Title

Paradoxical consequences of early hippocampal damage: greater atrophy is associated with better recall, working memory and visuospatial perception in developmental amnesia

Authors/Affiliations

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Abstract

Despite bilateral hippocampal damage dating to perinatal or early-childhood period, patients with developmental amnesia (DA) exhibit well-developed semantic memory, but severely impaired episodic memory. It is not clear, however, whether the residual hippocampus plays a role in encoding and/or retrieval of new information, or the surrounding cortical areas rescue aspects of these critical cognitive memory processes after early injury. We used manual MRI segmentation to estimate the volume of three hippocampal subregions and three surrounding cortical areas in 23 patients with DA and 32 controls. 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 (−23%). In contrast, volumes of entorhinal, perirhinal and parahippocampal cortices were smaller than those of controls, but not statistically different. Patients' recall, Verbal IQ, Working Memory Index and Processing Speed Index scores correlated negatively with the volume of the uncus while spatial perception/immediate memory performance correlated negatively with the volume of the subicular complex. We propose that in patients with DA, no other structure can perform the function of the hippocampus in episodic memory. However, cognitive memory processing is compromised as a function of extent of atrophy in hippocampal subregions, such that the greater the damage, the more likely that preserved surrounding cortical areas will be recruited to rescue the putative functions of the damaged subregions. Our findings document for the first time not only the extent, but also the limits of circuit reorganization occurring in the young brain following bilateral hippocampal damage.

Introduction

Developmental amnesia

We previously identified a group of patients with hippocampal atrophy who had suffered hypoxic-ischaemic 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. 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, and severely restricting recall and recognition processes (Bayley and Squire, 2005; Manns et al., 2003; Scoville and 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, and spatial processing deficits, but relatively preserved semantic memory, working memory, and recognition performance. We have labeled this dissociated form of memory function 'developmental amnesia' (DA, 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 organization that has occurred in patients with DA is likely to be distinct from what is observed in patients with hippocampal damage acquired in adulthood. Also, in patients with acquired hippocampal lesions, the damage has occurred to already-established, and normally-functioning memory circuits, whereas in patients with DA, the early bilateral lesions have probably led to the development of a different memory system. For these reasons, it is difficult, and somewhat inappropriate, to compare memory function and cognitive profiles in patients with DA to those of patients with adult-onset amnesia (Elward and Vargha-Khadem, 2018, P: 24-26).

To date, a cohort of 18 patients with DA has been reported, each patient having suffered an episode of hypoxia-ischaemia in early life (Dzieciol et al., 2017). Importantly, irrespective of the underlying aetiology (Geva et al., 2020), or age at onset (Vargha-Khadem et al., 2003), the hypoxic-ischaemic event was the cause of hippocampal damage and cognitive impairment (Cooper et al., 2015).

Memory circuit reorganization

Among the many questions that have arisen from the study of patients with DA, the foremost concerns the regions of the medial temporal lobe (MTL) and/or preserved hippocampal subregions that could be involved in memory circuit reorganization following early hippocampal damage.

In the model of hierarchical organization of cognitive memory proposed by Mishkin and colleagues (1997; see also: Baddeley, 2020; Vargha-Khadem and Cacucci, 2021), recollection and familiarity depend on different MTL structures. According to this model, the perihippocampal gyrus, and in particular the perirhinal cortex, may support familiarity, while the hippocampus may support recollection (Argyropoulos et al., 2021). The selectivity of impairment observed in patients with DA has provided strong support for this dual-process model.

Because patients with DA have both neuroradiological and quantitatively-confirmed bilateral hippocampal atrophy, but no visible abnormality within the parahippocampal region, it has been proposed that their episodic memory impairment, and recall/recollection deficits are due to their hippocampal pathology, whereas their relatively intact semantic memory, and

recognition/familiarity processes are due in part to the preservation of the perihippocampal gyrus.

Hippocampus

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 (Schmidt-Kastner and Freund, 1991) while the adjacent CA3 remains less vulnerable (Wang and 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 of patients who suffered ischemic episodes in adulthood have reported neural cell loss either restricted to the CA1 region, or distributed in the dentate gyrus, subiculum, uncus and entorhinal cortex (Rempel-Clower et al., 1996; Zola-Morgan et al., 1986). The preservation of circumscribed hippocampal subregions following injury of early-onset in DA could account for the increased activation of the residual hippocampus during different memory tasks (Maguire et al., 2001; Rabin et al., 2016), although activation *per se* does not necessarily imply correspondingly intact function (Elward et al., 2021).

