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Against memory systems

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The medial temporal lobe is indispensable for normal memory processing in both human and non-human primates, as is shown by the fact that large lesions in it produce a severe impairment in the acquisition of new memories. The widely accepted inference from this observation is that the medial temporal cortex, including the hippocampal, entorhinal and perirhinal cortex, contains a memory system or multiple memory systems, which are specialized for the acquisition and storage of memories. Nevertheless, there are some strong arguments against this idea: medial temporal lesions produce amnesia by disconnecting the entire temporal cortex from neuromodulatory afferents arising in the brainstem and basal forebrain, not by removing cortex; the temporal cortex is essential for perception as well as for memory; and response properties of temporal cortical neurons make it impossible that some kinds of memory trace could be stored in the temporal lobe. All cortex is plastic, and it is possible that the same rules of plasticity apply to all cortical areas; therefore, memory traces are stored in widespread cortical areas rather than in a specialized memory system restricted to the temporal lobe. Among these areas, the prefrontal cortex has an important role in learning and memory, but is best understood as an area with no specialization of function.

Keywords: cortical specialization; prefrontal cortex; learning; plasticity

1. INTRODUCTION

Large medial temporal lesions in the human brain produce an amnesic syndrome in which the acquisition of new memories is impaired in a devastating fashion (Scoville & Milner 1957; Corkin *et al.* 1997). Equally, medial temporal lesions in macaque monkeys (rhesus monkeys, *Macaca mulatta*, and cynomolgus monkeys, *Macaca fascicularis*) produce severe impairments in many memory tasks (Mishkin 1982; Gaffan *et al.* 2001). The inference has frequently been drawn that the cortex of the primate medial temporal lobe, including the hippocampal cortex and the rhinal cortex, can be characterized as a memory system (Mishkin 1982; Squire & Zola-Morgan 1991). A modification of this view is that the temporal lobe contains multiple memory systems, since smaller lesions within the temporal lobe produce dissociable impairments in different memory tasks (Gaffan 1994*a*). This idea, of multiple memory systems within the temporal lobe, is now widely accepted (Aggleton & Brown 1999; Kim & Baxter 2001).

Objections to the inference of a memory system or systems in the brain, from the existence of the amnesic syndrome, have been expressed forcefully, but only rarely (Horel 1978; Vanderwolf & Cain 1994). The arguments against that inference are now more powerful than ever. My purpose in reviewing them here is not just to point out the weaknesses in the hypothesis of memory systems. I also explore ideas about memory processing and cortical plasticity, and ideas about cortical localization of function, that might replace the idea that some cortical areas are functionally specialized as memory systems.

Section 2 presents evidence that the functions of temporal cortical areas are not just in memory, but also in perception and in the control of locomotion. Section 3 summarizes recent findings which show that dense amnesia after medial temporal lobe lesions is not due to the removal of specific cortical areas, but to the widespread disruption of temporal cortical function that is produced by disconnection of temporal cortex from the projections ascending to it from the basal forebrain and midbrain. Section 4 shows from the properties of normal human memory that the nature of some memories makes it impossible that they could be acquired in the temporal lobe, in the light of what is known about the response properties of temporal lobe neurons. In § 5 I argue that the plasticity of frontal cortex makes this cortex a plausible site for memory storage; however, all cortex is plastic. In § 6 I propose that cortical localization of function is not arbitrary, but hierarchical, and in § 7 I propose that the prefrontal cortex is not just the apex of a hierarchy of specialized cortical areas, but also the level at which the principle of hierarchically organized localized specialization of function is discarded. Section 8 discusses the rules of cortical and subcortical plasticity: the simplest hypothesis of a rule for cortical plasticity, consistent with the observations discussed here, is that the activity of cortical neurons comes to perform whatever function maximizes the probability of cortical arousal subsequent to that activity. In the concluding § 9, I argue that the concept of memory systems is harmful.

One contribution of 14 to a Discussion Meeting Issue 'The physiology of cognitive processes'.

