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Amnesia and neglect: beyond the Delay–Brion system and the Hebb synapse

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SUMMARY

Hippocampal damage in people causes impairments of episodic memory, but in rats it causes impairments of spatial learning. Experiments in macaque monkeys show that these two kinds of impairment are functionally similar to each other. After any lesion that interrupts the Delay–Brion system (hippocampus, fornix, mamillary bodies and anterior thalamus) monkeys are impaired in scene-specific memory, where an event takes place against a background that is specific to that event. Scene-specific memory in the monkey corresponds to human episodic memory, which is the memory of a unique event set in a particular scene, as opposed to scene-independent human knowledge, which is abstracted from many different scenes. However, interruption of the Delay–Brion system is not sufficient to explain all of the memory impairments that are seen in amnesic patients. To explain amnesia the specialized function of the hippocampus in scene memory needs to be considered alongside the other, qualitatively different functional specializations of other memory systems of the temporal lobe, including the perirhinal cortex and the amygdala. In all these specialized areas, however, including the hippocampus, there is no fundamental distinction between memory systems and perceptual systems. In explaining memory disorders in amnesia it is also important to consider them alongside the memory disorders of neglect patients. Neglect patients fail to represent in memory the side of the world that is contralateral to the current fixation point, in both short- and long-term memory retrieval. Neglect was produced experimentally by unilateral visual disconnection in the monkey, confirming the idea that visual memory retrieval is retinotopically organized; patients with unilateral medial temporal-lobe removals showed lateralized memory impairments for half-scenes in the visual hemifield contralateral to the removal. Thus, in scene-memory retrieval the Delay–Brion system contributes to the retrieval of visual memories into the retinotopically organized visual cortex. This scene memory interpretation of hippocampal function needs to be contrasted with the cognitive-map hypothesis. The cognitive-map model of hippocampal function shares some common assumptions with the Hebb-synapse model of association formation, and the Hebb-synapse model can be rejected on the basis of recent evidence that monkeys can form direct associations in memory between temporally discontiguous events. Our general conclusion is that the primate brain encompasses widespread and powerful memory mechanisms which will continue to be poorly understood if theory and experimentation continue to concentrate too much, as they have in the past, on the hippocampus and the Hebb synapse.

1. INTRODUCTION

This volume offers a rare opportunity to consider the hippocampus, and its role in the explanation of memory and amnesia, in a broad context including other brain structures and other clinical disorders, as the abstract above indicates. To cover these topics in a short space does not allow full consideration of all the relevant evidence. Instead, a short review of the most important points in each topic is given.

2. DOES HIPPOCAMPAL DAMAGE IN HUMANS CAUSE AMNESIA?

It is now widely accepted that human amnesia after surgical removal of the medial temporal lobe (Scoville & Milner 1957) cannot be ascribed to the hippocampus alone, because many other structures involved in these removals, such as the amygdala and the perirhinal cortex, have important functions of their own in memory. There is less complete consensus, however, about the assessment of two other sources of clinical evidence: amnesia after ischaemic–anoxic hippocampal damage, and after surgical damage to the fornix.

Delay & Brion (1969) published sections of the brain of a patient who had developed severe amnesia postcomitially. The only area of cell death was in the CA1 field of the hippocampus bilaterally. Similar selective damage was seen by Zola-Morgan *et al.* (1986) in a patient who developed mild amnesia after an anoxic incident. Warrington & Duchen (1992) reported a patient who developed severe amnesia after the

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unilateral surgical removal of one medial temporal lobe, a removal that did not cause amnesia in many other similar patients. Post-mortem histological analysis revealed discrete sclerosis in area CA1 in the temporal lobe contralateral to the surgical removal. These cases appear to show that bilateral damage to the CA1 field of the hippocampus can be sufficient to cause severe amnesia. However, the area of functional disorder after anoxic damage may be wider than the area of cell death. Bachevalier & Mishkin (1989) investigated the effects in monkeys of ischaemia experimentally induced by bilateral occlusion of the posterior cerebral artery. Some of the monkeys had cell death only in area CA1 of the hippocampus and had severe impairments in visual recognition memory, similar in severity to the same impairment in Warrington & Duchen's patient. However, the memory impairment in these monkeys was much more severe than that which was produced, in other monkeys, by surgical removal of the whole hippocampus bilaterally. The most likely explanation of these findings is that anoxia produces more widespread functional disorders than those that result in cell death, perhaps axonal damage for example. Therefore, the severe amnesia seen in the patients of Delay & Brion (1969) and Warrington & Duchen (1992) may result from undisclosed damage outside the hippocampus.