In the study reported by Dzieciol and colleagues (Dzieciol et al., 2017), the degree of hippocampal atrophy in patients with DA ranged from 28% to 62% compared to healthy controls. 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. It would thus be possible to assess whether the compensatory response in patients with DA is dependent on the extent of atrophy in the hippocampal subregions. One way to address this is to evaluate the association between task-dependent neuropsychological performance and volumes of hippocampal subregions

Perihippocampal gyrus

While 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), 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 DA didn't find abnormality in the subhippocampal structures within the medial temporal lobe, 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 DA was similar to controls (Elward et al., 2021). However, the structural integrity of the perihippocampal gyrus, and by implication, the integrity of the hypothesized substrate of semantic memory and other preserved mnemonic processes remain to be quantitatively assessed in patients with DA.

Here, we have used manual segmentation of MRI scans to obtain estimates of the volume of three hippocampal subregions: the uncus [uncal portion of the hippocampus (Zeidman and Maguire, 2016)], the CA-DG (including CA fields and dentate gyrus) and the subicular complex (including subiculum, presubiculum and parasubiculum), and three surrounding cortical areas (entorhinal, perirhinal

and parahippocampal cortices) in patients with DA and healthy controls. Controls and patients were assessed with neuropsychological tests of intelligence (WISC or WAIS), recall/recognition for verbal and visual material (Doors and People Test) and spatial perception/memory (Four Mountains Test). Finally, we investigated the relationships between degree of atrophy of hippocampal subregions and cognitive deficits.

We predicted that: (i) residual hippocampal subregions and/or surrounding cortical areas were sufficiently preserved to rescue some aspects of hippocampal function, and (ii) plastic changes in these regions occurred as a function of hippocampal damage in all patients with DA.

We documented several paradoxical inverse relationships: i) between the volume of the residual uncus and patients' recall memory performance, Verbal Comprehension Index, Working memory Index and Processing Speed Index, and ii) between the volume of the residual subicular complex and patients' performance on spatial perception/memory. We also reported an absence of structural damage in the surrounding cortical areas in patients with DA.

Results

Volumetric 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 DA (N = 23) groups (Fig. S1).

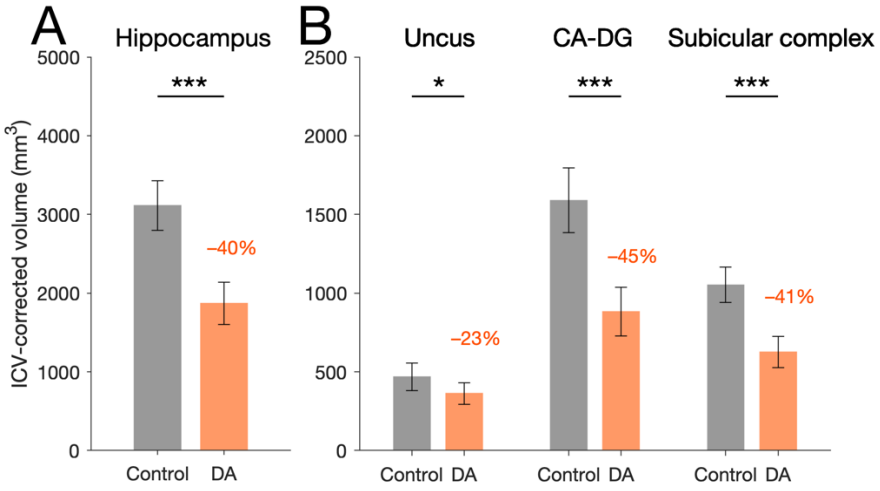

Fig. 1. Volume of the hippocampus and its subregions. Volume of the hippocampus (**A.**) and its subregions (**B.**, uncus, CA-DG, and subicular complex) in control (grey; N = 32) and DA (orange; N = 23) groups. Data are represented as mean ± SD. Percentage values refer to the mean difference to control group. Volumes are calculated as the average of left and right hemisphere volumes. All volumes are corrected for intracranial (ICV) volume. *: P < .05; ***: P < .001.

The volume of the hippocampus as a whole was 40% smaller in the DA than in the control group (range: −26% to −53%; $t_{(53)} = -15.32$; P < .001) (Fig. 1; Table S1). The volume of the hippocampal subregions was also significantly smaller in the DA than in the control group (2-way ANOVA, $F_{(1,159)} = 392.5$, P < .001). The

uncus was 23% smaller (range: +4% to −49%; Tukey's HSD post-hoc test: P = .037), the CA-DG subregions were 45% smaller (range: −28% to −59%; P < .001), and the subicular complex was 41% smaller (range: −22% to −56%; P < .001). The level of atrophy of the patients' hippocampal subregions differed significantly from each other ($F_{(2,66)} = 23.0$, 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).