2. THE FUNCTIONS OF TEMPORAL CORTICAL AREAS ARE NOT JUST IN MEMORY

Two of the most prominent temporal cortical areas that have been assigned a memory function are the hippocampal and perirhinal cortices. In rodents the memory function of the hippocampus is specifically in spatial memory, and this role in memory function can be seen as just a part of a hippocampal specialization for processing certain kinds of spatial information and for controlling locomotion (Horel 1978; Whishaw & Maaswinkel 1998). In addition, in macaques hippocampal lesions lead to severe impairments in spatial tasks (Murray *et al.* 1998), as do lesions of the main output pathway of the hippocampus, the fornix (Gaffan & Harrison 1989*b*). However, in this species, and also in humans, the picture is complicated by the fact that some of the impairments following lesions either to the hippocampus or to the fornix are in tasks which are not overtly spatial, such as scene learning and story recall. These, however, can be attributed to the important part played by spatial information in contextual retrieval (Gaffan 1992, 1994*c*). Moreover, discrete hippocampal lesions in monkeys can leave many powerful forms of non-spatial memory intact (Murray *et al.* 1993; Murray & Mishkin 1998), or only very mildly impaired (Baxter & Murray 2001*a*,*b*; Zola & Squire 2002), and discrete fornix lesions do not reliably impair some demanding memory tasks, either in humans (Aggleton *et al.* 2000) or in monkeys (Gaffan *et al.* 1984). Further complications arise from the uncertain specificity of hippocampal lesions in humans (Gaffan & Hornak 1997) and in monkeys (Baxter & Murray 2001*a*,*b*; Zola & Squire 2002). The controversial history of hippocampal involvement in memory function has recently been reviewed in detail elsewhere (Gaffan 2001). In brief, many non-spatial aspects of memory function are substantially independent of the hippocampus and fornix, and the main role of the hippocampus in primates as well as in rodents is in spatial information processing rather than in memory *per se*.

It should be noted, however, that denial of the status of memory system to the hippocampus does not depend specifically on accepting its spatial role. The data clearly show that hippocampal or fornix lesions do not lead to global severe memory impairments; if, in addition, they do lead to impairments in some specific kind of information processing, then the function of the hippocampus is less appropriately described as memory than as processing that specific kind of information, whether or not it happens to be spatial information (Ridley & Baker 1991; Brasted *et al.* 2002).

For the perirhinal cortex a similar argument leads to the conclusion that this area cannot be characterized as having only a memory function. Experiments on object-recognition memory in monkeys, in the tasks of delayed matching or non-matching to sample, appeared to indicate a role in memory function for the perirhinal cortex, either alone or in combination with the entorhinal cortex (Meunier *et al.* 1993; Eacott *et al.* 1994). In these experiments the monkeys with the cortical ablations appeared to simply forget the sample object faster than the controls: they performed the task at almost normal levels when there was a short retention interval between the sample presentation and the test trial, but their impairment became more severe as the retention interval lengthened. However, an alternative interpretation of this result is possible. A series of subsequent experiments has shown visual perceptual impairments in monkeys with lesions limited to the perirhinal cortex (Buckley *et al.* 1997, 2001; Buckley & Gaffan 1997, 1998*a–c*).

One aspect of these perceptual impairments that is particularly important is that they interact with task difficulty. For example, Buckley *et al.* (2001) investigated effects of perirhinal cortex lesions in an oddity judgement task. The monkeys were shown an array of six objects on each trial, and were required to choose the odd object in each array. The five non-odd objects were five different views of a single object, but the odd object was a different object; the objects which played the role of odd and non-odd objects in each array changed randomly from trial to trial, ensuring that the monkeys had to proceed by oddity judgements rather than by learning about individual objects as predictors of reward. However, some objects are quite easy to recognize as the same object in different views, while other objects appear very different in different views. It was thus possible to classify the different objects used in the experiment, on the basis of the monkeys' preoperative performance in the oddity task, into six levels of difficulty. The impairment produced by perirhinal cortex ablations in this task was not noticeable with the objects that were easy to recognize, but increased markedly as the level of difficulty increased.