Damage or complete section of the fornix is a risk in the surgical removal of colloid cysts from the third ventricle inferior to the fornix, and patients with fornix lesions show memory disorder (for a review see Gaffan & Gaffan (1991)). Furthermore, the severity of memory disorder after colloid-cyst removal is correlated with the amount of destruction to the fornix, not with other variables such as the route of surgical approach (McMackin *et al*. 1995). These patients show impairments in some kinds of episodic memory, the memory for discrete personally experienced events. Their memory impairments are revealed in the standard clinical tests of delayed reproduction of the Rey figure and in delayed recall of a story (the 'logical memory' test in the Wechsler memory scale). Furthermore, their impairments in everyday life are clinically significant and require a sheltered lifestyle. Nevertheless, these patients do not suffer from amnesia in the full clinical sense of that term. For example, they score in the normal range on the Warrington Recognition Memory Test. It may be asked whether the relatively mild amnesia seen in these patients results from the fact that the hippocampus itself is intact although the fornix is damaged or destroyed. Evidence from animals gives no support to such a possibility, however. Discrete lesions of the hippocampus in monkeys produce a less severe effect than surgical transection of the fornix in the same animals (O'Boyle *et al*. 1993). Thus, the implication from the colloid-cyst patients is that the hippocampus–fornix system facilitates the normal performance of human episodic memory in some way, but is not essential for some other kinds of memory that are impaired in the clinical amnesic syndrome.

Amnesic patients frequently have lesions in the mamillary nuclei; the well-known hypothesis put forward by Delay & Brion (1969) was that amnesia is caused by any bilateral interruption of a connected system of structures including the hippocampus, fornix and mamillary nuclei. However, because the main pathway into the mamillary nuclei is the fornix, it is difficult to see how the effects of a lesion in the mamillary nuclei could be more severe than the effects of fornix transection. Evidence from monkeys (reviewed below) indicates that the effects of discrete lesions in the mamillary nuclei are similar to the effects of fornix transection. Thus, given that fornix transection in humans does not cause severe amnesia, it is difficult to believe that mamillary nuclei lesions alone are sufficient to do so. Furthermore, amnesic patients with neuronal death in the mamillary nuclei frequently or always have additional neuronal death elsewhere, and the inflammatory disease process in Wernicke–Korsakoff pathology may, like anoxia or ischaemia, produce dysfunction more widespread than that which reveals itself in cell death, particularly by interfering with axonal conduction (Victor *et al*. 1971, p. 157).

In conclusion, the effects of discrete hippocampal or mamillary damage in man are not known with any certainty. The effects of fornix transection are to impair episodic memory without producing a full amnesic syndrome.

3. SCENE MEMORY: A FUNCTIONAL CONNECTION BETWEEN HUMAN EPISODIC MEMORY AND ANIMAL SPATIAL MEMORY

It is widely accepted that discrete damage to the hippocampus or fornix in animals leads to impairments in spatial memory. What exactly is meant by 'spatial memory' is not so clear, however. The cognitive-map hypothesis of O'Keefe & Nadel (1978) is only one possible account of the cognitive abilities that underlie tests of spatial memory in animals. An alternative possibility has recently been developed from experiments with monkeys. This idea, beginning with Gaffan & Harrison (1989), is that monkeys have a snapshot-like memory, that is, a memory of the objects in a complex scene and their spatial relations to each other from the point of view of the witness. Tasks that require such a snapshot-like memory were impaired by fornix transection, while other tasks that required the monkeys to learn about places in the world objectively defined were not (Gaffan & Harrison 1989). Recently these experiments have been extended to investigate the relationship between snapshot spatial memory and episodic memory. O'Keefe & Nadel (1978, pp. 390 onwards) put forward the idea that human memory frequently relies on spatio-temporal context. However, human episodic memory frequently involves the reconstruction in memory of a the subjectively witnessed scene in which a discrete personally experienced event took place, rather than the objective place in the world. If you remember a conversation with a friend, what comes out of your memory, subjectively, is not simply the words but the whole event, the room in which the conversation took place

