Title

Greater hippocampal atrophy in developmental amnesia is associated with better recall and working memory performance

Authors/Affiliations

Loïc J. Chareyron[a,b], W.K. Kling Chong[c], Tina Banks[c], Neil Burgess[d], Richard C. Saunders[e], Faraneh Vargha-Khadem[a]*

[a] Cognitive Neuroscience and Neuropsychiatry, Developmental Neurosciences, University College London Great Ormond Street Institute of Child Health, London, UK

[b] Laboratory of Brain and Cognitive Development, Institute of Psychology, University of Lausanne, Switzerland

[c] Developmental Imaging & Biophysics, Developmental Neurosciences, University College London Great Ormond Street Institute of Child Health, London, UK

[d] Institute of Cognitive Neuroscience, University College London, London, UK.

[e]Laboratory of Neuropsychology, National Institute of Mental Health, National Institutes of Health, Bethesda, MD 20892.

Corresponding Author

* Faraneh Vargha-Khadem.

Email: f.vargha-khadem@ucl.ac.uk

Abstract

Despite early-life bilateral hippocampal damage, developmental amnesic (DA) patients exhibit well-developed semantic memory, but severely impaired episodic retrieval. It is unclear, however, whether the residual hippocampus plays a role in encoding and/or retrieval of new information. Here, we report that in DA patients the extent of atrophy in CA-DG subregions and subicular complex is above 40% while the atrophy of the uncus is only moderate (−23%). Importantly, the perihippocampal cortices are unaffected. Paradoxically, patients' recall, Verbal IQ, Working Memory, and Processing Speed scores correlate *negatively* with the volume of the uncus. We propose that in DA patients, the uncus serves as "gatekeeper" providing signals that may inhibit compensatory mnemonic functions by the preserved surrounding cortical areas. Our findings highlight the role of uncus in recall, and document not only the extent, but also the limits of functional plasticity and circuit reorganization in the young brain after early bilateral hippocampal damage.

Introduction

Develomental 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 [1,2]. 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 recall and recognition processes [3–6]). 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' (DA) [1,7–10]. Given the early onset of hippocampal damage, the compensatory reorganization that has occurred in patients with DA, 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 [11]. In patients with adult-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 differently-organized 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 [12].

To date, a cohort of 18 patients with DA has been reported, each patient having suffered an episode of hypoxia-ischaemia early in life [2]. Importantly, irrespective of the underlying aetiology [13], or age at onset [14], the hypoxic-ischaemic event was the cause of hippocampal damage and cognitive memory impairment in each case[15] .

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 [15], recollection and familiarity depend on different MTL structures [16,17]. According to this model, the perihippocampal gyrus, and in particular the perirhinal cortex, may support familiarity, while the hippocampus may be critical for recollection [18]. The selectivity of impairment observed in patients with DA has provided strong support for this dual-process model [12,16].

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 [19,20] while the adjacent CA3 remains less vulnerable [21]. In humans, while damage to CA1 is consistently reported following cerebral ischemia, damage to additional hippocampal regions is much more variable [22]. 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 [23,24]. 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 [25,26], although activation *per se* does not necessarily imply correspondingly intact function [27].

In the study reported by Dzieciol and colleagues [2], 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 [24], 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 [28]. 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 [29]. Also, a recent study demonstrated that parahippocampal activity during scene reinstatement in patients with DA was similar to controls [27]. 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 studied the largest cohort of patients with the rare condition of developmental amnesia ever assembled to test the impact of plastic changes and circuit reorganization in the compensation of hippocampal function. 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) [30,31], 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), and recall/recognition for verbal and visual material (Doors and People 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 extent of hippocampal damage in all patients with DA.

We reported various level of atrophy of the hippocampal subregions and an absence of structural damage in the surrounding cortical areas in patients with DA. Also, we documented several paradoxical inverse relationships between the

volume of the residual uncus and patients' recall memory performance, Verbal Comprehension Index, Working memory Index and Processing Speed Index.

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-S2).

