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Dissociations in cognitive memory: the syndrome of developmental amnesia

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The dearth of studies on amnesia in children has led to the assumption that when damage to the medial temporal lobe system occurs early in life, the compensatory capacity of the immature brain rescues memory functions. An alternative view is that such damage so interferes with the development of learning and memory that it results not in selective cognitive impairments but in general mental retardation. Data will be presented to counter both of these arguments. Results obtained from a series of 11 amnesic patients with a history of hypoxic ischaemic damage sustained perinatally or during childhood indicate that regardless of age at onset of hippocampal pathology, there is a pronounced dissociation between episodic memory, which is severely impaired, and semantic memory, which is relatively preserved. A second dissociation is characterized by markedly impaired recall and relatively spared recognition leading to a distinction between recollection-based versus familiarity-based judgements. These findings are discussed in terms of the locus and extent of neuropathology associated with hypoxic ischaemic damage, the neural basis of 'remembering' versus 'knowing', and a hierarchical model of cognitive memory.

Keywords: recognition; episodic memory; semantic memory; hippocampus; premature birth; event-related potentials

1. INTRODUCTION

Until recently, there were few reports of amnesia occurring in children at any age, and none of an amnesic syndrome resulting from brain damage incurred in infancy. The cases that had been reported were of patients who had sustained medial temporal lobe damage between the ages of 8 and 10 years (Wood *et al.* 1982; Ostergaard 1987; Broman *et al.* 1997), and of these, only the patient of Broman and colleagues was examined with modern neuroimaging techniques. That study of a young man who had suffered from an anoxic encephalopathic illness and respiratory arrest at the age of 8 years, and who subsequently showed severe and chronic memory impairment, demonstrated clearly that anterograde amnesia could result from bilateral hippocampal pathology incurred in childhood.

Yet in the absence of any reports of amnesic cases with hippocampal injuries sustained still earlier in life, it was possible to suppose that there was an age below which such injury would not lead to amnesia. There were two plausible explanations why this might occur. One was that very early damage to the memory system would so compromise cognitive development that the resulting syndrome would be one not of a selective memory disorder but rather of profound mental delay and global learning disability. At the other extreme was the possibility that such damage would fail to produce any memory disorder, because the plasticity and reorganizational capacity of the immature brain would lead to rescue of memory function. Neither of these notions proved to be correct, for we have since described a group of patients with onset of bilateral hippocampal pathology that can be dated within the first year of life and with atrophy in this structure averaging *ca.* 40%, each of whom is suffering from a very clear amnesic syndrome (Vargha-Khadem *et al.* 1997; Gadian *et al.* 2000). Theirs is a limited form of amnesia, however, for although they commonly forget the events of everyday life, signifying a marked impairment in episodic memory, they have acquired an impressive amount of factual knowledge about the world, indicating relative sparing of semantic memory. To distinguish this limited form of memory impairment from adult-onset amnesia, which typically encompasses both episodic and semantic memory (Scoville & Milner 1957; Stefanacci *et al.* 2000), we have termed the new syndrome 'developmental amnesia' (DA) (Gadian *et al.* 2000).

The hippocampal damage found in the five young patients (Gadian *et al.* 2000) is likely to be due to hypoxic ischaemia, inasmuch as each of them had one or more early hypoxic episodes (perinatally in four patients, and at 1 year of age in the fifth), and voxel-based morphometry of their magnetic resonance (MR) scans showed bilaterally reduced grey-matter density not only in the hippocampus but also in the putamen and ventral parts of the thalamus, a pattern consistent with atrophy of hypoxic-ischaemic origin (Rutherford *et al.* 1994, 1995; Barkovich & Hallam 1997; Mercuri *et al.* 1999).

Unlike cases with more severe hypoxia and the more extensive neuropathology associated with it, these

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patients have no motor or other neurological signs, although early in life some were said to have shown clumsiness from which they have recovered. Furthermore, their spared semantic memory ability has enabled them to develop average to low-average levels of intelligence, language, literacy and social skills. On the other hand, their impairment in episodic memory is a striking one and is evident on such everyday tasks as remembering routes, belongings, appointments, messages and other daily events. These memory difficulties, first reported by parents and teachers about the time the children entered school, and which are easily confirmed with objective laboratory measures of everyday memory and delayed recall, are so severe and chronic as to preclude independence and employment later in life.