as viewed from the place where you were sitting. In this way episodic memory differs from general knowledge, because in general knowledge facts are retrieved that are not set in any specific scene. More technically, analysis of sources of interference in long-term memory suggests that retrieval of the background or scene in which some target event took place facilitates the accurate retrieval of the target event itself; importantly, this facilitation only occurs where different target events have taken place in different background scenes (Gaffan 1992, 1994*b*). Thus, the very poor performance of the patients with fornix damage in delayed story recall could represent an impairment in the subjectively familiar process of reconstructing the scene of a past conversation with a friend. Now the spatial learning impairments of animals with fornix damage are also seen in tasks where memory of a whole scene is potentially relevant. In spatial recognition memory, for example, in which rats and monkeys with fornix section have equivalent impairments (Murray *et al*. 1989; Markowska *et al*. 1989), memory of going left or going right on a previous trial can be facilitated by remembering spatial relations among any or all of a large number of objects in the scene of the trial. In object–reward association learning in the Wisconsin General Test Apparatus, by contrast, in which monkeys with fornix transection perform perfectly normally (Moss *et al*. 1981), all the objects are presented in a constant identical background scene; therefore, remembering whether an individual object was rewarded or not on a previous trial cannot be facilitated by remembering the scene in which that event took place. Thus, a common feature of the tasks in which fornix transection was known to produce an impairment (episodic memory in humans, and 'spatial' tasks in animals) was that memory of whole scenes, as opposed to memory of discrete objects independent of their setting, could facilitate their performance. This common feature suggested that the fornix might subserve a single common function, scene memory, both in animals and in humans.

To test this idea, scene memory was investigated in the monkey in a task that was not a spatial memory task (Gaffan 1994*b*). Artificially created foreground objects were presented on artificially created backgrounds. Each scene was unique, both in its foreground objects and in its background. The task for the monkeys was to learn which of the foreground objects in each scene produced reward. Fornix transection produced a severe impairment in this task. Note that the task is similar to human memory for a discrete event, involving some object situated in a particular place in a particular background. The importance of scene memory as opposed to memory for objects in themselves, independent of their setting, was demonstrated in a control experiment where the monkeys learned whether foreground objects were rewarded or not, but the backgrounds were not uniquely linked to individual objects. For example, object A might be consistently rewarded, but every time it was presented it was set in a new background that had never been seen before. Monkeys with fornix transection learned normally in this control object-only condition. The main task, the scene memory or object-in-background task, has subsequently been given to groups of monkeys with other experimental lesions. One main purpose of these studies was to test the validity of the Delay–Brion hypothesis as to the functional unity of the hippocampus–fornix–mamillary system. The predictions of this hypothesis were verified. Lesions of the mamillary nuclei or of the anterior thalamic nuclei (which receive the main output of the mamillary nuclei through the mamillothalamic tract, and form a subsequent stage of the Delay–Brion system) produced quantitatively similar impairments of scene memory quantitatively similar to that produced by fornix transection; furthermore, as the hypothesis of functional unity requires, the combination of two lesions within the system (fornix transection plus mamillary nuclei lesion) produced no more severe an impairment than that which was produced by either of these lesions alone (Parker & Gaffan 1997*a*,*b*). Thus, although the interpretation of amnesic pathology put forward by Delay & Brion (1969) needs to be substantially modified because discrete lesions in the Delay–Brion system do not produce severe amnesia (§2), nevertheless the functional unity that Delay & Brion suggested does apply to the specialized function of this system in scene memory.