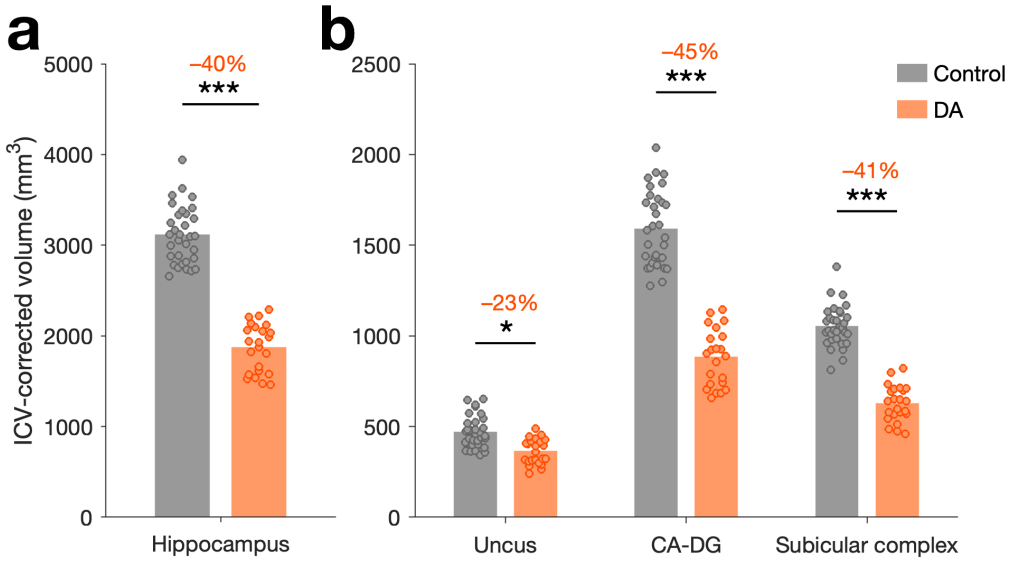

Fig. 1. Volume of the hippocampus and its subregions. Volume of the hippocampus (**A.**) and its subregions (**B.**, uncus, CA-DG, and subicular complex) in control (grey; N = 32) and DA (orange; N = 23) groups. Data are represented as mean ± SD. Percentage values refer to the mean difference to control 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. S3). 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.

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'): $r_{(22)} = -0.55$; $P = .007$; Fig.2AB]. No other correlations for other subtests or other regions of interest in the DA group were significant (all $P > .09$; Table S3). 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. 2C). 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 S3).

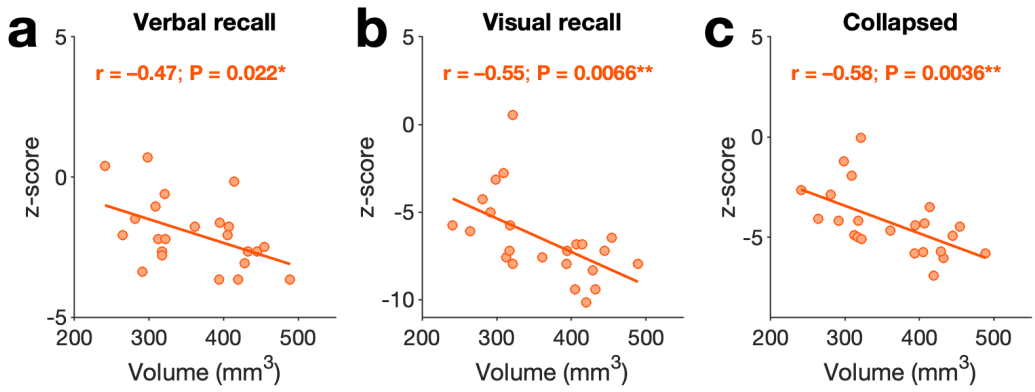

Fig. 2. *Doors and People* recall scores correlations with the volumes of the uncus in patients with DA. The patients' scores (N = 23) on recall subtests of the *Doors and People Test* correlated negatively with the volume of the uncus. **A.** Verbal recall ('People') subtest. **B.** Visual recall ('Shapes') subtest. **C.** Collapsed scores. Pearson's correlation coefficient. All volumes are corrected for intracranial (ICV) volume. *: P < .05; **: 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. Delayed (cued) verbal and visual recall were tested after completion of the verbal and visual recognition subtests, respectively. Collapsed recall scores were inversely correlated with the volume of the uncus in the DA group for all of the three trials as well as for the delayed recall (all $r_{(22)} < -0.43$; all P < .05; Fig. S4)

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).

