The role of the hippocampus in organic amnesia

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Abstract
Organic amnesia is a neurological disorder characterised by severe impairment in episodic memory. In the past, hippocampal damage has been assumed to be both necessary and sufficient to cause organic amnesia, however more recent research refutes this, instead suggesting the contribution of an array of brain processes. The anatomically narrow research focus on the hippocampus must now be revised in order to advance our understanding of amnesia, and the workings of human memory. One structure alone does not explain the diversity of research findings in the laying down of memories. We must look beyond the hippocampus in the search for better ways to find memories that have been lost.

Keywords
Amnesia, memory, hippocampus, neuropsychology, cholinergic processes
Organic amnesia is a neurological disorder characterised by severe memory impairment. Understanding amnesia would not only allow for the development of effective rehabilitation procedures for amnesic individuals, but would vastly extend our knowledge regarding the psychological and neurological underpinnings of memory. Whilst neuropsychological research is characterised by exploration and examination of the functions of various brain regions, in the past amnesia research relied heavily on investigation of a single brain region: the hippocampus. Recent evidence suggests that the hippocampus may not play such an independently causal role in amnesia as was once thought. As such, the anatomically narrow focus of previous research may have hindered the advancement of our understanding of both the psychological and neurological framework that underlies organic amnesia.

Perhaps the most well-known case study in neuropsychology is that of Henry Molaison (H.M.). Scoville and Milner (1957) reported that subsequent to surgery involving bilateral removal of the hippocampus to relieve his severe epilepsy, patient H.M. exhibited extensive anterograde amnesia. In contrast, patients with minor hippocampal damage showed fewer or no memory impairments. This research implicated the hippocampus as the determining factor of severe amnesia. Whilst this revolutionary work had extensive benefits in terms of establishing theories of modularity, and substantiating the distinction between declarative and procedural memory (Squire & Wixted, 2011), it resulted in amnesia becoming intrinsically linked with this single brain structure (Bussey, 2004; Warburton & Brown, 2010). Subsequent years saw the publication of a plethora of experiments, case studies and models of memory focussing on the hippocampus alone (Cohen & Eichenbaum, 1993; Rempel-Clower, Zola, Squire, & Amaral, 1996; Redish, 2001).

The vast literature on the role of the hippocampus in organic amnesia also stems from the availability of research participants. Patients with hippocampal damage are relatively common due to its susceptibility to various pathologies including oxygen deprivation resulting from ischemia, anoxia or stroke, encephalitis, viral infection and temporal lobe surgery (Spiers, Maguire, & Burgess, 2001). As a result, the effects of hippocampal lesions in vivo can be studied far more readily than lesions of other brain regions that may play a role in amnesia.

Whilst it is undoubtedly true that the hippocampus plays a role in memory, the extent to which this single brain structure is responsible for amnesia has been fundamentally overstated. Despite evidence from non-human animal research that hippocampal lesions did not result in the severe amnesia observed in H.M. (Mahut, 1971; Mishkin, 1978; Murray and Mishkin, 1986), only rarely did researchers challenge the hippocampus’ supremacy (Horel, 1978; Vanderwolf & Cain, 1994). However, several decades after the initial report of H.M. by Scoville and Milner (1957), Corkin, Amaral, Gonzalez, Johnson, and Hyman (1997) demonstrated using magnetic resonance imaging (MRI) not only that the damage in H.M.’s brain extended far beyond the hippocampus to the adjacent rhinal cortices and the surrounding white matter, but also that the caudal section of the hippocampus contrarily remained largely intact. The presence of this extensive damage was subsequently verified by a post-mortem of H.M.’s brain (Annese et al., 2014).

More recently, reports of patients with localised hippocampal damage have indicated less dense amnesia (Spiers, Maguire, & Burgess, 2001), suggesting that the additional extra-hippocampal damage in H.M. may have significantly contributed to the severity of his memory impairments. As such, the case of H.M. can no longer be classed as an
example of a selective hippocampal lesion that resulted in amnesia, as was so often stated in the past, and does not imply that hippocampal damage is either necessary or sufficient to cause organic amnesia. Despite this, H.M. is still used erroneously in the literature as evidence of amnesia resulting from purely hippocampal damage (Squire & Wixted, 2011).

