding (Borders et al., 2022). Our observation of a negative correlation between uncus volume and working memory performance suggests that the uncus may be recruited for recall and working memory in patients with DA.

We propose that the perirhinal, entorhinal, and parahippocampal cortices normally involved in the binding of information in the short term (Miyashita, 2019) may be subject to plastic changes in patients with developmental amnesia and that these plastic changes may depend on the degree of hippocampal damage. The possibility that the hippocampal damage in patients with developmental amnesia may not influence memory performance directly, but indirectly via reorganization of the MTL circuit is explored below.

4.4 | Functional hypotheses

Experimental studies in nonhuman primates have reported similar counterintuitive findings to those reported in the present study. Monkeys with small hippocampal lesions exhibit greater memory loss on a Delayed Nonmatching-to-Sample (DNMS) task than that found in animals with greater damage (Bachevalier & Mishkin, 1989).

Furthermore, a positive correlation between the extent of damage to the hippocampus and scores on a DNMS task has been reported in experimentally lesioned monkeys (Murray & Mishkin, 1998). Several hypotheses have been proposed to explain why discrete lesions result in greater memory impairment (Bachevalier & Mishkin, 1989; Baxter & Murray, 2001; Beason-Held et al., 1999). However, it is difficult to relate these findings obtained following adult experimental lesions in the monkey to observations in patients with early hippocampal damage whose circuits might have undergone massive compensation. One hypothesis to explain our observations is that the level of hippocampal damage would likely have a strong direct influence on the organization of the MTL memory circuits in the adult. Following an early event of hypoxia-ischemia, greater hippocampal damage might induce greater compensatory reconfigurations in the neural circuits and enable other structures, in particular the surrounding cortical areas normally recruited by the hippocampus, to assume important aspects of memory function. In contrast, when the hippocampus is only partially damaged, the information flow would remain present in the hippocampus and could result in incomplete, and possibly disruptive information processing. Our observation could thus reveal the existence of multiple, redundant routes within the residual hippocampal subregions and surrounding cortical areas in patients with developmental amnesia (Aggleton et al., 2000). These parallel circuits could compete for the control of behavior and disrupt memory performance (Baxter & Murray, 2001).

Our findings are consistent with the hypothesis that a close relationship can be evidenced between the volume of remaining hippocampal subregions and the severity of cognitive deficits in patients with hippocampal damage; in the case of patients with developmental amnesia, this relationship was inverse. Our observations also provide further support for the model of hierarchical organization of cognitive memory (Mishkin et al., 1997) by proposing that surrounding cortical areas normally involved in the encoding of associative relations between decontextualized (semantic) information (Miyashita, 2019) could reorganize to enhance the capture of content, though not context, of memoranda, thus partially compensating for hippocampal dysfunction following early hippocampal damage. The absence of hippocampal competition may not be the only explanation for the superior semantic memory of patients with DA, as patients with late-acquired hippocampal damage show altered semantic and recognition memory (Bayley & Squire, 2005; Manns et al., 2003; Scoville & Milner, 1957). Our hypothesis is that following hippocampal damage during early development, structural and/or functional reorganization leads MTL cortical structures to rescue some of the hippocampal functions. The limits of this reorganization, however, may be determined by the extent of damage to the hippocampal subregions.

Evidence for such reorganization has already been reported in a nonhuman primate model of early hippocampal damage. Monkeys with early bilateral hippocampal lesion can learn new spatial relational information in striking contrast to monkeys with adult lesion (Banta Lavenex et al., 2006; Lavenex et al., 2007). Interestingly, in these monkeys with early hippocampal lesions, the surrounding cortical areas were largely preserved and were shown to contribute to spatial

learning in the absence of functional hippocampal circuits (Chareyron et al., 2017). Also, a recent report showed that the number of immature neurons in the entorhinal and perirhinal cortices was higher in monkeys with early hippocampal lesions than in controls (Villard et al., 2023). This increase in the number of immature neurons was paralleled by an increase in the number of mature neurons in the entorhinal cortex of neonate-lesioned monkeys compared to controls. These structural changes may contribute to some functional recovery after early hippocampal injury (Villard et al., 2023).

One could speculate that the functional reorganization of the perihippocampal structures (normally devoted to the processing of decontextualized information) to compensate hippocampal function could, in turn, benefit the processing of semantic memory and lead to better context-free memory performance in patients (see (Kapur et al., 2013)). Indications of increased memory performance have indeed been reported in two different patients with developmental amnesia. Jonin et al. (2018) studied patient “KA” presenting with 55% hippocampal volume reduction and preserved perihippocampal structures. While patient KA displayed few, if any, residual episodic abilities, this patient was able to accurately retrieve semantic memories, and show evidence of superior or even very superior access to these memories compared to controls. Another patient with developmental amnesia, patient “Jon,” has often produced response accuracy levels that are higher than those of control participants in previous experimental explorations of visuospatial working memory (Allen et al., 2014, 2022; Baddeley et al., 2010). Jon was numerically superior to the control mean on recognition-based measures of shape-color binding (Baddeley et al., 2010). In measures of color-location memory, Jon's recognition accuracy matched the highest achieving control participant, while his reconstruction performance was superior to six of the seven controls (Allen et al., 2014). Across four tasks measuring binding between color and orientation, or color and location using simultaneous or sequential presentation of stimuli, Jon's response accuracy was high, and always numerically superior to the control mean (Allen et al., 2022).

These observations from single patient studies together with the present findings, obtained in a large cohort of patients with developmental amnesia, support the hypothesis of a reorganization of the relatively preserved perihippocampal areas following early hippocampal damage.

Structural and/or functional reorganization in patients with DA may not be restricted to MTL regions and may involve other brain areas, including frontal, parietal, and visual cortices. In controls, in addition to the parahippocampal gyrus, the precuneus and middle temporal gyrus may be involved in episodic retrieval (Joensen et al., 2024), while frontotemporal interactions are crucial for working memory maintenance, especially when the hippocampus is involved (Daume et al., 2024; Malik et al., 2022; Spellman et al., 2015). When asked to construct scenes in his imagination, a patient with DA was shown to recruit frontal regions, retrosplenial cortex, and posterior parietal cortex to a greater extent than control participants (Mullally et al., 2014). Also, scene reinstatement effects were stronger in patients with DA than controls in areas extending posteriorly to the

retrosplenial cortex toward the occipital cortex (Elward et al., 2021). It was proposed that the low-level representational capabilities of the primary visual cortex could be recruited in DA to support associative memory (Rosenthal et al., 2016, 2018). These observations in patients with DA suggest that the rescue of some aspects of hippocampal function following early damage may involve a number of brain regions not limited to the MTL.

5 | CONCLUSIONS

Our results have important implications for understanding the organization of the memory circuit following early hippocampal injury. These observations highlight the counterintuitive finding that in patients with developmental amnesia, greater hippocampal damage can be associated with better performance in different cognitive processes, such as recall memory, verbal comprehension, perceptual reasoning, working memory, and speed of information processing. In contrast, less severe damage, leaving behind relatively preserved hippocampal subregions, can lead to more pronounced cognitive deficits. These unexpected findings can disentangle the functional organization of the MTL memory system and attribute a central role in the compensation of cognitive memory to extra-hippocampal structures in patients with early hippocampal damage.

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CONFLICT OF INTEREST STATEMENT

The authors report no competing interests.

DATA AVAILABILITY STATEMENT

The anonymized participant data will be available upon reasonable request.

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