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).

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 3; Table S4). 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 ($r_{(22)} = 0.46$; $P = .029$).

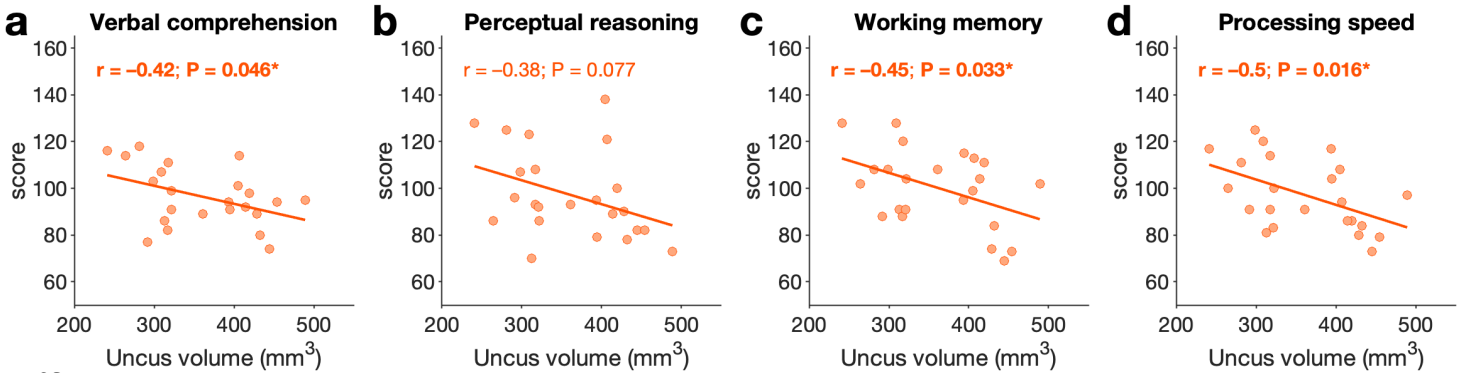

Fig. 3. Inverse correlations between WISC/WAIS indexes scores and the volume of the uncus in patients with DA. Patients' scores on Wechsler Intelligence Scales WISC or WAIS (N = 23). **A.** Verbal comprehension Index; **B.** Perceptual Reasoning Index; **C.** Working Memory Index; **D.** Processing Speed Index. Pearson's correlation coefficient. All volumes are corrected for intracranial (ICV) volume. *: $P < .05$.

Discussion

In this study, we addressed the question of whether the volumes of residual hippocampal subregions and parahippocampal areas are associated with cognitive memory performance in patients with hypoxic-ischemic-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 between the volume of the residual uncus and patients' performance on recall memory, Verbal comprehension Index, Working memory Index and Processing speed Index. The effects reported here suggest that in patients with DA, the uncus, either via its connections with the contralateral uncus or with other anterior temporal lobe areas, and depending on its extent of damage, provides signals that may inhibit compensatory mnemonic development by the preserved surrounding cortical areas. This process could occur either because normally silent connections promote compensation, or because signals (either typical or pathological) inhibit compensation. However, whatever the extent of hippocampal damage in DA, and 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, 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

292 of the MRI scans. However, analyses of MR images for estimating the extent of
293 hippocampal damage in amnesic patients have been validated by postmortem
294 examinations [24]. In particular, a clear concordance has been reported in the
295 appearance of the damaged hippocampus on the MRI and in the histological
296 sections [24]. The border between cytoarchitectonic hippocampal subregions were
297 estimated based on delineation of these regions on histological sections [32]. The
298 delineation on MR images of the perihippocampal and parahippocampal cortical
299 areas were based on that described in [33]. It is not clear to what extent these borders
300 would be affected in the brains of DA patients with significant hippocampal
301 volume reduction. Our observations of an absence of significant volume reduction
302 of the entorhinal, perirhinal and parahippocampal cortices in patients with DA is
303 consistent with previous report showing an absence of significant volume
304 reduction in patients with adult-onset amnesia [28], and in a patient with DA [29].
305 Also, intact parahippocampal activity during scene reinstatement has been
306 described in patients with DA [27].

