Neuropsychologia 48 (2010) 2231–2233

Contents lists available at ScienceDirect

Neuropsychologia

journal homepage: www.elsevier.com/locate/neuropsychologia

Animal models of amnesia

The papers in this Special Issue of Neuropsychologia aim to show how animal research has and is helping us to understand human amnesia. Research with animals has a number of advantages. In particular, the use of animal models allows investigation of the effects of damage to specific and well-circumscribed areas of the brain, something that is almost never possible in humans. Furthermore, pharmacological models in animals are key for determining how selected neurotransmitter–receptor systems are involved in various aspects of cognitive function that are affected in amnesia. More recently developed techniques—such as genetic manipulations, electrophysiological recording of neuronal activity, viral vectors that can alter cellular function, and identification of immediate early gene activity, in which regional patterns of activity can be tracked at different points in a given task—are proving highly informative and hold much promise for the future. Finally, studies in animals allow us exquisite control in behavioural experiments as we can modulate the specific experiences—for example, the stimuli seen in the course of a lifetime—of our subjects precisely, which helps to narrow down the mechanism underlying functional impairment.

The papers in this Special Issue provide a showcase of some of the most important work—both historically and more recently—that has been done in this area. The articles collectively show that although translation from human to animal and back is not always straightforward, particularly when concepts such as conscious recollection are involved, animal work has significantly increased our understanding of the functions of the connected system of structures, damage to which causes some or all of the symptoms of the human amnesic syndrome.

Clark and Squire kick off the issue with a beautiful historical account of the search for an animal model of amnesia. Focusing on object recognition memory, these authors show how this animal model has been critical to the development of what might be regarded as the standard, multiple memory systems view of amnesia, according to which structures within the medial temporal lobe such as the hippocampus and perirhinal cortex contribute in a cooperative manner to object recognition, and indeed all forms of declarative long-term memory. A second major tenet of this view is that these structures do not have a role in nondeclarative, implicit long-term memory, which is thought to be mediated by structures outside of the medial temporal lobe such as the striatum.

Our second article by Turchi and colleagues fits squarely into this multiple memory systems framework, although these authors prefer the terms "cognitive memory" versus "habit" to refer to the different putative memory systems. Following a brief historical introduction which grounds the topic in animal learning theory, the authors introduce a new study in which the two systems are targeted pharmacologically, using scopolamine and haloperidol, thought more or less selectively to target the cognitive and habit systems, respectively. Their results suggest that in certain tasks, the cognitive and habit systems are capable of working in concert. They also suggest an anatomical basis for the convergence of these two putative systems.

Like Clark and Squire, Winters and colleagues focus on object recognition as an animal model of amnesia. While this article agrees wholeheartedly with Clark and Squire's assertion that object recognition is an exceedingly useful paradigm with which to study memory, it also outlines some fundamental disagreements. Most notably, Winters *et al.* argue that elements of the putative medial temporal lobe memory system are dissociable and not all are critical for object recognition *per se*. However, regions within the medial temporal may interact in the service of complex memories that require integration of different types of information, a theme also taken up by several other articles in this issue. This paper also explores the utility of the object recognition paradigm for studying the *stages* of object recognition memory: encoding, storage/consolidation, and retrieval.

The themes of dissociability and interactivity of brain regions implicated in memory are taken further by Warburton and Brown, who consider not only object recognition memory, but also memory for the occurrence of a particular object in a particular place, and memory for when a particular object was experienced. These considerations lead these authors to consider not just medial temporal lobe structures such as perirhinal cortex and hippocampus, but the medial prefrontal cortex as well. The authors conceive of these three regions as forming an integrated network underlying various forms of recognition memory.

These aspects of the memory of a given experience—object, place, and time, or what has been referred to as "what, where, and when"—have been claimed by some to be three essential components of episodic memory, a type of memory that is clearly affected in amnesia. As this type of memory has usually been linked to explicit, conscious recollection, demonstration of true episodic memory in animals that do not have language to express their subjective experience has been difficult. However, in recent years various models of "episodic-like" memory in animals that capture object, place and temporal components have been developed, and studies have shown that birds, mice and rats have a capacity for episodic-like memory. Eacott and Easton provide a review of these studies and a theoretical discussion of the thorny issues surrounding modelling episodic memory in animals, and argue that the "what, where, when" definition of episodic memory may be too

0028-3932/$ – see front matter
doi:10.1016/j.neuropsychologia.2010.06.015

restrictive. Instead, they suggest a broader "what, where, which" definition in which episodic memory does not necessarily need to incorporate explicitly temporal information, but that it must contain information that helps the animal to identify a specific occasion.

Eichenbaum and colleagues take the development of an animal model of episodic memory in a different direction, and focus on the widely held view that recognition memory can be supported by two processes: episodic recollection of an event and a sense of familiarity for previously experienced stimuli. In the human literature, these two processes have been characterized using Receiver Operating Characteristics (ROCs), and different ROC functions have been demonstrated depending on the relative contribution of recollection and familiarity to the experimental condition. In their paper, Eichenbaum and colleagues review the development of a model that enables the use of ROCs in rodents, and argue that there is strong evidence for the existence of separable recollection and familiarity processes in recognition memory. They go on to discuss their studies using this procedure that support the idea that the hippocampus is particularly important for the recollection component whereas cortical regions of the medial temporal lobe are critical for the familiarity component of episodic memory.