4. MULTIPLE DISTINCT FUNCTIONAL SPECIALIZATIONS IN THE TEMPORAL LOBE

The unique role of the perirhinal cortex in object memory was first suggested by the electrophysiological findings of Brown *et al*. (1987) and the cooling studies of Horel *et al*. (1987), and it was first conclusively verified by the selective ablation experiments carried out by Meunier *et al*. (1990, 1993). Subsequently the behavioural effects of selective lesions of the perirhinal cortex or of the perirhinal plus entorhinal cortex ('rhinal cortex') was investigated in greater detail by Gaffan & Murray (1992), Murray *et al*. (1993), Eacott *et al*. (1994), Buckley *et al*. (1997) and Buckley & Gaffan (1997). To summarize these studies, it is clear that the perirhinal cortex is involved in memory for individual objects whether assessed by recognition memory for multiple objects, by configural learning or associative learning about objects, or by the ability to identify a familiar object in a new scene. Scene memory (§3) requires information about object identity to be put together with information about the spatial relations of the objects. As this account predicts, scene memory is severely impaired by disconnecting the fornix from the perirhinal cortex (Gaffan & Parker 1996). Nevertheless, the role of the perirhinal cortex can be differentiated quite clearly from the role of the fornix, as shown by double-dissociation experiments. In a simple spatial learning task involving only two identical objects, fornix transection produced a severe impairment but monkeys with perirhinal cortex ablations were normal; the relative severity of impairment of these two groups was reversed (double dissociation) in a visual recognition memory task

involving many different objects (Gaffan 1994*a*). Thus, the roles of the perirhinal cortex and the fornix can be distinguished from each other qualitatively, even though in many memory tasks (such as the scene memory task) both play a part. Therefore, it is wrong to think of different memory impairments, produced by different temporal-lobe lesions, as reflecting simply a quantitative gradation of severity of impairment in a single memory system, as suggested by Squire & Zola-Morgan (1991). Severe amnesia after medial temporal lesions in humans, for example in surgical cases (Scoville & Milner 1957), is best thought of as resulting from combined damage to at least three functionally different structures: the hippocampus, the perirhinal cortex and the amygdala. The effects of amygdala lesions on memory can be doubly dissociated from the effects both of perirhinal cortex lesions and of fornix transection (Gaffan 1994*a*).

Yet further specializations of function have been shown within the macaque temporal lobe. The effects of perirhinal cortical lesions on visual memory are quite clearly qualitatively different from the effects of lesions in the adjacent visual cortex of the middle temporal gyrus. Lesions of the middle temporal gyrus impaired colour discrimination much more than object memory, but perirhinal cortex lesions impaired object memory more than did middle temporal gyrus lesions while leaving colour discrimination quite unaffected (Buckley *et al*. 1997).

These specializations suggest a loosely hierarchical arrangement of function in the temporal lobe. Visual features of objects, such as colour, are analysed in the neocortex of the middle and inferior temporal gyri; this information about isolated features can then be put together, and combined with non-visual object qualities, in the perirhinal cortex to form coherent representations of individual objects. Information about individual objects can then be combined in the hippocampus with spatial information, derived from both visual and non-visual modalities, to represent a spatially organized scene of foreground and background objects. Since a witnessed 'scene' is represented perceptually by the total exteroceptive information available to the observer at any one moment, the hippocampus is necessarily at the top of this loose hierarchy. The specializations of function within all these cortical areas of the temporal lobe are derived hodologically, that is by the nature of the afferent information that each cortical area receives (Gaffan 1996), rather than from specialized types of processing as is suggested by the cognitive-map hypothesis of hippocampal function (O'Keefe & Nadel 1978) or by many other once popular hypotheses of hippocampal function. Further, consistent with this hodological account of functional localization, the plasticity of what we think of as perceptual cortical areas, in perceptual learning, is not fundamentally different from the plasticity of what we think of as memory areas (Gaffan 1996).

5. NEGLECT AND MEMORY

Retrieval of spatially organized memories is disordered in neglect patients (Bisiach *et al*. 1979; Meador *et al*. 1987). For example, when a neglect patient was asked to describe from memory the street in which his home was situated, one side or the other of the street was omitted from the description, depending on the direction in which the patient imagined himself to be facing (Meador *et al*. 1987). A deeper understanding of neglect, therefore, should add to our understanding of memory for spatially organized complex scenes. The evidence reviewed in §3 above indicates that the hippocampus–fornix system is involved in just this kind of memory retrieval, the reconstruction from memory of a familiar scene such as one's home street. Why should this process fail unilaterally in a neglect patient?