307 ***Differential effect of early hypoxia-ischemia on hippocampal subregions***
308 Our observation that the CA-DG were the most affected hippocampal subregions
309 in patients with DA is congruent with documented reports of greater sensitivity of
310 this subregion to hypoxia-ischemia. It has long been known that hypoxia and
311 ischemia result in selective neuronal death in the CA1 field [19], although the reason
312 for this selectivity is still debated [21]. Neurohistological studies of patients who
313 suffered ischemic episodes in adulthood have reported cases with neural cell loss
314 restricted to the CA1 region bilaterally whilst the CA1' region of the uncus, the
315 subiculum, CA3 and surrounding cortices were all preserved [23,24]. High-resolution
316 magnetic resonance imaging showed that CA1 was always affected in patients
317 with hippocampal damage [22].
318 In contrast, the uncus showed a low sensitivity to hypoxia in our patient cohort
319 which could be a reflection of the distinct vascularization of this hippocampal
320 subregion. The branches of the posterior cerebral artery (PCA) coming from the
321 vertebral artery irrigate the posterior part of the hippocampus, while the branches
322 of the anterior choroidal artery (AchA) originating from the internal carotid artery
323 irrigate the uncal portion of the hippocampus [34–36]. High-resolution angiography
324 and anatomical studies have highlighted that the anterior hippocampal region
325 could receive a mixed blood supply (from both the PCA and the AchA) in about
326 half of the individuals [34,37]. A mixed blood supply could provide more vascular
327 reserve and lower vulnerability to neuronal injury and atrophy [38]. The uncus,
328 which receives a distinct blood supply compared to the rest of the hippocampus,
329 might thus exhibit greater resistance to the adverse effects of hypoxic-ischemic
330 events than the other hippocampal regions.

331 ***Uncus and recall memory***
332 The residual uncus could be partly functional in patients with DA and could be
333 recruited for recall memory. We reported here that the volume of the uncus
334 correlated negatively with recall scores as well as working memory performance
335 in patients with DA. In the WAIS/WISC test, Working Memory Index is made up
336 of two subtests (Digit Span and Letter Number Sequencing) both requiring verbal
337 recall within the span of working memory. The function of the uncus is not well
338 understood mainly because its structure-function mapping remains to be

339 determined in rodents [39], but in humans, the uncus has been proposed to be
340 involved in the long-term recall of scenes [40]. Connectivity studies in nonhuman
341 primates have shown that the uncus is less connected to other regions of the
342 hippocampus, and that it has its own associational system of connections [41].
343 Notably, the uncus is also the only hippocampal region reciprocally connected to
344 its contralateral counterpart [42]. The uncus' unique connectivity could allow this
345 region to support some information processing despite severe damage to the other
346 hippocampal areas.
347 Notwithstanding the importance of the uncus in relation to severity of
348 atrophy during delayed recall, this subregion maintains its role during encoding
349 and learning of memoranda in both low and high severity subgroups equally.
350 Thus, we noted that despite their poor performance overall, both patient subgroups
351 incrementally increased their scores across the three learning trials of the *People*
352 and *Shapes* subtests of the *Doors and People Test*. The absence of a difference in
353 performance between the subgroups during encoding and learning, but not during
354 delayed recall, highlights the role of the uncus in retrieval of auditory verbal
355 memory after a delay in patients with DA.
356 Interestingly, we also reported an inverse relationship between the volume of
357 the uncus and patients' performance in delayed verbal, but not visual recall.
358 Impairment in delayed verbal recall in relation to extent of atrophy of the uncus
359 highlights the vulnerability of auditory verbal information to recall after a delay [43].
360 The above, together with ontogenetic lateralization of verbal output via the left
361 hemisphere language network, and the unique reciprocal connection of the uncus
362 to its contralateral counterpart, could account for the 'gatekeeping' role that the
363 uncus might play in verbal recall.