Kesner and Goodrich-Hunsacker, too, focus on the hippocampus. Their contribution is unique in that the authors spend considerable time dealing with the putative pattern separation function—the ability to encode events separately—of the hippocampus, a function which has lately gained much attention. Also discussed is the role of the hippocampus in a number of different forms of spatial and temporal learning and memory, and the roles of each of the CA1, CA3 and DG subfields of the hippocampus in these functions.

Sanderson and colleagues continue the focus on the hippocampus; however these authors are interested in the lower level mechanisms of spatial memory, and accordingly have studied genetically modified animals to understand functions of glutamate receptor subunits. This work makes contact with previous articles in this issue not only in terms of hippocampal function, but also in terms of a multiple memory systems approach. Whereas other authors have focused on declarative versus nondeclarative dichotomy, or cognitive versus habit memory, these authors' work reveals dissociations between "working" versus "reference" spatial memory. These findings are interpreted in the context of Wagner's dual-process model of memory.

The next two articles focus on structures that have been associated with amnesia, but which have been discussed far less often than medial temporal structures such as the hippocampus. These are the mammilary bodies, discussed by Vann, and the retrosplenial cortex, covered by Aggleton. In the first of these articles, Vann argues forcefully for the need to reconsider the role of the mammilary bodies in amnesia, marshalling evidence from human and animal work, including anatomical, lesion and electrophysiological studies. Vann considers the mammilary bodies as part of a wider circuit underlying memory.

In similar fashion, Aggleton carries the torch for the retrosplenial cortex. Once neglected and now rediscovered in part due to the hypometabolism of this structure in Alzheimer's Disease, animal work shows clearly that the retroplenial cortex is important for memory—although it does not, it seems, have much involvement in the object recognition tasks shown in the first several articles of this issue to depend on structures within the medial temporal lobe. Aggleton argues the case for the role of retrosplenial cortex in memory, and presents possible models for understanding the specific contribution of this area to memory. He also discusses the evidence for functional dissociations between subregions of retrosplenial cortex, and the interesting point that this region seems to be sensitive to damage in distal sites, which may have significant implications for our understanding of both diencephalic and temporal lobe amnesias, as well as Alzheimer's Disease.

Winocur, Moscovitch and Bontempi then turn to the issue of systems-level consolidation, the popular idea that memory is initially hippocampus-dependent but over time undergoes a consolidation process by which it is transferred to a distributed neocortical network independent of the hippocampus. In this paper, the authors analyze the theory behind this idea, and provide evidence that is incompatible with several central assumptions of the theory. They then go on to propose an alternative view, which assumes that memory is transformed and changed over time. On this view, which is based on multiple trace theory, initial episodic memories are context-bound and remain dependent on the hippocampus for some time. Over time, however, this hippocampal memory supports the development of a neocortical memory, which may differ from the hippocampal memory in several respects. At retrieval, there is interaction between both types of memory that is dependent on the particular conditions at the time.

Sutherland, Sparks and Lehmann focus more specifically on one of the phenomena associated with systems-level consolidation, the pattern of temporally-graded retrograde amnesia. They provide a comprehensive review of the animal studies investigating this phenomenon, assessing factors that have varied across experiments such as extent of hippocampal damage, temporary inactivation, type of memory task and variables in initial learning. Their conclusion is that the bulk of the rodent evidence is not in favour of a lengthy period of hippocampally-dependent systems-level consolidation, and they offer a rather different dual-store hypothesis to explain the cases of spared remote memory in hippocampal retrograde amnesia—the Distributed Reinstatement Theory—which suggests that, whereas usually the hippocampus will overshadow memory acquisition by other systems, these cases involve initial learning parameters that favour acquisition by non-hippocampal networks.

In our contribution to this issue, we review a representational-hierarchical model of cortical function that we and others have been developing over the past 10 years or so. We argue that because the mapping of psychological constructs such as memory or perception onto specific regions of the brain is inherently difficult, and may well be impossible, a better strategy may be to try to understand the brain as a hierarchically organized continuum of representations, each of which is useful for a variety of cognitive functions. This theory has been grounded in animal studies, and we review these data first, followed by examples of how the tasks have translated to humans. We then show how impairments in object recognition memory can be understood within the representational-hierarchical framework, and how this can be used to make novel predictions related to classic issues in amnesia research, namely whether amnesia is due to a deficit of encoding, storage or retrieval, and the related issue of the role of interference in amnesia.

In our final article, Murray and Wise provide some serious food for thought. In sharp contrast to other articles in this issue, Murray and Wise question the utility of "short-term" memory tests such as object recognition as a model of the kind of memory impairment seen in amnesia. The corollary to this is that structures known to mediate this form of memory should be excluded from neurobiological models of amnesia; instead the focus should be on the hippocampus and the type of conscious long-term memory thought to be mediated by this structure. The authors provide suggestions as to the way forward for developing a more valid model of amnesia in nonhuman primates, and suggest that an important focus of future research should be the interactions between the prefrontal cortex and the medial temporal lobe. In the final section of this highly original piece, the authors tackle the thorny issue of consciousness—a suitably lofty note on which to conclude.

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