Here we review some recent studies in which we have gathered additional information concerning the syndrome of DA. In the first part, we describe two group studies that address the questions of whether the memory profile seen after bilateral hippocampal injury in childhood differs depending on age at injury (Salmond *et al.* 2000) and extent of damage (Isaacs *et al.* 2000*a*). In the second part, we review two additional investigations carried out on one of the patients, 'Jon', who was selected for these follow-up studies because of his age (20 years) and well-preserved intelligence quotient (IQ) (114). Regarding the latter investigations, we had obtained evidence in our initial report (Vargha-Khadem *et al.* 1997) that patients with DA may show a dissociation not only between episodic and semantic memory but also between recall and recognition. Thus, on neuropsychological tests, recall (like episodic memory) was markedly impaired, whereas recognition (like semantic memory) seemed to be relatively preserved. We explored this issue further with Jon, using both neuropsychological (Baddeley *et al.* 2001) and electroencephalographic techniques (Düzel *et al.* 1999, 2001).

2. EFFECTS OF AGE AT HIPPOCAMPAL INJURY

Unlike adult-onset cases with profound amnesia affecting both episodic and semantic memory, a disorder most often associated with extensive bilateral damage to the medial temporal lobe, the patients with DA have a seemingly selective pattern of medial temporal neuropathology. Thus, whereas bilateral hippocampal atrophy is clearly visible on their MR scans, there is no obvious pathology on visual inspection of the underlying parahippocampal region, consisting of the entorhinal, perirhinal and parahippocampal cortices. This seemingly isolated hippocampal damage, supported by the results of the quantitative MR techniques that have been applied thus far (Vargha-Khadem *et al.* 1997; Gadian *et al.* 2000), has led us to speculate that whereas the DA patients' episodic memory impairment is presumably due to their hippocampal pathology, their relatively preserved semantic memory could be related to the integrity of the underlying cortices (Mishkin *et al.* 1997, 1998). There are of course alternative possibilities, namely, that the limited form of amnesia in our young patients is due instead to either (i) partial sparing of the hippocampal formation or (ii) a degree of functional reorganization and compensation after very early injury that is not possible after damage acquired later in life.

Recently, as we uncovered more cases with memory disorders of childhood onset, most often directly attributable as in the original cases to hypoxic ischaemia, we had the opportunity to conduct a limited test of the early-injury proposal. Several of the new cases we saw had acquired hippocampal pathology in later childhood, and consequently we were able to compare memory outcome during adolescence in two distinct groups, one whose age at injury ranged from birth to 1 year (Early Group, $n=6$), and the other, from 6 to 14 years (Late Group, $n=5$). We reasoned that if the timing of the hippocampal injury was the critical factor accounting for the preservation of the Early Group's semantic memory, then the Late Group should show a profile of impairment resembling more closely the global amnesia commonly seen in adult-onset cases.

Quantitative MR techniques indicated that the hypoxic episodes in the Late Group had yielded a pattern of neuropathology that was very similar to the pattern described above (§ 1) for the Early Group. Interestingly, despite the later onset of their damage, the patients in the Late Group showed no signs of motor impairment in association with the putamen and thalamic damage. By contrast, their memory impairment, associated with about the same degree and apparent selectivity of medial temporal lobe pathology as those found in the Early Group, was apparent immediately after they had incurred the injury.

The neuropsychological comparison of the two groups revealed few significant differences between them. Both groups were equally impaired on tests that are considered to be measures of episodic memory, such as the Rivermead Behavioural Memory Test of everyday events (Wilson *et al.* 1985) (figure 1*a*) and delayed recall of verbal and non-verbal material in both the visual and auditory modalities. Most importantly from the standpoint of the study's aims, both groups showed equivalent sparing on tests of semantic memory, as indicated by their composite scores on (i) the Information, Vocabulary, and Comprehension subtests of the Wechsler Intelligence Scale (WISC) (Bracken 1992) (figure 1*b*) and (ii) single word reading, spelling and reading comprehension subtests of the Wechsler Objective Reading Dimensions Scale (Rust *et al.* 1993).