364 ***Working memory***
365 We reported here, in addition to an absence of working memory impairment, a
366 negative association between uncus volume and working memory performance in
367 patients with DA. The more established view proposes that the hippocampus plays
368 an important role in episodic memory, spatial cognition, and navigation, while it
369 is not critically contributing to working memory [44,45]. But an alternative view
370 proposes that the hippocampus may contribute to any memory task, including
371 working memory [46,47], in particular in supporting high-precision binding [48]. This
372 latter possibility is challenged however by the fact that patients with DA
373 presenting with severe hippocampal damage have repeatedly shown unimpaired
374 working memory performance [49–51]. Recent work extended these findings by
375 showing that high resolution working memory performance was unimpaired, and
376 even often superior, relative to control group in a patient with DA [52]. Our
377 observation of a negative correlation between uncus volume and working memory
378 performance suggests that the perirhinal, entorhinal, and parahippocampal cortices
379 normally involved in the binding of information in the short term [53] may be
380 subject to plastic changes in patients with DA and that these plastic changes may
381 depend on the degree of hippocampal damage. The possibility that the
382 hippocampal damage in patients with DA may not influence working memory
383 performance directly, but indirectly via reorganization of the MTL circuit is
384 explored below.

385 ***Functional hypotheses***
386 Experimental studies in nonhuman primates have reported similar paradoxical
387 findings to those reported in the present study. Monkeys with small hippocampal
388 lesions exhibit greater memory loss on a Delayed Nonmatching-to-Sample
389 (DNMS) task than that found in animals with greater damage [54]. Furthermore, a
390 positive correlation between the extent of damage to the hippocampus and scores
391 on a DNMS task has been reported in experimentally lesioned monkeys [55].
392 Several hypotheses have been proposed to explain why discrete lesions result in
393 greater memory impairment [54,56,57]. However, it is difficult to relate these findings
394 obtained following adult experimental lesions in the monkey to observations in
395 patients with early hippocampal damage whose circuits might have undergone
396 massive compensation. One hypothesis to explain our observations is that the
397 level of hippocampal damage would likely have a strong direct influence on the
398 organization of the medial temporal lobe memory circuits in the adult. Following
399 an early event of hypoxia-ischemia, however, greater hippocampal damage might
400 induce greater compensatory reconfigurations in the neural circuits and enable
401 other structures, in particular the surrounding cortical areas normally recruited by
402 the hippocampus, to assume important aspects of memory function. In contrast,
403 when the hippocampus is only partially damaged, the information flow would
404 remain present in the hippocampus and could result in incomplete, and possibly
405 disruptive information processing. Our observation could thus reveal the existence
406 of multiple, redundant routes within the residual hippocampal subregions and
407 surrounding cortical areas in patients with developmental amnesia [58]. These
408 parallel circuits could compete for the control of behavior and disrupt memory
409 performance [57].
410 Our findings are consistent with the hypothesis that a close relationship
411 can be evidenced between the volume of remaining hippocampal subregions and
412 the severity of cognitive deficits in patients with hippocampal damage, in the case
413 of patients with DA this relationship was inverse. Our observations also provide
414 further support for the model of hierarchical organization of cognitive memory [15]
415 by proposing that surrounding cortical areas normally involved in the encoding of
416 associative relations between decontextualized information [53] could reorganize to
417 contribute to hippocampal function following early hippocampal damage. The
418 limits of this reorganization, however, may be determined by the extent of damage
419 to the hippocampal subregions.
420 Evidence for such reorganization has already been reported in a nonhuman
421 primate model of developmental amnesia. Monkeys with early bilateral
422 hippocampal lesion can learn new spatial relational information in striking
423 contrast to monkeys with adult lesion [59,60]. Interestingly, in these monkeys with
424 early hippocampal lesions, the surrounding cortical areas were preserved and were
425 shown to contribute to spatial learning in the absence of functional hippocampal
426 circuits [61]. A recent report showed that the number of immature neurons in the
427 entorhinal and perirhinal cortices was higher in monkeys with early hippocampal
428 lesions than in controls [62]. This increase in the number of immature neurons was
429 paralleled by an increase in the number of mature neurons in the entorhinal cortex
430 of neonate-lesioned monkeys compared to controls. These structural changes may
431 contribute to some functional recovery after early hippocampal injury [62].
432 One could speculate that the functional reorganization of the
433 perihippocampal structures (normally devoted to the processing of