Formally this interaction of the lesion effect with task difficulty is similar to the results from object-recognition memory (Meunier *et al.* 1993; Eacott *et al.* 1994). In both cases, the impairment increases as the difficulty of the task increases. Forgetting, as the retention interval increases, is just one way of increasing task difficulty. But the oddity impairment is not a memory impairment, as the task requires no memory from trial to trial except memory for the oddity principle, and the results from the easy levels of task difficulty showed that the monkeys with rhinal cortex lesions had not forgotten the principle of oddity judgement. Thus, the simplest summary of these results is that rhinal or perirhinal cortex lesions impair a monkey's ability to identify individual objects. The impairment emerges most clearly when this ability is taxed, either by requiring object-recognition memory function across an interval, in delayed matching to sample, or by making object identity difficult to judge perceptually, in oddity judgements with different views of the same object.

3. DENSE AMNESIA AFTER MEDIAL TEMPORAL LOBE LESIONS IS NOT DUE TO THE REMOVAL OF SPECIFIC CORTICAL AREAS, BUT TO THE WIDESPREAD DISRUPTION OF TEMPORAL CORTICAL FUNCTION BY SUBCORTICAL DISCONNECTION

Since the early unsuccessful attempts by Orbach *et al.* (1960) and by Correll & Scoville (1965) to replicate in the monkey the severe and global amnesia seen in the patient H.M. (Scoville & Milner 1957), it has repeatedly been shown that temporal cortical ablations in monkeys do not produce dense global amnesia. Although medial temporal ablations that are intended to remove the hippocampus and amygdala bilaterally do produce in the

monkey severe impairment in object-recognition memory (Mishkin 1982), these lesions leave memory function in reward-association tasks unimpaired (Malamut *et al.* 1984) or only very mildly impaired (Correll & Scoville 1965: see also Gaffan & Lim 1991). This pattern of results is quite different from what is seen in human amnesia, because reward-association memory is severely impaired in human amnesia (Oscar-Berman & Zola-Morgan 1980; Hood *et al.* 1999). Although the emphasis in recent years has switched to the entorhinal and perirhinal cortex for an explanation of the impairments produced by these lesions in the early experiments with monkeys, the same problem arises: ablations of these rhinal cortical areas in the monkey similarly leave reward-association memory unimpaired (Gaffan & Murray 1992) or impaired only in special circumstances (Buckley & Gaffan 1997). A frequently proposed solution to this problem, to the effect that reward-association memory is truly memory in the human brain but not truly memory in the monkey brain (Mishkin & Petri 1984; Fernandez-Ruiz *et al.* 2001), is merely circular reasoning (Horel 1978; Gaffan 2001). Of course, if a bilateral temporal cortical ablation in the monkey is made extensive enough to include the cortex in the lateral temporal lobe, lateral to the perirhinal and parahippocampal cortex, then a more severe impairment in visual reward-association tasks appears; but in this case the perceptual effects are even more severe than those of perirhinal cortex lesions, and the effect as a whole is more appropriately described as being perceptual rather than a memory impairment (Heywood *et al.* 1995).

We have recently found, however, that a much more global and severe memory impairment can be produced in the monkey by surgically interrupting the axons in the white matter of the medial temporal lobe, rather than removing the medial temporal cortex. These axons include projections that rise from the basal forebrain and midbrain to innervate widespread areas of lateral as well as medial temporal cortex. The ascending axons reach the temporal cortex through three routes (Selden *et al.* 1998): in the fornix–fimbria; in fibres of passage through the amygdala; and in the anterior temporal stem (the white matter surrounding the amygdala dorsally and laterally). All three of these routes are interrupted by surgical excisions in patient H.M. (for the anterior temporal stem damage, see panels H–J of fig. 2 in the report by Corkin *et al.* (1997)). When all three routes (but not any subset of only two routes) are interrupted in the monkey, a severe memory impairment results (Gaffan *et al.* 2001; Maclean *et al.* 2001) and this includes not only impairment in object-recognition memory but also, crucially, impairment in reward-association memory, that was absent from the earlier attempts to replicate in the monkey the global amnesia seen in the patient H.M.