Among the many measures on which the two groups were compared, the only ones that differentiated the two groups were those of immediate memory. For example, in both immediate recall of stories and first-trial learning of verbal paired associates of the Wechsler Memory Scale, unlike the delayed recall measures on these same two subtests, the Late Group was significantly inferior to the Early Group. It is unclear whether these relative impairments in the Late Group reflect poorer episodic memory or a reduced sensory processing capacity and working memory ability. In either case, the semantic memory ability of the two groups does not appear to differ. The findings thus lead to the tentative conclusion that if DA is indeed a special syndrome related to the early occurrence of hypoxia-induced hippocampal damage, then the effective age at injury could extend from birth to puberty.

Yet these results do not rule out the broader notion that DA is a syndrome restricted to childhood-onset injury. Examining this possibility will require direct comparison

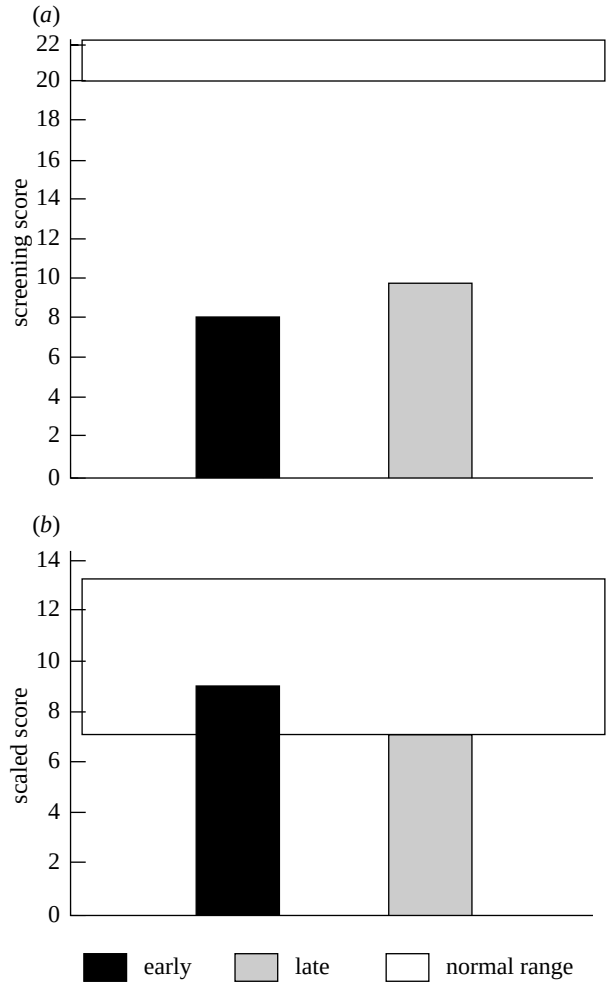

Figure 1. (*a*) Rivermead Behavioural Memory Test. (*b*) Composite of the Vocabulary, Information, and Comprehension subtests of the Verbal IQ Scale of the WISC-III. Scores are means for the Early and Late Groups compared with the range for normals. The two groups of patients with DA show statistically indistinguishable degrees of deficit in (*a*) and of preservation in (*b*).

with patients who have had still later onsets of the same amount and apparent selectivity of medial temporal pathology as those described here. Recently, at least three patients have been reported whose anterograde amnesia was incurred in adulthood and whose damage appears to be restricted to the hippocampus (Kitchener *et al.* 1998; Holdstock *et al.* 2000; Verfaellie *et al.* 2000). It is of interest that, despite the presence of a severe episodic memory impairment in each of these patients, each has also shown at least some degree of new semantic learning, although the extent of the newly acquired information is minimal compared with the level acquired by our patients with DA. Moreover, several other case studies of patients with adult-onset injury seemingly limited to the hippocampus have failed to uncover any evidence of preserved semantic memory ability (Kartsounis *et al.* 1995; Reed & Squire 1998). Whether this difference in semantic memory outcome is due in fact to the different ages at injury is still uncertain, however, inasmuch as there could still be undetermined differences between the adult- and childhood-onset cases in the extent of the neuropathology. Indeed, further quantitative study of the neuropathology in the hippocampus and parahippocampal region in both the childhood and adult forms of amnesia is needed to help decide among the possible explanations for the specific memory profile seen in DA.