434 decontextualized information) to compensate hippocampal function could, in turn,
435 benefit the processing of semantic memory and lead to better context-free memory
436 performance in patients (see: [63]). Indications of increased memory performance
437 have indeed been reported in two different patients with DA. Jonin et al. [29] studied
438 patient 'KA' presenting with 55% hippocampal volume reduction and preserved
439 perihippocampal structures. While patient KA displayed few, if any, residual
440 episodic abilities, this patient was able to accurately retrieve semantic memories,
441 and show evidence of superior or even very superior access to these memories
442 compared to controls. Another patient with DA, patient 'Jon', has often produced
443 response accuracy levels that are at least higher than those of control participants
444 in previous experimental explorations of visuospatial working memory [49,51,52]. Jon
445 was at least numerically superior to the control mean on recognition-based
446 measures of shape-color binding [51]. In measures of color-location memory, Jon's
447 recognition accuracy matched the highest achieving control participant, while his
448 reconstruction performance was superior to 6 of the 7 controls [49]. Across four
449 tasks measuring binding between color and orientation, or color and location
450 using simultaneous or sequential presentation of stimuli, Jon's response accuracy
451 was high, and always numerically superior to the control mean [52].
452 These observations from single patients studies together with the present
453 findings, obtained in a large cohort of patients with DA, support the hypothesis of
454 a reorganization of the preserved perihippocampal areas following early
455 hippocampal damage.

456 Conclusions

457 Our results have important implications for understanding the organization of the
458 memory circuit following early hippocampal injury. These observations highlight
459 the paradoxical finding that in patients with DA greater hippocampal damage can
460 be associated with better performance in recall memory, Verbal comprehension
461 Index, Working memory Index, and Processing speed Index. In contrast, less
462 severe damage, leaving behind relatively preserved hippocampal subregions, can
463 lead to more pronounced cognitive deficits. These unexpected findings can
464 disentangle the functional organization of the medial temporal lobe memory
465 system, and attribute a central role in the compensation of cognitive memory to
466 extra-hippocampal structures in patients with early hippocampal damage.

467 Materials and methods

468 ***Participants***
469 The patients with DA were characterized by (i) a history of episodes of hypoxia-
470 ischemia in early life, (ii) quantified hippocampal volume reduction above 25%
471 relative to a group of controls, and (iii) severely impaired episodic memory [2]. The
472 most common aetiology was perinatal hypoxic-ischemic encephalopathy (Table
473 S2). While long-term neurodevelopmental outcome depends on the severity of the
474 hypoxic-ischemic episode, subtle cognitive deficits and behavioral alterations
475 have been revealed through long-term evaluations even in mild forms of hypoxia-
476 ischemia [64].
477 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.

The DA group included three patients (DA05, DA06, 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 one), and late (between 6-14 years) groups exhibit similar profiles, and thus concluded that the effective age at injury for developmental amnesia extends from birth to puberty [14].

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).

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.

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 [65].

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 [66].

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) [67]. Manual tracing is still the gold standard for measuring hippocampal volume and is particularly appropriate for samples of relatively small size [68], presenting with various levels of hippocampal atrophy [69], or including children and adolescents [70]. All manual measurements of the ROIs were carried out by one of the authors (LJC) who remained blind to participant identity (Fig. S1-S2).

The hippocampus comprises the CA fields (CA3, CA2, CA1), the dentate gyrus (DG), subiculum, presubiculum, and parasubiculum [71]. The human uncus [also termed the "uncal portion of the hippocampal formation" [42]] is situated antero-medially and consists of slightly modified DG, CA3, CA2, CA1, and subiculum [72]. For the segmentation of the hippocampus and its subregions, we followed the guide provided by Dalton et al. [73]. 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 [72]], 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 [33,74–77].

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 [78], as described in detail in [8,79]. 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).

Statistical analysis

We followed the recommendations of Rothman [80], arguing that "not making adjustments for multiple comparisons is preferable because it will lead to fewer errors of interpretation when the data under evaluation are not random numbers but actual observations on nature," and Saville [81], who argued that a procedure without correction is preferable because it provides greater consistency to compare results between studies.

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Data availability

Anonymized participant data will be available upon reasonable request.

Competing interests

The authors declare no conflict of interest.

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