Hornak (1992, 1995) put forward a representational explanation of visual neglect. In this view, the disordered retrieval from long-term memory in neglect is only one sign of a much broader deficit: neglect patients 'have a poor internal representation of space to the left of their current direction of gaze' (Hornak 1995, p. 323). Eye-movement recordings showed that when neglect patients inspected incomplete drawings, such as their own attempt to copy a drawing of a butterfly, they consistently failed to fixate the missing parts of the drawings. Similarly, when inspecting complete drawings of symmetrical objects, they never fixated the left half. When inspecting asymmetrical objects that could not be identified from the right half alone, however, the patients did fixate the left half, showing that their neglect did not simply reflect an oculomotor impairment. These disorders could not be explained by perceptual disorders in the left visual field of neglect patients, because patients without neglect but with hemianopia accurately made saccades into parts of drawings that lay in their blind field at the beginning of the saccade.

The representational hypothesis of neglect implies that not only the perceptual analysis of current retinal input, but also the retrieval of visual memory, is organized in a retinotopic fashion. If so, then visual neglect should be produced by depriving one hemisphere of all visual input, so that visual memories can no longer be laid down or retrieved in that hemisphere. We (Gaffan & Hornak 1997) tested this prediction in the monkey by combining unilateral optic-tract section with forebrain commissurotomy (section of the corpus callosum and anterior commissure), thus disconnecting one hemisphere from both halves of the retinas. These animals showed neglect in a visual search task, whereas animals with hemianopia alone did not. Furthermore, monkeys with cortical ablations in the parietal lobe and frontal eye field did not show neglect, although monkeys with lesions in the white matter inferior to the intraparietal sulcus did.

These findings, both from patients and from monkeys, imply that memory retrieval is retinotopically organized. Cortical cells that show retinotopically organized responses lie, of course, in visual cortical areas that are usually thought of as being perceptual in function. However, it is an oversimplification to think that the function of the visual cortex is vision. Rather, we suggest that the function of

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the visual cortex is to maintain a representation of the visible world, based not only on analysis of the current retinal input but also on memory. The influence of the Delay–Brion system on retrieval of scene memory is mediated, according to this view, by widespread influences on cortical areas that are thought of as perceptual in function. Delay & Brion themselves suggested that the output of the anterior thalamus in their system was conveyed to the cingulate cortex, the final proposed step in their system; however, Parker & Gaffan (1997*a*) showed that cingulate-cortex lesions do not produce the predicted effect on scene memory, and reviewed evidence that the anterior thalamus projects to widespread cortical areas, not to the cingulate cortex alone.

6. HEMIAMNESIA

If visual memories are retrieved retinotopically, as the data from neglect indicate, then one should expect that each temporal lobe should be relatively more involved in memories that relate to the contralateral visual hemifield than in those that relate to the ipsilateral visual hemifield. Hornak *et al*. (1997) tested this prediction in patients who had received unilateral partial surgical removals of the medial temporal lobe, including the amygdala and hippocampus in most cases, for the relief of epilepsy. Recognition of tachistoscopically presented half-scenes was markedly superior in the hemifield ipsilateral to the temporal lobe removal, irrespective of the side of the removal.

These patients do not have any known perceptual impairments in the parts of the visual field that were used for the half-scene memory tests. Nevertheless, one is tempted to ask whether hemiamnesia, i.e. the lateralized memory impairment shown by these patients, is secondary to some subtle, as yet undiscovered perceptual impairment. This question is less interesting than it seems, however. According to the interpretations put forward in §4, the functional specialization of memory systems derives from the afferent information that they receive, and both perceptual and memory systems show plasticity. Thus memory impairments may quite generally go along with some subtle perceptual impairments. Certainly, lesions in the rhinal cortex, which produce profound impairments in object memory, also produce some impairments in non-delayed matching judgments about objects (Eacott *et al*. 1994). It would not be surprising if future work were to reveal that a bilateral fornix lesion, for example, produces some subtle perceptual disorder in the processing of scene information (although, because different scenes can only be presented successively, not simultaneously, one can envisage that it might be logically very difficult to distinguish a perceptual from a memory disorder in the processing of scene information). If it turns out that patients with unilateral medial temporal-lobe removals have some subtle perceptual deficit in processing half-scenes contralateral to their removal—for which there is no evidence as yet—then presumably it would also be true that patients who are amnesic as a result of bilateral medial temporal damage would show the same subtle perceptual deficit bilaterally. The classification of a disorder as 'perceptual' or 'mnemonic' is not of fundamental importance.