3. EFFECTS OF EXTENT OF HIPPOCAMPAL INJURY

Having determined that hippocampal injury at any time during childhood yields the characteristic profile of DA, we next sought to determine whether this syndrome appears only if the hippocampal damage reaches a certain minimal extent (Isaacs *et al.* 2000*a*). We addressed this question by comparing the group of patients described above (Group DA, $n=11$) with a group of children born extremely preterm (Group PT, $n=11$), who were found to have sustained hippocampal damage possibly as a result of lung immaturity, for which they had required intubation and artificial ventilation (Isaacs *et al.* 2000*b*). A control group consisted of normal children born full term (Group C, $n=8$). Each of these three groups was examined at a mean age of *ca.* 14 years.

Relative to hippocampal volumes in their age-matched normal controls, the reduction in hippocampal volume for each hemisphere in Group DA averaged 40% (range, 29–55%), whereas in Group PT it averaged 10% (ranging up to 25%). None of the children in Group PT is amnesic, and although the group did show deficits on a few items of the Rivermead Test of everyday memory, this group had no deficits on any of the other tests considered to be measures of episodic memory, such as delayed recall of verbal and non-verbal material. As a result, on every episodic memory measure in which Group DA was impaired relative to Group C, it was also impaired relative to Group PT. By contrast, there were no differences between the DA and PT Groups on any of the tests considered to be measures of semantic memory, such as the Information, Vocabulary and Comprehension subtests of the Wechsler Intelligence Scale or the subtests of the Wechsler Objective Reading Dimensions Scale.

The results suggest that hippocampal volume must undergo a reduction of at least 25–30% on each side before DA is likely to result. The relationship between degree of memory deficit and amount of hippocampal atrophy (and possibly subhippocampal atrophy, see § 2) could of course be continuously graded rather than all-or-none, but resolving this issue will require study of larger numbers of patients with early hippocampal injury than have been identified so far.

4. RECALL VERSUS RECOGNITION AFTER HIPPOCAMPAL INJURY

As already noted, evidence obtained in our first report on DA suggested that, like semantic memory, recognition memory may also show a surprising degree of preservation. Among the tests given to the three patients and normal controls of that study were ones that assessed one-trial recognition for lists of items, one-trial associative recognition for lists of paired items, and multi-trial associative recognition for lists of paired items within and across modalities. Of these, all but the cross-modal tests were performed by the patients at normal or near-normal

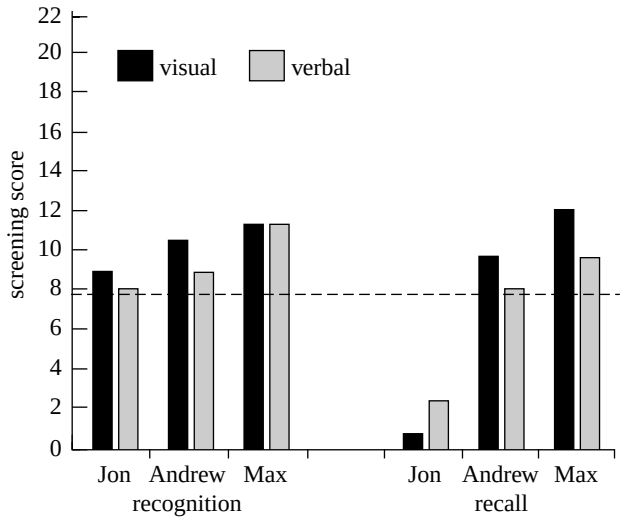

Figure 2. Doors and People Test. Scores of Jon, the patient with DA, and his two age- and IQ-matched controls (normal mean, 10; standard deviation, 1.5). Jon shows preserved recognition ability, but markedly impaired recall, for both visual and verbal material.

levels, a finding strikingly different from their poor performance on the numerous tests of delayed recall. Yet, we could not be confident of a recall–recognition dissociation in our patients because the two measures differ so greatly in difficulty.

To address this problem, we turned to the Doors and People Test (Baddeley *et al.* 1994) in which recall and recognition of both visual and verbal stimuli were deliberately designed to be of equal difficulty through the incorporation of 'easy' recall and 'hard' recognition tests plus the use of scaled scores derived from performance of a large population of normal young adults. We gave this and other recognition tests that have normative data for young adults to Jon, one of the patients with neonatal injury. As already noted, Jon was 20 years old at the time of testing and had a full scale IQ of 114 (Verbal IQ (VIQ), 108; Performance IQ (PIQ), 120). We compared Jon's scores on these several measures with those of two normal control subjects who were matched to Jon for age and IQ, as well as to those of less well matched but larger groups from the published literature. The results (Baddeley *et al.* 2001) confirmed the initial findings; in particular, on the Doors and People Test, Jon scored below the fifth percentile on both visual and verbal recall, while scoring between the 50th and 75th percentile on both visual and verbal recognition (figure 2). His two control subjects, by contrast, obtained scores between the 50th and 75th percentile on visual and verbal recall as well as recognition. On each of the other measures of recognition, whether immediate or delayed, Jon's performance likewise fell solidly within the normal range.

It is important to note here that the case of adult-onset amnesia reported by Holdstock *et al.* (2000) also showed a remarkable degree of sparing of recognition memory, and several amnesic cases cited by Aggleton & Shaw (1996) had less but still substantial sparing of this ability.

The above findings on recognition memory are of special interest in connection with evidence that has accumulated recently regarding the neural substrate of recognition in animals. The results of these lesion studies show clearly that, within the medial temporal lobe, the tissue most critical for recognition memory is the group of cortical areas that comprise the parahippocampal region. The long list of severe deficits that have been observed in rats and monkeys after selective damage to these cortical areas (i.e. the entorhinal, perirhinal and parahippocampal cortices) includes item recognition in the visual, tactile and olfactory modalities, as well as the recognition of visual–visual, visual–tactile, object–reward and object–place associations (reviewed in Mishkin *et al.* 1997, 1998). By contrast, selective damage to the hippocampus yields comparatively mild impairment or, in the majority of instances, no impairment at all on these same tasks. Importantly, neonatal damage in monkeys to the perirhinal cortex, the subhippocampal area that is most important for non-spatial recognition, produces an impairment in this ability later in life that is as severe as that produced by similar lesions in adulthood (Malkova *et al.* 1998). The findings in animals thus suggest that spared recognition ability in patients with DA, like the proposal regarding the preserved semantic memory ability in these cases, is due to the apparent preservation of the parahippocampal region.

The neuropsychological study conducted with Jon (Baddeley *et al.* 2001) also helped clarify how children with DA might acquire factual information, which is of course not limited simply to its recognition. Jon, for example, has no difficulty recalling the definitions of words, naming and describing historical figures and events, or discussing at length such subjects as current politics and computer games, both of which are his hobbies. To track his acquisition of new material, we presented Jon with a series of videos based on two newsreels of events that pre-dated his birth by many years. One reel was shown only once, while the other was shown four times over 2 days. Tested for recognition after either one or four viewings, Jon's recognition scores were generally comparable with those of his two age- and IQ-matched controls, whereas his recall score after one viewing was markedly impaired. After four viewings, however, Jon's recall score rose substantially, nearly matching those of his controls, demonstrating that his recall deficits can be minimized, given sufficient practice. A possible interpretation of this finding is provided by the episodic memory theory of Tulving (1985), namely, that through repetition Jon can recall information because he is now familiar with or 'knows' it, a characteristic of semantic memory, although he is not able to 'remember' or recollect it, i.e. bring it back to mind, the hallmark of episodic memory.

5. EVENT-RELATED POTENTIALS (ERPs) DURING RECOGNITION AFTER HIPPOCAMPAL INJURY

We recently obtained support for the foregoing interpretation from the results of an ERP study in Jon (Düzel *et al.* 1999, 2001). Word recognition experiments have shown that normal subjects can correctly recognize some words that they recollect studying, being able to report something that happened or that they had thought about when they had studied those particular words, and others on the study list that they do not recollect but nevertheless judge as familiar (e.g. Gardiner *et al.* 1996). These two