Another line of convincing evidence suggesting damage to the hippocampus alone could cause amnesia came from patients with ischemic damage (Rempel-Clower et al., 1996). Ischemic individuals such as R.B. (Zola-Morgan, Squire, & Amaral, 1986), who developed amnesia subsequent to oxygen deficits in the brain, endured restricted damage to the CA1 subfield of the hippocampus. The resulting severe amnesia was therefore seen as hippocampal dependent. However, more recent evidence suggests ‘hidden’ pathology resulting from ischemia may also contribute to the impairment (Bachevalier & Meunier, 1996; Markowitsch, Weber-Luxemburger, Ewald, Kessler, & Heiss, 1997). This can include damage to the rhinal cortices, thalamus, cerebellum, and the amygdala (Smith, Auer, & Siesj, 1984). As such, even ischemic damage that is often used in arguments defending the hippocampus, does not provide evidence of an exclusive hippocampal role in amnesia. This also emphasises the problem arising from reliance upon clinical studies, which are so often used to implicate the hippocampus in amnesia.

Supporting the idea that the hippocampus is not an all-encompassing memory structure, and thus is not the sole cause of amnesia, is evidence demonstrating that memory deficits can occur independently of hippocampal damage. The first observations of amnesia based on loss of a structure other than the hippocampus occurred in patients with Korsakoff syndrome (Pergola & Suchan, 2013). Such patients suffer from thiamine deficiency, often as a result of excessive alcohol consumption, which can cause damage in the thalamus and mammillary bodies, as seen in patient P.Z. (Butters & Cermak, 1988). Amnesia can also result from thalamic stroke (Carlesimo, Lombardi, & Caltagirone, 2011), firmly implicating the thalamus in amnesia. Another example of amnesia subsequent to non-hippocampal damage comes from individuals with visual memory deficit amnesia (VMDA), resulting from damage to the visual association cortices (Rubin & Greenberg, 1998). Such patients show mild anterograde, and severe retrograde amnesia. Although these symptoms differ in severity to those found in hippocampal patients, it is evident that the hippocampus is not necessarily responsible for all cases of amnesia.

Several other regions have also been implicated in amnesia such as the rhinal cortices (Meunier, Bachevalier, Mishkin, & Murray, 1993). Due to their neural connections to the hippocampus such regions have previously been thought to be of secondary importance, however it has recently been postulated that these structures provide novel information that is essential for memory function, thus reversing the conventional hierarchy topped by the hippocampus (Vann, 2010; Aggleton et al., 2013). A lack of research in the past into such regions as a result of the hesitancy regarding their importance (Vann, 2010) has prevented advancement in the understanding of structures which may contribute to amnesia.

The typical concept of ‘classic’ anterograde amnesia is that it involves loss of both recall and recognition memory (Brown & Aggleton, 2001; Warburton & Brown, 2010). Due to the hippocampal focus, it was inevitably assumed that both processes were hippocampal dependent. In the past, studies investigating the effects of hippocampal lesions utilised surgical aspiration lesions, which necessarily involves the removal of rhinal cortices (Baxter & Murray, 2001). A resultant deficit in recognition memory strengthened
the view that it was a hippocampal dependent process. Whilst this idea is still embraced by some (Squire, Wixted, & Clark, 2007), double dissociations subsequent to lesions of the hippocampus and perirhinal cortices suggest this assumption was ungrounded (Easton & Parker, 2003). A meta-analysis completed by Baxter and Murray (2001) found that after perirhinal cortices damage, subsequent damage to the hippocampus was inversely correlated with recognition memory as assessed by a delayed-non-match-to-sample (DNMS) task: whilst perirhinal damage impairs recognition memory, additional hippocampal damage has a protective effect. This contradicts the view that greater damage of the medial temporal lobe memory system results in more severe amnesia (Zola-Morgan, Squire, & Ramus, 1994), instead suggesting that recall and recognition are independent processes, reliant on differential brain regions rather than the hippocampus alone.

