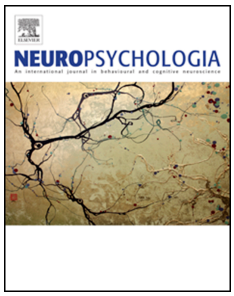

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A Brief History of Developmental Amnesia

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The first encounter

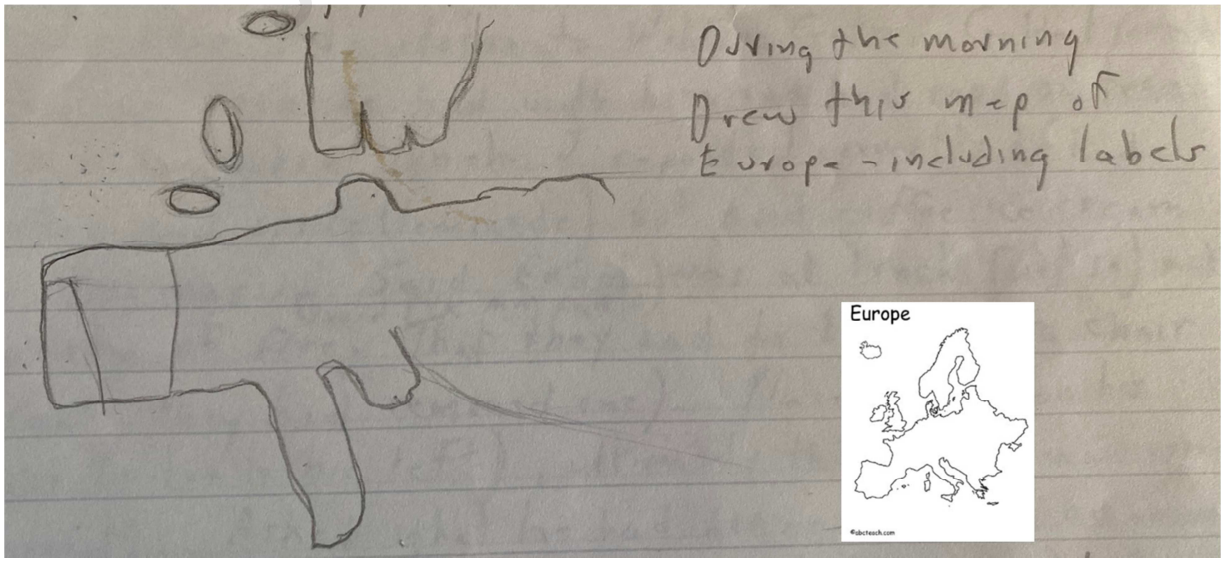
July 1st, 1997 was a glorious day in London with the Wimbledon season calling tennis lovers, including Endel Tulving, to the centre court to witness the challenging games. At the same time, a no less engaging challenge of a different sort was about to unfold at UCL Great Ormond Street Institute of Child Health where a team of neuroscientists consisting of Mort Mishkin, Endel Tulving, David Gadian and Faraneh Vargha-Khadem, had assembled to welcome a teenager diagnosed with developmental amnesia. Jon, the young man who had been investigated since the age of 11 because of his chronic and disabling memory problems, had graciously agreed to spend the better part of the day performing memory tasks that the researchers had developed on the go, and were eager to put to test. Despite their different expertise, the team members were united in one goal: to understand how declarative memory encompassing facts and personal events was organised in the mind of this able young person who at the start of life had lost half of his hippocampi, brain structures known to be responsible for encoding, storing, and retrieving one's personal autobiography and dictionary of world knowledge.

In what follows, highlights of that memorable day 23 years ago are brought to life through notes and recordings to chart the progress made in researching the syndrome of developmental amnesia, and to delineate the challenges that this form of mnemonic disorder poses for our understanding of human memory.

The striking dissociations

Jon quickly impressed his audience with his remarkable repository of semantic knowledge, displayed through a conversation about World War I, with statements such as “at the time of World War I, the British Empire occupied about 1/3 of the planet’s land mass.” Not only was Jon capable of using eloquent language to communicate general facts, he was also knowledgeable about historical events. He discussed details about Archduke Ferdinand and his assassination in Sarajevo leading to World War I, pointing out that the assassination itself was not the actual cause of war, but because of other political events it proved to be “the last straw that broke the camel’s back”! Equally impressive was his awareness of current and future world affairs, including details of a major event that was about to unfold later that day in July 1997, namely, the British hand-over of Hong Kong to China, although he was unable to identify the source of his memory, or to explain how he “knew what he knew.”

Later in the day, Tulving quizzed Jon on his knowledge of geography. Did Jon know where Estonia was in relation to Sarajevo, and could he draw a map of Europe? In response, Jon sketched the map of Western Europe from memory, while naming the major countries (see below; handwritten text by Mishkin).



Clearly Jon could retrieve old factual memories at will, but was he able to encode, store and recall newly-learned information? Together with Gadian, Tulving presented his word-phrase paired-associate list for learning over two trials followed by delayed recall after several hours. This task proved challenging for Jon. He accurately recalled nine words each from the list of 30 on the first and second learning trials. Sometimes, Jon recalled a word from the correct semantic category, but not the correct target word (e.g. “bug” for cockroach; “museum” for statue; “pathologist” for coroner, the latter he had recalled correctly on the first trial). After the long delay, Jon’s recall performance deteriorated further with only three words correctly recalled. Then came the second surprise of the day: Jon was given the 30 original paired-associates along with 30 distractor pairs in a recognition format. He achieved an accuracy score of 57/60.

Later in the afternoon, Gadian, Mishkin, and Vargha-Khadem accompanied Jon for lunch to a nearby restaurant; Tulving stayed behind to develop the next set of questions aimed at recollection of the day’s events. During the walk to the restaurant, photographs of salient landmarks were taken to test Jon’s spatial awareness and recollection of the route. Upon his return to the Institute, Jon was asked specific details about his lunch break: (a) who went to lunch; (b) how many chairs were at the table; (c) who was sitting to the left and right of Jon; (d) what topics were discussed; (e) what did Jon draw; (f) what route was taken, and (g) which landmarks could be recalled, or recognized?

Jon provided the following answers – correct responses shown in parentheses: (a) all five members of the group went to lunch (Tulving had not joined the lunch); (b) a chair had to be added to make a table for five (a chair was removed to make a table for four); (c) Jon reversed the seating position of the team several times, including Tulving’s, but still failed to recall the correct seating arrangement; (d) Europe and America were discussed (British colonies, and English vs American football were discussed); (e) a map of Europe was drawn (a map of Gadian’s office, where Jon had spent the morning, was drawn); (f) could not describe the route taken; (g) could recognise 4/10 photographs of the landmarks he had passed along the way, but not their location relative to the restaurant. Further questioning of Jon elicited the response that he had difficulty seeing images in his mind.

Jon seldom produced a “can’t remember” response; rather, he provided answers that were reasonable and within context. He confabulated scenarios based on generalities rather than specific details. This led to the conclusion that he could not distinguish between “knowing” and “recollecting”; as Tulving elaborated: “....for the simple reason that he has never been able to remember!”.

And so it was that, within the space of a few hours, Jon had demonstrated all three dissociations in cognitive memory that have become the defining features of this developmental form of amnesia which is associated with hypoxia-induced bilateral hippocampal atrophy. Clearly, Jon had well-developed semantic memory, but severely impaired episodic memory, preserved recognition memory despite profoundly deficient recall, and a strong sense of familiarity in the absence of explicit awareness of recollection. Tulving was incredulous, and reflecting on the findings, he announced: "...my impression is that he [*Jon*] does not resemble any other kind of patient who has ever been described", and "...the discrepancy between his ability to recall and recognise is unprecedented, unheard of, it is a new record....".

But why was Jon's pattern of spared and impaired functions so surprising? To answer this question, it is necessary to consider the historical context and the theoretical framework within which the amnesic syndrome in humans was interpreted at the time. Following the decades-long studies of H.M. dating to the 1950s and beyond, the prevailing view of the organisation of memory was the "unitary model" which posited that both semantic and episodic memory are subserved by the medial temporal lobe. In this framework, injury to the hippocampus should result in equivalent deficits in both semantic and episodic memory, and in the associated processes of recognition and recall. This model had influential advocates such as Alan Baddeley, who then adhered to the modal view of episodic and semantic memory (Baddeley, this issue), Larry Squire and Stuart Zola (Squire and Zola, 1996), and even Tulving, who by his own admission "... went through that phase .... [*I*] tried to see the similarities between recall and recognition. I tried very hard. I was a unitarian in that respect for a long time and then finally the data forced me to adopt the idea [*that*] there is a difference and we don't know what produces it...."

Adult- versus neonatal-onset hippocampal damage leading to developmental amnesia

It is noteworthy that up to 1997, when the first account of three young patients with selective hippocampal atrophy and developmental amnesia was published (Vargha-Khadem et al., 1997), almost all existing publications on amnesia resulting from damage to the memory network had been reported in adults. During the course of their lives, these patients had developed a normally-organised cognitive memory system. Arguably, their amnesic profile could have been due to a combination of the selectivity of hippocampal/medial temporal lobe damage, and/or a chronic failure to access a previously functioning memory network. In developmental amnesic patients, however, a radically different process involving compensation and reorganisation must have unfolded as hippocampal damage occurred bilaterally *before* any mnemonic functions

had emerged. Here, all world knowledge, intellect, academic skill, language, and indeed the autobiography of personal experiences had to have been acquired from the start in the presence of severe hippocampal damage. Clearly, the unitary model could not accommodate the dissociations characteristic of patients with developmental amnesia. New models were therefore required to account for the ontogenetic emergence and organisation of memory.

An anatomo-functional model of cognitive memory development

Tulving published his seminal paper “Organization of memory: Quo Vadis?” (1995), where he proposed a hierarchical model to account for the emergence of the cognitive memory system and its components. Based on his work with patient K.C. who had suffered extensive brain injury and had become amnesic at the age of 30 following a motorcycle accident, Tulving proposed that the core deficit in human amnesia is an episodic memory impairment, but learning of some semantic information is feasible, at least under controlled experimental conditions, even in adult-acquired amnesia, provided associative interference is kept to a minimum.

The following year, another influential paper (Aggleton and Shaw, 1996), reported that some patients with focal damage to the hippocampus, fornix, or mammillary bodies showed evidence of spared recognition memory despite their severe amnesia. This and other ensuing reports (e.g. Yonelinas, 2002), strengthened the notion that recognition and recall, and familiarity and recollection could dissociate in some patients suggesting that these processes may have distinct neural substrates. Importantly, animal models of human amnesia produced convincing evidence that recognition memory in the monkey is supported by the rhinal cortex, rather than the hippocampus (Murray and Mishkin, 1998). Finally, the advent of magnetic resonance imaging techniques provided the means through which different components of the medial temporal lobe structures could be identified and their integrity quantified (e.g. Jackson et al., 1993).

Against this background, the anatomo-functional model of memory organisation (Mishkin et al., 1997) helped to reconcile the two contending views of the unitary versus the episodic-specific modes of hippocampal function. We hypothesised that the rhinal cortices situated below the hippocampus are necessary for the processing of both semantic and episodic memoranda, but only episodic memory is critically dependent on the further contextual stimulus processing afforded by the hippocampus. In the ensuing studies of the growing number of patients diagnosed with developmental amnesia, this model served as the framework within which different aspects of hippocampal structure and function were analysed.

Structure-function mapping in patients with developmental amnesia

An event-related potential (ERP) study of Jon using word recognition sought to identify the neural signature of familiarity, and possibly that of recollection through residual hippocampal function (Duzel et al., 2001). Results showed that an ERP index of recollection (the late positive component) was absent in Jon, whereas a decrease of the ERP amplitude (the FN400 effect, associated with stimulus familiarity in controls), was well-preserved.

A series of experiments then followed to determine whether Jon's recognition performance could be enhanced by depth of processing manipulations that typically boost episodic remembering (e.g. Gardiner et al., 2006). Indeed, Jon's recognition was found to be enhanced when a study task was deeply processed as meaningful compared to one which was less meaningful. However, although Jon claimed that he could experience episodic remembering, he could not support his claim by describing what he remembered.

These findings suggest that, because the requisite neural substrate for recollection-based performance is severely damaged in Jon, his recognition memory is supported primarily by familiarity-based retrieval. Such retrieval, we reasoned, may be mediated not by the hippocampal circuitry per se, but by the neocortical system subjacent to the hippocampus.

Further support for this scenario is provided by a functional MRI study of context memory in a small group of patients with developmental amnesia, including Jon (Elward, Rugg, Mishkin and Vargha-Khadem, 2017). Here, patients and controls viewed words overlaid on a scene or a scrambled image for recognition after a delay. Similar to healthy controls, patients activated the 'reinstatement' network, showing context memory effects for scenes in the parahippocampal and the retrosplenial cortices. However, unlike the controls, patients' context memory performance was strikingly impaired. Thus, despite neural evidence that context memory processing was intact (as indexed by reinstatement of activity in limbic cortices), this was not sufficient to support patients' accurate context memory judgments. It appears that the integrity of the hippocampus is critical for the product of the cortically-retrieved memoranda to be translated into accurate memory performance.

Probing the extent of encoding and learning capacities of a semantic memory system that has developed alongside a compromised hippocampus, we reported that despite a profound deficit at encoding, learning and cued recall of short texts over six

consecutive trials (~30%), patients with developmental amnesia displayed recognition scores comparable to matched controls (~ 80%), one week after the study sessions (Elward and Vargha-Khadem, 2018). It is clear therefore that these individuals are capable of encoding and consolidating new semantic information, but similar to their failure of context memory performance during fMRI detailed above, they are unable to access the consolidated information through cued recall.

The availability of a large cohort of patients with hippocampal damage caused by early life hypoxia/ischaemia enabled us to document the relationship between degree of hippocampal atrophy and extent of deficit in recall, but not recognition (Patai et al., 2015). Importantly, we recently discovered that the deficit in recall is specific to the integrity of the anterior region of the hippocampus, namely, the uncus (Chareyron, Bastos, Buck, Saunders, Mishkin, Gadian and Vargha-Khadem, 2020). Here, we observed an *inverse* relationship between memory recall and residual uncal volumes in a uniquely large group of patients with developmental amnesia. This paradoxical finding suggests that increased volume of residual uncal tissue may actually prevent functional reorganisation of mnemonic processes to intact neighbouring cortical tissue.

In this context, it is important to note, that even when severity of hippocampal damage is such that reorganisation of memory function is achieved, the information that is encoded simultaneously by a damaged hippocampus and a reorganised cortical system is not as high fidelity as when both regions are intact. Indeed, depending on the extent of compensation by the cortical system, or the degree of interference by the residual hippocampus, pattern separation processes at encoding, and/or pattern completion for consolidation and retrieval can be compromised. This may explain why Jon, when asked what he remembered about the lunch that had just taken place, could remember something about chairs, but could not recall correctly that a chair had to be removed from (rather than added to) the table. Jon's is a memory system that appears to process the gist of events (Robin and Moscovitch, 2017), with its memory output possessing a distinctive semantic flavour.

Conclusions

We have provided a brief historical account emphasizing how the study of developmental amnesia has shaped our growing understanding of memory organisation in the face of early hippocampal injury. We propose that hippocampal integrity is essential for the development of recall, and the emergence of recollective processes involved in self-awareness. Our hypothesis is that it is the intentional, detail-specific, binding-enabled, and self-generated nature of recollective retrieval that relies on the integrity of hippocampal function. In the absence of this, cortical reorganisational

processes may partially compensate depending on the severity of the hippocampal damage, but this will result in the development of a sui generis semantic memory system.

Endel Tulving's contribution to the study of human memory stands out amongst the sources of inspiration to our work. In particular, Tulving's ideas have been pivotal in catalyzing our interest in the evolutionary and developmental contributions to memory processing. His voice has been fundamental in kindling interest in cross-species studies, and in inspiring the study of the developmental origins of hippocampal networks supporting spatial and mnemonic functions.

Tulving's ideas have shaped the debate around the uniqueness of human memory for decades. We take the position that human memory is unique and distinctive by nature because unlike other animals, humans are creatures embedded not only in a personal past (and future), but in a collective weave of cultural histories. Perhaps the roots to the uniqueness of human memory are to be found in the inter-generational transmission of information afforded by language and facilitated by formal inter-individual instruction, and in the human drive towards mythopoiesis and story-telling. These processes are, of course, rooted in a biological make up that is shared with many other species; however, during the past tens of thousands of years, their evolutionary unfolding in the human species has resulted in a significant qualitative difference between memory in humans and other animals.

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