7. THE HEBB SYNAPSE, THE COGNITIVE MAP AND TEMPORAL CONTIGUITY

The original, purely psychological specification of the cognitive-map hypothesis by Tolman (1932) dealt with maze learning in rats. The proposal was that, with experience of running through a maze, rats built up a map-like knowledge of the connected parts of the maze. Thus, a rat put in the start box of the maze could by a chain of association retrieve an 'expectancy of the specific character of the terminal parts of the maze' (Tolman 1932, p. 134). Behavioural evidence leaves no doubt that rats can retrieve such an expectancy (Gaffan & Gowling 1984) but it remains an open question whether this is the only mechanism or even the most important mechanism at work in maze learning by rats (the expectancy effects revealed in Gaffan & Gowling's experiment were statistically significant, but small). One of the alternative explanations to Tolman's is Hull's (1943) proposal that the animal's choices at all the choice-points in a maze, even those that are spatially distant from the goal box, can be directly associated with the primary reward that is ultimately discovered in the goal box. Hull's proposal requires that events can be directly associated with each other even when quite considerable temporal delays, of the order of tens of seconds, intervene between the two events to be associated. Tolman's proposal, on the other hand, allows spatially and temporally distant events to be associated with each other indirectly by a chain of mediating associations, each of which links parts of the maze that are perceived simultaneously or with millisecond delays.

There is thus an alliance between the cognitive-map explanation of maze learning and the Hebb-synapse model of associative learning (Hebb 1949, p. 62) according to which association formation takes place by the strengthening of a synaptic connection when action potentials are virtually simultaneous in the pre- and the postsynaptic cell. Long-term potentiation has been frequently proposed as a mechanism of associative learning that realizes the Hebb-synapse model (Brown *et al*. 1990) but behavioural pharmacological studies do not support the idea that long-term potentiation underlies associative learning (Saucier & Cain 1995; Gutnikov & Gaffan 1996; Hoelscher *et al*. 1997; but see Morris & Frey, this volume). It is therefore appropriate to reassess the evidence for the role of temporal contiguity in associative learning, because the assumed necessity of temporal contiguity underlies so much theory and experiment, not only in the hippocampus but more broadly in the almost universal acceptance of the Hebb-synapse model of associative learning.

There is no doubt that animals can learn not only spatial but also non-spatial tasks when there is, operationally speaking, a temporal delay between the animal's choice and the reward that is dependent on that choice (Wolfe 1934; Perin 1943), but an experiment by Grice (1948) has been widely accepted as showing

that delayed choice–reward associative learning can only proceed if it is mediated by two separate associations that are each between temporally contiguous events, that is, between the choice and a secondary reinforcer and between the secondary reinforcer and primary reward. Grice argued that when the mediation of secondary reinforcement was eliminated then associative learning showed a sharp gradient of temporal delay, such that a delay of 500 ms between choice and reward was enough to retard dramatically the rate of associative learning, by comparison with zero delay. In view of the importance of this issue to modern neurobiological investigations of the mechanism of associative learning based on the Hebb synapse model, Gutnikov *et al*. (1997; S. A. Gutnikov and D. Gaffan, unpublished results) decided to reinvestigate the temporal gradient of associative learning.

In the first experiment (Gutnikov *et al*. 1997) monkeys chose between two visual patterns on a screen by touching one. Immediately upon the animal's choice, both patterns disappeared. Then, either immediately (zero delay) or after a delay of 500 or 1000 ms, an audible food reward was delivered if the pattern chosen had been the correct one. The animals learned several sets of such associative learning 'problems' with ten new problems (pairs of new visual patterns) in each set. The learning curves were indistinguishable in the three delay conditions, all showing rapid learning.

Subsequently we investigated the effect of a filled delay, in which monkeys learned reward associations to a series of sequentially presented visual patterns. For example, an animal faced a choice between two patterns, say A and D. If A was chosen then immediately both A and D disappeared and A was replaced by B; 1250 ms later, B was replaced by C; after a further 1250 ms, by now 2.5 s after the animal's choice, C disappeared and food reward was delivered. Similarly, if D was chosen then A and D disappeared, D was replaced by E for 1250 ms, then E by F for 1250 ms, but, because D was the wrong choice, no food reward was delivered. Monkeys easily learned to choose the correct pattern (A in the example) in sets of ten problems of this kind. Furthermore, transfer tests showed that the animals learned about all three stimuli in each sequence; for example, having learned the sequence A–B–C reward they chose B or C if B or C was then presented as a choice stimulus.