Evidence opposing the hippocampus’ role in recognition comes from patients with fornix damage (Easton & Parker, 2003). Whilst such patients show impaired episodic memory, recognition memory remains unimpaired (Aggleton et al., 2000). Furthermore, patient K.N. presented by Aggleton et al. (2005) was unimpaired on tests of recognition despite having bilateral damage to the hippocampus, further suggesting the hippocampus is important in recall alone, with its role in other memory domains having been overemphasised in the past.

Aggleton and Brown (1999) propose two dissociable systems to account for the explicit recollective and familiarity components of recognition memory, postulating that whilst the former relies on the hippocampus, the latter relies upon a system involving the perirhinal cortices and the thalamus. According to this view, hippocampal damage does not necessarily cause impairment of recognition tasks. This duel process model has been largely supported by animal studies (Warburton & Brown, 2010), as well as clinical and neuroimaging research with human participants (Brown, Warburton, & Aggleton, 2010). This demonstrates how models incorporating extra-hippocampal regions can convincingly explain some aspects of amnesia. However, the underlying neural processes remain elusive.

One problem that still plagues the literature since the advocacy of the hippocampus as the essential memory structure, is the resulting emphasis on a single or set of structures, rather than processes in the majority of subsequent research on amnesia. Several decades ago a theory presented by Horel (1978) broke this trend, but was quickly discounted (Zola-Morgan, Squire, & Mishkin, 1982), and subsequently ignored at the time. His research has resurfaced in the literature in more recent years (Gaffan, Parker, & Easton, 2001). Horel (1978) attributed amnesia to damage of the white matter in the temporal stem, which could prevent cholinergic medial temporal lobe input (Easton & Parker, 2003). Gaffan, Parker, and Easton (2001) proposed that the removal of cholinergic cells, which form the basis of a transmitter system between the medial temporal lobe, and frontal and inferior temporal cortices, would result in dense amnesia akin to that displayed by H.M. Indeed, this was subsequently shown to be the case in monkeys (Easton, Ridley, Baker, & Gaffan, 2002; Turchi, Saunders, & Mishkin, 2005), however research with rats yielded divergent results (Easton, Fitchett, Eacott, & Baxter, 2011). Whilst it still remains unclear whether the cholinergic process plays a vital role in amnesia, such work has combined study of areas outside of the hippocampus with that of a process, thus advancing the field of amnesic research, overcoming a previous fixation on brain structure and furthering our endeavour to gain a greater understanding of organic amnesia.
Recent technological advances have allowed for quicker research progression, with more reliable and detailed neuroimaging available for human participants, and more precise lesioning techniques for experiments with non-human animals. For example the role of extra-hippocampal areas in amnesia have recently been supported using functional magnetic resonance imaging (fMRI), which implicate both the prefrontal and retrosplenial cortices in episodic memory (Pergola & Suchan, 2013). As such, researchers are beginning to focus their research on areas beyond the hippocampus (Vann, 2010; Eichenbaum, 2013; Pergola, Ranft, Mathias, & Suchan, 2013), and are furthermore broadening the understanding of the functional relationships between structures, rather than just the function of the structures themselves (Allen & Fortin, 2013), and thus acknowledging amnesia has no independent causal structure but instead involves a number of different networks throughout the brain.

Retrospectively, it now seems remarkable that researchers once attributed such a complex neurological disorder as organic amnesia to a single brain structure, and this realisation demonstrates the extensive increase in understanding we now have of the disorder. However, in order to overcome this difficulty in its entirety it is important that traditional views of amnesia are tempered (Maguire & Mullally, 2013). It is apparent that brain regions damaged in H.M. other than the hippocampus are still largely under-researched and further studies are needed to address this. By also taking into account the advice of Gaffan (2005) to not assign a specific cognitive function to a specific brain region, but instead investigate the role of cortical networks, a greater understanding of organic amnesia will be achieved.

While the development of new techniques, alongside novel research perspectives have been partially successful in overcoming the historical focus on the hippocampus, further research is required in order to overcome this incessant bias in the literature. In turn, this should lead to improved treatments, such as better methods of rehabilitation for patients with amnesia following stroke or traumatic brain injury, and will ultimately lead to a greater understanding of the psychological and neurological mechanisms of amnesia.
References