Atrophy of the hippocampus in the DA group was significantly lower in its anterior (−36%) than its posterior (−44%) segment (paired t test, $t_{(22)} = 2.72$, P = .012; Fig. S2). Because no differences were observed between the anterior and the posterior segment of the CA-DG (paired t test, $t_{(22)} = 0.94$, P = .36) or subicular complex ($t_{(22)} = 1$, P = .33) subregions, the lower level of atrophy observed in the anterior part of the whole hippocampus can be attributed to the relatively more preserved uncus.

In contrast, there was no significant difference in the volume of the entorhinal, perirhinal and parahippocampal cortices between control and DA groups (Table S1; 2-way ANOVA, $F_{(1,159)} = 6.7$, P = .010; Tukey's HSD post-hoc tests, all P > .35). Also, we didn't observe any correlation between the volume of the hippocampus or hippocampal subregions and the volume of surrounding cortical areas in patients with DA (Pearson's correlation analysis, all P > .19).

Neuroradiological assessment

Neuroradiological ratings based on visual inspection of the MR images provided independently by one of the authors (WKC) revealed abnormally small fornix and mammillary bodies in all but two patients with DA (Table S2). 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 white matter 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 aetiology, and age at hypoxic-ischaemic-induced hippocampal damage.

WISC/WAIS

All patients with DA (N = 23) and 23 of the control participants were assessed on the WISC or WAIS. Patients were impaired relative to our group of controls only for the Perceptual Reasoning Index scores (2-way ANOVA, $F_{(1,176)} = 10.61$, P = .001; Tukey's HSD post-hoc test, P = 0.04; all other P > .25). There were significant inverse correlations between the volume of the uncus and patients' scores for the Verbal Comprehension Index (VCI), the Working Memory Index (WMI) and the Processing Speed Index (PSI) (all $r_{(22)} < –0.42$; all P < .05; Fig 2). Looking at PSI scores, we observed an inverse correlations between "Digit Symbol-Coding" score and the volume of the uncus ($r_{(22)} = –0.44$; P = .037) and between "Symbol Search" and the volume of the uncus and subicular complex ($r_{(22)} = –0.43$; P = .04 and $r_{(22)} = –0.44$; P = .037, respectively; Table S3). No other correlations for other ROIs in the DA group were significant. In controls, the WMI scores were positively associated with the volume of the subicular complex ($r_{(22)} = 0.46$; P = .029).

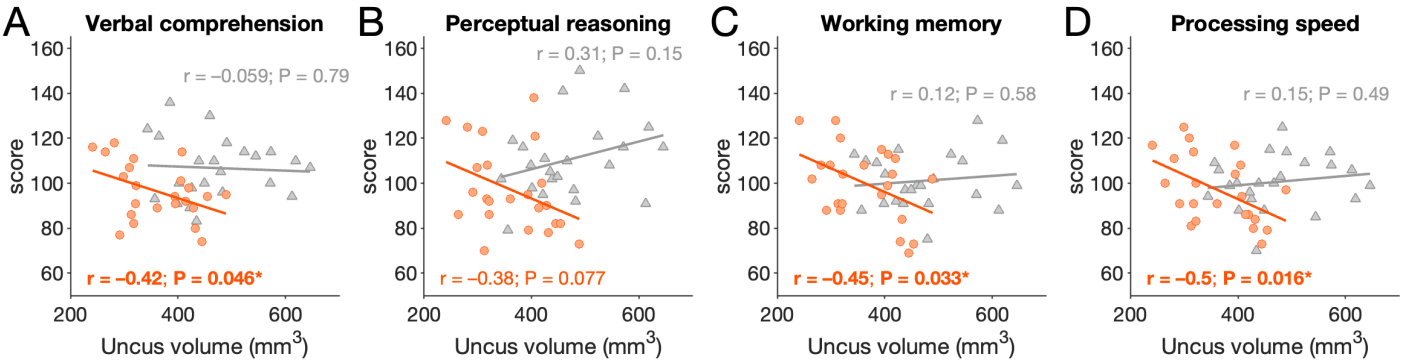

Fig. 2. Inverse correlations between WISC/WAIS indexes scores and the volume of the uncus in patients with DA. Participants' scores on Wechsler Intelligence Scales WISC or WAIS (patients: orange circles, N = 23; controls: grey triangles, n = 23). **A.** Verbal comprehension Index; **B.** Perceptual Reasoning Index; **C.** Working Memory Index; **D.** Processing Speed Index. Pearson's correlation coefficient. All volumes are corrected for intracranial (ICV) volume. *: P < .05.