In learning such sequences there are three different possible kinds of association to be formed. (i) The monkey could associate each visual pattern with the 'specific character' (in Tolman's sense, above) of the events that form each sequence. This is a cognitive-map explanation. The animal could look at A and retrieve the knowledge that A if chosen is followed by B, B by C, and C by reward. There is no doubt that monkeys can form visual–visual associations between successively presented patterns, albeit rather slowly (Murray *et al*. 1993), but the question at issue is whether they do so in the present task. (ii) The monkey could learn by associations involving conditioned reinforcement. According to this explanation, A is associated not with the 'specific character' of B, and so on; rather, the animal learns only that A is followed by a predictor (a tertiary reinforcer) of a predictor (a secondary reinforcer) of food. This is a Grice-like explanation. (iii) The animal could associate A directly with food, despite the temporal delay and the other intervening patterns. This is a Hull-like explanation. These three possibilities can be distinguished by including some problems that share a common path to the ultimate outcome (a procedure similar in principle to Grice's). For example, the monkey chooses between G and J, and a choice of G produces the sequence H–I–food whereas a choice of J produces (instead of K–L–no food, as in the standard procedure) the sequence H–I–no food. The common path H–I rules out both mechanisms (i) and (ii) in the list above, leaving only (iii). Monkeys learned the common-path problems G–H–I versus J–H–I just as easily as they did the standard problems A–B–C versus D–E–F. Thus, they showed direct visual–reward associative learning across a delay even when the delay was filled with other visual stimuli and those intervening stimuli were themselves attended to and learned about, as the transfer tests showed.

These findings appear to rule out a model of associative learning by simultaneous depolarizations. The pattern of action potentials in visual association cortex that encodes the perception of A must necessarily be replaced by a different pattern to encode the perceptions of B and then C. These patterns of action potentials cannot all be simultaneous with the pattern that represents the delivery of food reward. One might argue that at least some cells might still encode a 'shadow' of A even when C is perceived. However, visual objects have a distributed representation in the visual association cortex, and the discriminability of objects depends critically on the number of cells taking part in the representation (Rolls *et al*. 1997). In keeping with this concept, the effects of a partial ablation of visual association cortex on visual associative learning can be modelled by a reduction in the number of cells taking part in a distributed representation of the stimuli (Gaffan *et al*. 1986). Therefore, if the number of cells encoding the shadow is much smaller than the number of cells encoding the actual perception, then associative learning should be much slower with the shadows, which was not observed.

These experiments should be followed up to see whether similar direct associations between temporally noncontiguous events underlie maze learning by rats. At least in visual–reward associative learning in the primate brain, however, the code in which a predictive event enters into associative memory-trace formation (that is, the form in which the predictor is encoded at the time the event to be predicted occurs) cannot be action potentials. Rather, that code must consist of some long-lasting consequence of action potentials. To suggest what the code might be would be premature, but it is encouraging to note that electrophysiological studies have already begun to identify intracellular processes other than action potentials by which temporally discontiguous events can be integrated at the single-cell level (Batchelor & Garthwaite 1997).

8. GENERAL CONCLUSIONS

The hippocampus is important for scene memory and this is required for normal performance (both in monkeys and in people) in non-spatial episodic memory and in spatial memory tasks. However, damage to the hippocampus–fornix–mamillary system is not sufficient to explain the full range of deficits in the human amnesic syndrome. Even within the realm of scene memory, the hippocampus is only one of the structures involved in a retrieval process which, as the data from neglect and hemiamnesia show, involves posterior retinotopically organized cortical areas that have previously been thought to have a perceptual function only. Furthermore, associative learning between temporally non-contiguous events shows that the brain mechanism of associative learning allows far greater temporal integration than is provided for in the Hebb-synapse model of association formation, which has been widely accepted as the basis of learning within the hippocampus and elsewhere. In conclusion, therefore, the primate brain encompasses widespread and powerful memory mechanisms which will be poorly understood if theory and experimentation continue to concentrate too much, as they have in the past, on the hippocampus and the Hebb synapse.

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PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES