Human memory: insights into hippocampal networks in epilepsy

This scientific commentary refers to 'Differential influence of hippocampal subfields to memory formation: insights from patients with temporal lobe epilepsy', by Coras et al., (doi:10.1093/brain/awu100).

Memory is one of the core cognitive abilities that shapes our sense of self-identity and we strive to maintain and improve our memory function throughout our lives. Memory impairments are a key component of a number of neurological and psychiatric diseases, and represent a large part of the disease burden in many patients. The hippocampus has been central to the study of human memory, having been implicated in episodic and long-term memory, novelty detection, sleep-dependent memory consolidation, the ability to imagine the future, as well as spatial navigation and the binding of temporally and spatially distributed representations (Bartsch, 2012). What’s more, the hippocampus is also involved in neurobiological mechanisms beyond memory formation such as the regulation of emotion, fear, anxiety, and stress. Notably, the hippocampus displays a particular vulnerability to hypoxic, ischaemic, or neurotoxic insults, and is thought to be involved in the pathophysiology of various neurological and psychiatric diseases including epilepsy and neurodegeneration, as well as ageing. In this issue of Brain, Coras et al. use the memory performance of patients undergoing surgery for the treatment of temporal lobe epilepsy to obtain new insights into the anatomical basis of memory formation (Coras et al., 2014).

The hippocampus has an intriguing anatomy, although how this relates to the formation of episodic memory is still incompletely understood. The trisynaptic pathway from the perforant path to the dentate gyrus, to CA3 via mossy fibres and onwards to CA1 via Schaffer collaterals, is the principal sequential feed-forward neural circuit involved in the processing of information by the hippocampus. CA1 pyramidal cells project via the subiculum to deep layers of the entorhinal cortex and to various subcortical and cortical areas. Within the hippocampus, axon collaterals of CA3 pyramidal neurons synapse onto other CA3 neurons, forming recurrent autoassociative networks. Animal experiments show that these networks perform differential computations in different cognitive tasks. Through the use of animal models and, more recently, functional imaging in patients, researchers have sought to correlate components of the hippocampal subnetworks with distinct cognitive mnemonic operations. For example, it has been argued that the dentate gyrus is involved in pattern separation—a function that is impaired in ageing and mild cognitive impairment—whereas the CA3 network is involved in pattern completion, and the CA1 network is engaged in input integration, novelty and mismatch detection (Bakker et al., 2008; Duncan et al., 2012). The CA1 region is also involved in autobiographical memory retrieval (Bartsch et al., 2011). High-resolution imaging in humans shows an involvement of CA3 and the dentate gyrus in memory encoding and early retrieval, and an involvement of CA1 in late retrieval, consolidation and recognition (Mueller et al., 2011). In accordance with the cognitive-map theory, which suggests that allocentric spatial representations of locations are processed in the hippocampus, the CA1 subregion is involved in our ability to learn a map-like representation of an environment (Bartsch et al., 2010).

Recently, it has been suggested that distinct clinical disorders affect hippocampal subregions in different ways, which could account for the variety of cognitive deficits observed in amnesic disorders. Deficits in memory encoding correlated specifically with CA1 subfield atrophy in mild cognitive impairment and in Alzheimer’s disease (Mueller et al., 2010). Apolipoprotein E4 status has an effect on the volume of CA3/dentate gyrus in healthy controls and in patients with Alzheimer’s disease (Mueller and Weiner, 2009).

In this issue of Brain, the Erlangen epilepsy group addresses the question of subfield-associated mnemonic processes from a different perspective (Coras et al., 2014). They studied the functional subfield anatomy of the hippocampus in patients with temporal lobe epilepsy and hippocampal sclerosis, and correlated subfield lesion patterns with the verbal memory deficits revealed by presurgery intracarotid amobarbital testing. One hundred patients were tested before
and after epilepsy surgery. Histopathologically quantified cell loss in hippocampal subfields was assessed using the new international consensus classification for hippocampal sclerosis, which delineates CA1 predominant cell loss (type 2), combined cell loss in all subfields [CA1, CA4 and dentate gyrus (type 1)] and CA4 predominant cell loss (with lesser CA3–dentate gyrus changes). Interestingly, patients with CA1 predominant cell loss did not show declarative memory impairment and were indistinguishable from patients without any hippocampal cell loss. In contrast, patients with combined cell loss in all other subfields (types 1 and 3) showed significant declarative memory dysfunction. The authors conclude that CA1 seems to be less pivotal involved in human declarative memory formation than dentate gyrus or CA3/4 pyramidal cells.

These surprising results can be better judged in the context of the specific patient population used in the study. The authors point out a number of caveats, such as the fact that only the midbody of the hippocampus was analysed; the possibility of functional differentiation in anterior or dorsal regions cannot therefore be excluded. Furthermore, neuronal cell loss in CA1 (type 2) was less than 80%, leaving open the possibility of intact neuronal pathways in the affected CA1 as well as in the contralateral hippocampus. The authors also highlight the existence of an alternative pathway (excluding CA1) via dentate gyrus-CA3-fimbria, and of CA3 collaterals projecting to the subiculum, suggesting that the hippocampus can communicate with the rest of the brain without CA1. With this in mind, Coras et al. note that the patients had an average epilepsy duration of 14 years and a considerable seizure load, which may have induced plastic compensatory processes in hippocampal and extrahippocampal memory networks. Indeed, this kind of plasticity in patients with operated temporal lobe epilepsy has recently been described, with intact memory found to be related to compensatory brain reorganization. These processes were dependent locally on the activation of the contralesional hippocampus as well as remotely on the activation of neocortical memory networks. Such data strongly suggest the existence of an efficient hippocampal-neocortical mechanism that compensates for hippocampal dysfunction in patients with epilepsy (Finke et al., 2013). Moreover, the findings of Coras et al., (2014) should be considered in the light of another study in which verbal memory impairment in patients with temporal lobe epilepsy with mesial temporal lobe sclerosis was indeed associated with CA1 loss (Mueller et al., 2012), and of their own report of no association between subfield pathology and memory performance (Witt et al., 2014).

In conclusion, the work of Coras et al. raises interesting questions regarding the contribution of hippocampal subfields and intrahippocampal pathways to mnemonic processes and regarding neuroplastic changes in temporal lobe epilepsy. Further understanding of this system will be important, both for the cognitive science of memory and, because of its potential implications, for the surgical and rehabilitative treatment of epilepsy.

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References