Doors and People Test

All patients with DA (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 DA group [Verbal recall ('People'): Pearson's $r_{(22)} = –0.47$; P = .02; Visual recall ('Shapes'): $r_{(22)} = –0.55$; P = .007]. No other correlations for other subtests or other regions of interest in the DA group were significant (all P > .09; Table S4). Collapsing across test material confirmed that scores on recall were inversely correlated with the volume of the uncus in the DA group ($r_{(22)} = –0.58$; P = .004; Fig. 3A). As a corollary, we observed that patients with more preserved uncus had significantly lower scores on recall than patients with more damaged uncus (Z = −2.74; P = .006). In the control group, no correlations for any subtests or regions of interest were significant (all P > .11; Table S4).

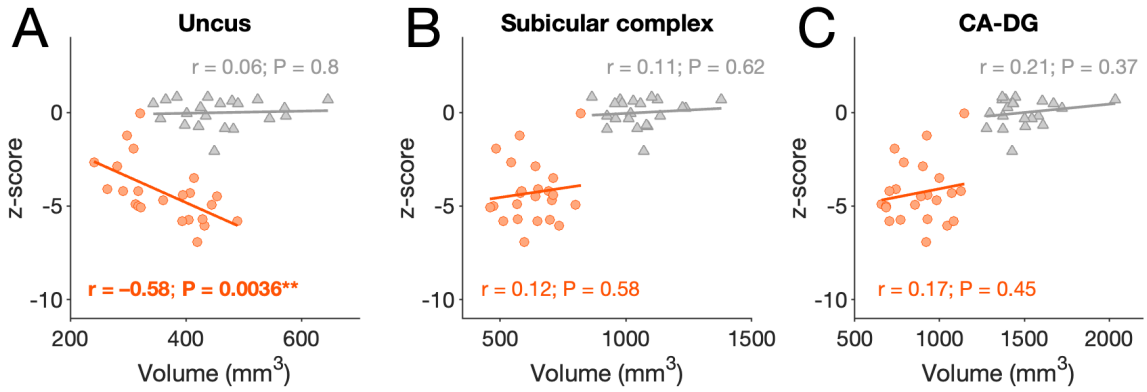

Fig. 3. *Doors and People* recall scores correlations with the volumes of hippocampal subregions. The patients' scores (orange circles; N = 23) on recall subtests of the *Doors and People Test* correlated negatively with the volume of the uncus (**A.**) but not with the volumes of the subicular complex (**B.**) or CA-DG (**C.**). The controls' scores (grey triangles; n = 21) did not correlate with the volume of any subregion. Pearson's correlation coefficient. All volumes are corrected for intracranial (ICV) volume. **: P < .01.

During *Doors and People* testing, the procedures for recall subtests are repeated until all items (names or shapes) are correctly recalled, or for a maximum of three presentations. The patients' scores differed significantly from each other between the three trials of the visual recall ('Shapes') subtest (Friedman's test: $\chi^2_{(2,n=20)} = 8.00$, P = .018) and between the three trials of the verbal recall ('People') subtest ($\chi^2_{(2,n=20)} = 14.15$, P < .001). Post hoc Wilcoxon signed-ranks tests indicated that scores obtained on trial-1 were significantly lower than scores obtained on trial-3 for the visual recall ('Shapes') subtest (Z = −2.72; P = .006) and for the verbal recall ('People') subtest (Z = −2.88; P = .004). Interested to determine potential differences in learning between patients depending on whether they presented with severe or moderate uncus atrophy, we compared increases in patients' scores between trial-1 and trial-3. There was no difference in learning scores between patients with a larger uncus (above group mean volume) and patients with a smaller uncus (Mann-Whitney U test; visual recall ('Shapes'): Z = −1.26; P = .21; verbal recall ('People'): Z = 0.61; P = .54).

Delayed (cued) verbal and visual recall were tested after completion of the verbal and visual recognition subtests, respectively. We found a correlation between patients' scores for the delayed verbal recall ('People') subtest and the volume of the uncus (Pearson's $r_{(20)} = -0.5$; P = .02) while the correlation with delayed visual recall ('Shapes') scores was not significant ($r_{(20)} = -0.3$; P = .18).

Four Mountains Test

Fourteen patients with DA and 19 of the control participants were assessed on the *Four Mountains Test* to examine their perception and immediate memory for topographical information in spatial scenes. Patients' subtest scores converted to z-scores were not significantly below zero (Wilcoxon signed rank test: 'Spatial Perception': P = .75; 'Spatial Memory': P = .13), indicating that many of the patients were not impaired relative to our group of controls. Patients' scores were significantly lower for the 'Spatial Memory' than for the 'Spatial Perception' subtest (Z = −2.67; P = .008). There were significant inverse correlations between patients' scores for the 'Spatial Perception' and 'Spatial Memory' subtests and the volume of the subicular complex ($r_{(13)} = -0.59$; P = .025 and $r_{(13)} = -0.58$; P =

.03, respectively). Collapsing across test material confirmed that scores were strongly inversely correlated with the volume of the subicular complex in the DA group ($r_{(13)} = –0.63$; P = .015) (Fig. 4B). Patients' scores for the 'Spatial Perception' subtest were also negatively associated with the volume of the uncus ($r_{(13)} = –0.54$; P = .047). In the control group, no correlations for any ROIs were significant (all P > .49; Table S5).

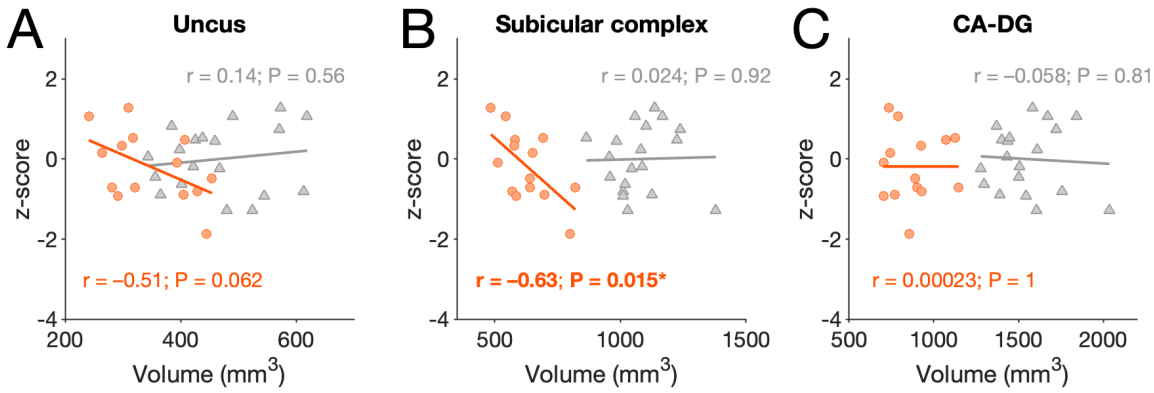

Fig. 4. *Four Mountains* scores correlations with the volumes of hippocampal subregions. The patients' scores (orange circles; n = 14) correlated negatively with the volume of the subicular complex (**B.**) but not with the volumes of the uncus (**A.**) or CA-DG (**C.**). The controls' scores (grey triangles; n = 19) did not correlate with the volume of any subregion. Pearson's correlation coefficient. All volumes are corrected for intracranial (ICV) volume.

Discussion

In this study, we addressed the question of whether the volumes of residual hippocampal subregions and parahippocampal areas are associated with memory and spatial processing performance in patients with hypoxic-ischaemic-induced hippocampal damage of early-onset. Using a combination of neuropsychological test results and volumetric estimations in a large cohort of patients with developmental amnesia (DA), we documented several inverse relationships: i) between the volume of the residual uncus and patients' performance on recall memory, Verbal comprehension Index, Working memory Index and Processing speed Index, and ii) between the volume of the residual subicular complex and patients' performance on spatial perception/memory. The effects reported here suggest that following an early-life exposure to hypoxia-ischemia, the function of hippocampal subregions showing greater damage will more likely be compensated by preserved extra-hippocampal structures. By contrast, hippocampal subregions with milder injury could increase system disruption by maintaining their putative functions. Despite these compensatory reorganizations, hippocampal-dependent episodic memory recall remains irreversibly compromised.

Limitations

Although manual tracing is still the gold standard for measuring the volumes of hippocampal subregions and cortical areas on MRI acquisitions, 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 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). The border between cytoarchitectonic hippocampal subregions were estimated based on delineation of these regions on histological sections (Rosene and Van Hoesen, 1977). The delineation on MR images of the perihippocampal and parahippocampal cortical areas were based on that described in (Insausti et al., 1998). It is not clear to what extent these borders would be affected in the brains of DA patients with significant hippocampal volume reduction. Our observations of an absence of significant volume reduction of the entorhinal, perirhinal and parahippocampal cortices in patients with DA is consistent with previous report showing an absence of significant volume reduction in patients with adult-onset amnesia (Shrager et al., 2008), and in a patient with DA (Jonin et al., 2018). Also, intact parahippocampal activity during scene reinstatement has been described in patients with DA (Elward et al., 2021).

Differential effect of early hypoxia-ischemia on hippocampal subregions

Our observation that the CA-DG were the most affected hippocampal subregions in patients with DA 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 and Freund, 1991), although the reason for this selectivity is still debated (Wang and 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).

The subicular complex was less affected than the CA-DG subregion in patients with DA and this difference could be related to the different levels of maturation of the hippocampal subregions at birth. Quantitative volumetric measurements in non-human primates revealed that the subiculum, presubiculum and parasubiculum develop earlier than the dentate gyrus, CA3, and CA1 (Jabès et al., 2011) and this progressive maturation of the hippocampal circuits may participate in the differential protracted maturation of relational memory processes (Jabès and Nelson, 2015). The level of maturation of the hippocampal subregions at birth could also influence their vulnerability to hypoxia-ischemia (Vannucci and Hagberg, 2004).

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 uncal portion of the hippocampus (Erdem et al., 1993; Huther et al., 1998; Marinković et al., 1992). High-resolution angiography and anatomical studies have highlighted that the anterior hippocampal region could receive a mixed blood supply (from both the PCA and the AChA) in about half of the individuals (Erdem et al., 1993; Perosa et al., 2020). A mixed blood supply could

provide more vascular reserve and lower vulnerability to neuronal injury and atrophy (Liebeskind, 2003). The uncus, which receives a distinct blood supply compared to the rest of the hippocampus, might thus exhibit greater resistance to the adverse effects of hypoxic-ischemic events than the other hippocampal regions.

Uncus and recall memory

The residual uncus could be partly functional in patients with DA and could be recruited for recall memory. We reported here that the volume of the uncus correlated negatively with recall scores as well as working memory performance in patients with DA. In the WAIS/WISC test, Working Memory Index is made up of two subtests (Digit Span and Letter Number Sequencing) both requiring verbal recall in the span of working memory. 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). 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.

Notwithstanding the importance of the uncus in relation to severity of atrophy during delayed recall, this subregion maintains its role during encoding and learning of memoranda in both low and high severity subgroups equally. Thus, we noted that despite their poor performance overall, both patient subgroups incrementally increased their scores across the three learning trials of the *People* and *Shapes* subtests of the *Doors and People Test*. The absence of a difference in performance between the subgroups during encoding and learning, but not during delayed recall, highlights the role of the uncus in retrieval of auditory verbal memory after a delay in patients with DA.

Interestingly, we also reported an inverse relationship between the volume of the uncus and patients' performance in delayed verbal, but not visual recall. Impairment in delayed verbal recall in relation to extent of atrophy of the uncus highlights the vulnerability of auditory verbal information to recall after a delay (Schulze et al., 2012).

Subiculum

Residual circuits of the subicular complex might participate in spatial perception and spatial memory in patients with DA. Here, we reported inverse correlations between spatial perception/memory performance and the volume of the residual subicular complex in patients with DA. The subiculum receives its major excitatory input from CA1, but it also receives a strong projection from the entorhinal cortex (Amaral and Lavenex, 2007; Matsumoto et al., 2019; Witter and Amaral, 2020). The subiculum is also the main source of subcortical projections directed to the hippocampus, and the presubiculum receives the only direct input from the anterior thalamic nucleus (Amaral and Lavenex, 2007; Matsumoto et al., 2019). The subiculum, presubiculum and parasubiculum send dense projections to the entorhinal cortex (Saunders and Rosene, 1988; Witter and Amaral, 2020).

Thus, in the absence of functional CA-DG, the residual subicular complex could marginally participate in input processing through its other interconnections, and in particular, through interaction with the structurally preserved entorhinal cortex which constitutes the main entryway for much of the neocortical input reaching the hippocampus (Amaral et al., 1987).

Animal and human studies suggest that the subiculum plays an important role in spatial processing and spatial representation (Matsumoto et al., 2019). Grid, border, and head direction cells have been found in the subiculum of rodents and primates including humans (Boccara et al., 2010; Lee et al., 2018; Lever et al., 2009; Robertson et al., 1999). In the rat, cross-structural interaction between the subiculum and the ventral striatum has been reported to be critical for spatial memory consolidation (Torromino et al., 2019). In humans, the subiculum is suggested to be specifically involved in scene-based cognitive processing, including scene perception and scene construction during memory recall (Dalton and Maguire, 2017; Hodgetts et al., 2017; Zeidman et al., 2015).

Interestingly, we did not observe correlations between the volume of the subicular complex and patients' performance on the non-spatial tasks of the *Doors and People Test*, suggesting that the subicular complex might be playing a more prominent role in the processing of spatial inputs.

The Processing Speed Index of the Wechsler Scales is made up of two subtests ('Coding' which requires learning and memory and 'Symbol Search' which requires visual scanning/cancellation, and visual stimulus matching, but without memory demands). Interestingly, the Coding scores are negatively correlated with the uncus volume while the Symbol Search scores are negatively correlated with both the uncus and the subicular complex. Our results tend to demonstrate that the hippocampus is involved in two cognitive processes of visual perception, and cognitive memory.