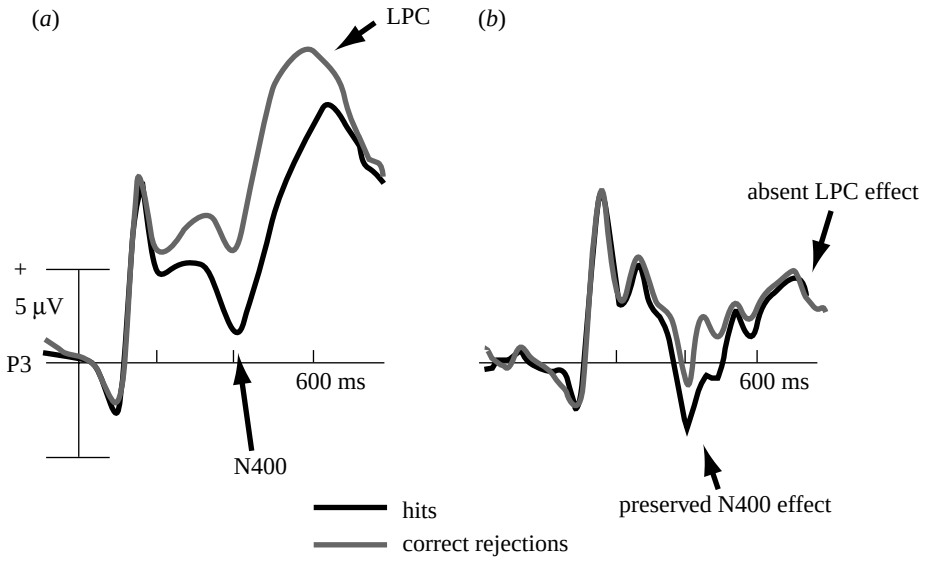

Figure 3. ERPs recorded from the left parietal electrode (P3) to visual word recognition after deep encoding of the words. In normal subjects, hits (i.e. correct recognition of old words) elicit greater positivity than correct rejections of new words in both the N400 and LPC time-windows. In Jon, hits elicit greater positivity than correct rejections in the N400 time-window only. (Adapted from Düzel *et al*. 1999.)

types of memory can be differentially enhanced by manipulating depth of processing during study. For example, asking the subject to judge whether the word's referent is living or non-living or is abstract or concrete (deep encoding) enhances the likelihood that the word will be recollected later, whereas asking the subject whether the word's letters are printed in small or capital letters or whether its first and last letters are in alphabetical order (shallow encoding) generally leads to familiarity judgements. Importantly, these two memory types were later found to be associated with qualitatively different ERP patterns (Paller *et al*. 1995; Rugg *et al*. 1998). Thus, during familiarity-based recognition, correctly recognized old words (hits) evoke significantly more positive waves than correctly rejected new words from fronto-central electrodes in the 300–500 ms time-window, a modulation that is often referred to as the N400 effect. By contrast, during recollection-based recognition, hits evoke significantly more positive waves than correct rejections from left parietal electrodes in the 500–700 ms time-window, sometimes referred to as the late positive component (LPC) effect. The temporal and topographical dissociation of these two ERP effects suggests that they are generated by different neuronal populations.

Based on this evidence, we investigated the recognition memory of Jon during ERP recording, using a deep encoding paradigm that reliably elicits both the N400 and LPC effects in normal subjects. Thus, as illustrated in figure 3, hits normally elicit more positive ERPs than correct rejections in both the N400 and LPC time-windows. In Jon, however, the ERPs showed a prominent N400 effect only, the LPC effect being entirely absent. Interestingly, in this deep encoding paradigm, Jon's recognition was not as good that of his controls, although he performed at a satisfactory level. The results are thus consistent with the notions that (i) the process of recollection is critically dependent on the hippocampus, (ii) recollection normally enhances recognition, but (iii) recognition can proceed fairly accurately without recollection, even after deep encoding, on the basis of the familiarity process alone.

6. SUMMARY AND CONCLUSIONS

Investigation of DA is still in its early stages, and therefore many questions surrounding the memory dissociations that seem to characterize this syndrome remain unanswered. Although the DA patients' impairments in episodic memory and recollection are very likely the result of the substantial hippocampal damage they have incurred, it is still unclear whether the relative sparing of their semantic memory and familiarity-based recognition are attributable to integrity of the subhippocampal cortices, to the partial sparing of the hippocampus, to the functional reorganization within these structures, or to some combination of these several factors. Reasons for favouring the possibility listed first come from the experimental studies in animals referred to earlier (§4) demonstrating the critical role of the subhippocampal cortices in recognition memory, even in cases of neonatal damage. The support provided by this experimental evidence for the subhippocampal proposal is only indirect, however. Further, this proposal leaves unexplained the differential outcome after childhood-onset and adult-onset hippocampal pathology, with the latter resulting in little if any preservation of semantic memory, and relatively few cases of preserved recognition memory. In sum, determining the precise neuropathological and neuropsychological explanation for the syndrome of DA remains a challenge for future research.

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