Working memory

We reported here, in addition to an absence of working memory impairment, a negative association between uncus volume and working memory performance in patients with DA. The more established view proposes that the hippocampus plays an important role in episodic memory, spatial cognition, and navigation, while it is not critically contributing to working memory (Eichenbaum, 2006; Eichenbaum et al., 1994). But an alternative view proposes that the hippocampus may contribute to any memory task, including working memory (Hannula and Ranganath, 2008; Libby et al., 2014), in particular in supporting high-precision binding (Borders et al., 2021). This latter possibility is challenged however by the fact that patients with DA presenting with severe hippocampal damage have repeatedly shown unimpaired working memory performance (Allen et al., 2014; Baddeley et al., 2011, 2010). Recent work extended these findings by showing that high resolution working memory performance was unimpaired, and even often superior, relative to control group in a patient with DA (Allen et al., 2022). Our observation of a negative correlation between uncus volume and working memory performance suggests 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 DA and that these plastic changes may depend on the degree of hippocampal damage. The possibility that the hippocampal damage in patients with DA may

not influence working memory performance directly, but indirectly via reorganization of the MTL circuit is explored below.

Functional hypotheses

Experimental studies in nonhuman primates have reported similar paradoxical findings to those reported in the present study. Monkeys with small hippocampal lesions exhibit greater memory loss on Delayed Nonmatching-to-Sample (DNMS) task than that found in animals with greater damage (Bachevalier and 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 and Mishkin, 1998). Several hypotheses have been proposed to explain why discrete lesions result in greater memory impairment (Bachevalier and Mishkin, 1989; Baxter and 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 medial temporal lobe memory circuits in the adult. Following an early event of hypoxia-ischemia, however, 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 perception and memory performance (Baxter and 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 DA 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 information (Miyashita, 2019) could reorganize to contribute to hippocampal function following early hippocampal damage. 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 developmental amnesia. 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 preserved and were shown to contribute to spatial learning in the absence of functional hippocampal circuits (Chareyron et al., 2017).

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 DA. 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 than controls. Another patient with DA, patient 'Jon', has often produced response accuracy levels that are at least higher than those of control participants in previous experimental explorations of visuospatial working memory (Allen et al., 2022, 2014; Baddeley et al., 2010). Jon was at least 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 6 of the 7 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 patients studies together with the present findings, obtained in a large cohort of patients with DA, support the hypothesis of a reorganization of the preserved perihippocampal areas following early hippocampal damage.

Conclusions

Our results have important implications for understanding the organization of memory following early hippocampal injury. These observations highlight the paradoxical finding that in patients with DA greater hippocampal damage can be associated with better performance in recall memory, Verbal comprehension Index, Working memory Index, Processing speed Index and spatial perception. 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 medial temporal lobe memory system, and attribute a central role in the compensation of memory and spatial cognition to extra-hippocampal structures in patients with early hippocampal damage.

Materials and methods

Participants

The patients with DA 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). The most common aetiology was perinatal hypoxic-

ischemic encephalopathy (Table S2). 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 and Jongmans, 2010).

When all the volumetric estimates were completed, one of the patients, who presented with moderate memory deficits and only 11.0% hippocampal volume reduction associated with two unconfirmed episodes of prolonged seizures at age 4, was excluded from the DA group.

Also, we excluded from the DA group a patient with temporal lobe epilepsy presenting with a 25.8% 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 (WKC) 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 DA.

We report here hippocampal volume estimates in 32 control participants (16 females; mean age: 17.7 years, SD 7.7, range 8−38) and 23 patients with DA (11 females; mean age: 19.5 years, SD 9.0, range 8−40).

Structural MRI

Participants were either scanned with a 1.5T-MRI scanner (24 control participants, 16 patients with DA) or with a 3T-MRI scanner (8 control participants, 7 patients with DA).

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 11ms; echo time 4.94ms; in-plane resolution 1mm×1mm; slice thickness of 1mm (Cooper et al., 2011).

Whole brain structural 3T-MRI scans were obtained using a 3T Siemens MRI system 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 1mm×1mm; slice thickness of 1mm; repetition time of 2,300ms; echo time of 2.74ms (Buck et al., 2019).

For the 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.

The hippocampus comprises the CA fields (CA3, CA2, CA1), the dentate gyrus (DG), subiculum, presubiculum, and parasubiculum (Amaral and 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 and Van Hoesen,

2015). For the segmentation of the hippocampus and its subregions, we followed the guide provided by Dalton et al. (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, 2015)], CA-DG (CA fields and dentate gyrus), and subicular complex (subiculum, presubiculum, and parasubiculum). The segmentation of the entorhinal, perirhinal and parahippocampal cortices was based on structural descriptions of human medial temporal lobe and segmentations protocols (Blaizot et al., 2010; Ding and Van Hoesen, 2010; Frankó et al., 2014; Insausti et al., 1998; Kivisaari et al., 2020).

The volumes in cubic millimeters were calculated by summing the number of voxels (1×1×1 mm) for each ROI. The volume of the hippocampus as a whole was calculated as the sum of hippocampal subregions' volumes (uncus, CA-DG, 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 $P > .06$; DA: all $P > .09$). There was no significant difference between volumetric estimates of the whole hippocampus or cortical areas obtained with the 1.5T-MRI scanner and the 3T-MRI scanner in control and DA groups (two-way ANOVA, both $F < 1.3$; both $P > .25$). Also there was no significant gender difference for the volumes of the whole hippocampus or cortical areas in control and DA groups (both $F < 0.08$; both $P > .79$). Volume estimates on 1.5T and 3T-MRI scans and volume estimates in males and females were thus presented together. There was a significant right larger than left volume asymmetry for the volume of the whole hippocampus in both control and DA groups (repeated measures two-way ANOVA: $F_{(1,53)} = 19.2$; $P < .001$; Tukey's HSD post-hoc test: both $P < .004$). The right CA-DG subregions were significantly larger than the left in both control and DA groups ($F_{(1,53)} = 26.1$; $P < .001$; both $P < .004$). There was no significant asymmetry for the volume of the other hippocampal subregions (all $P > .05$). Also, there was no significant asymmetry for the volume of the entorhinal or perirhinal cortices (all $P > .12$) but there was a significant right larger than left volume asymmetry for the volume of the parahippocampal cortex in the control group ($F_{(1,53)} = 7.0$; $P = .011$; Tukey's HSD post-hoc test: $P = .009$). The volume of all the ROIs was calculated as the mean of the left and right hemisphere measurements.

Intracranial volume (ICV) was manually measured on the sagittal dataset with a 1-in-10 random and systematic sampling strategy. The ICV was normally distributed (Shapiro-Wilk normality test; control: $P = .05$; DA: $P = .23$). The ICV was 6.8% smaller in the DA group than in the control group ($t_{(53)} = -2.70$; $P = .009$). Corrections, derived from the regression line of control ROI volume (V) versus ICV, were then made for ICV based on the formula [$\Delta V = a \times (\Delta ICV)$] where 'a' is the regression coefficient.

WISC/WAIS

The Wechsler Adult Intelligence Scale, 3rd Ed. (WAIS-III) and the Wechsler Intelligence Scale for Children, 4th Ed. (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 on-line immediate memory and executive control; and Processing Speed Index,

measuring speed of visuoperceptual discrimination, and copying of number-symbol associations. The four index scores are expressed as standard scores with a mean of 100 and a standard deviation of 15.

Scoring. The WISC-IV or WAIS-III were administered to all patients with DA (N = 23, 11 females, mean age: 19.5 years, SD: 9.0, range: 8−40) and to 23 controls (13 females, mean age: 18.0 years, SD: 8.4, range: 8.2–38). For the analysis of the data, we then used parametric tests as the data were normally distributed in all four indexes (Shapiro–Wilk test of normality; Control: all $P > .36$; DA: all $P > .10$).

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 (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 Supplementary Information for more details.

Scoring. The *Doors and People Test* was administered to all patients with DA (N = 23, 11 females, mean age: 19.5 years, SD: 9.0, range: 8−40) and to 21 controls (11 females, mean age: 17.6 years, SD: 8.6, range: 8−38). One of the patients performed all but the 'Names' subtest ('People', 'Doors', 'Shapes': N = 23; 'Names': n = 22). Given that the DA 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). 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: $P < .001$; DA: $P = .044$).

The Four Mountains Test

The *Four Mountains Test* was developed to examine hippocampal contribution to perception and short-term memory for topographical and nonspatial information in spatial scenes (Hartley et al., 2007). Briefly, this test involves computer-generated landscapes containing four mountains. In the 'Spatial Perception' task, participants selected one picture that matched the sample image (the same place from a different viewpoint) from four alternatives. In the 'Spatial Memory' task, the sample image was presented for approximately 8 sec. After a 2 sec. delay, participants were presented with four choices and selected the one previously viewed. See Supplementary Information for more details.

Scoring. The *Four Mountains Test* was administered to 14 patients with DA (7 females, mean age: 21.6 years, SD: 10.3, range: 8−40) and to 19 controls (11 females, mean age: 16.9 years, SD: 7.8, range: 8−35). We converted patients' raw scores to z-scores relative to the scores of our control group; raw scores (SD):

Perception, 11.6 (2.3); Memory, 9.95 (2.8). We then used nonparametric tests as the data in the Control group were not normally distributed [Shapiro–Wilk test of normality; $P < .05$].

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Competing interests

The authors declare no conflict of interest.

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