The effect of these disconnections in macaque monkeys is shown in figure 1*a*, TS + AM + FX. The plot shows the percentage of errors on successive trials in a reward-association task that tests a very powerful form of memory in the monkey, which we have called object-in-place memory, and which is similar in some respects to human memory for events (Gaffan 1994*c*). Notice that the effect of the three-part interruption (TS + AM + FX) is devastating, producing performance almost at chance even at levels of task difficulty which allowed almost perfect performance

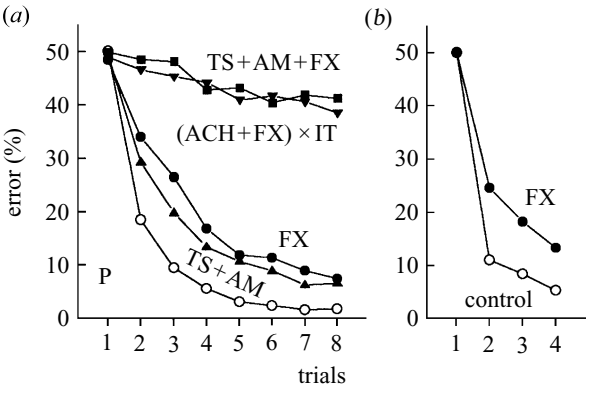

Figure 1. Data redrawn from experiments by Aggleton *et al.* (2000); Easton *et al.* (2002) and Gaffan *et al.* (2001). Both panels show learning in lists of 'object-in-place' scenes. (*a*) Results from macaque monkeys pre-operatively (pre, white circles) and following bilateral lesions to the anterior temporal stem and amygdala (TS + AM, black triangles), fornix (FX, black circles), and the combination of those three lesions (TS + AM + FX, black squares); also following the combination of a unilateral inferior temporal cortical ablation in one hemisphere with a unilateral fornix transection and cholinergic lesion in the other hemisphere ((ACH + FX) × IT, black inverted triangles). (*b*) Results from humans performing the same task after removal of colloid cysts from the third ventricle, divided into patients with bilateral fornix section (FX, black circles) and patients with fornix intact (control, white circles).

pre-operatively. Notice also that fornix transection alone in this task (FX in figure 1) produces a relatively mild impairment, just as it does in the human brain (Aggleton *et al.* 2000; figure 1*b*) and that the effect of the three-part disconnection is much more severe than that. Furthermore, the monkeys with this disconnection were able to retrieve at least some information that had been acquired pre-operatively (Gaffan *et al.* 2001). In all these three respects, the impairment produced by the three-part disconnection in the monkey resembles human dense amnesia. The effect can be attributed to axonal interruption rather than to the small amount of cortical damage that was produced by the section of anterior temporal stem and amygdala, because the powerful effect emerged only when fornix transection, which was carried out without any cortical damage at all, was added to the other two transections (TS + AM).

The same functional effect can be produced when the same structures are disconnected by a very different surgical manipulation in the monkey, namely disconnection by crossed unilateral lesions. In these experiments the inferior temporal cortex, through which visual information arrives in the temporal lobe, is ablated in only one hemisphere. In the other hemisphere either the cell bodies (Easton *et al.* 2002) or the axons (Easton & Gaffan 2000*b*, 2001; Easton *et al.* 2001) of the basal forebrain are ablated. Each of these unilateral lesions alone has little effect on memory, but when the two are present in opposite hemispheres the result is that the pathway from the basal forebrain to the temporal cortex is no longer available for visual information in either hemisphere, as the projections are almost exclusively ipsilateral. The effect of a unilateral subcortical lesion aimed at the cholinergic cells of the basal forebrain

and at the fornix in one hemisphere, and crossed with a unilateral inferior temporal cortex ablation in the other hemisphere (Easton *et al.* 2002), is also shown in figure 1*a*, (ACH + FX) × IT. The effect is indistinguishable from that of the combined transection of the pathways TS + AM + FX. The similar effects of these two very different surgical manipulations in the monkey, and the similarity of each of them to the effect of a yet different surgical procedure in the human brain (Corkin *et al.* 1997), support the idea that their common feature, namely the subcortical disconnection of temporal cortex, explains dense amnesia after temporal-lobe lesions, in both humans and monkeys.

A defining feature of human anterograde amnesia is that the acquisition of new memories is much more profoundly impaired than other, apparently equally demanding, tasks that demand the exercise of skills learned before the onset of amnesia, such as vocabulary knowledge and intelligence tests (Lezak 1983). Similar observations can be made in monkeys with experimentally induced temporal-lobe amnesia; these animals do not forget the general rules of the experimental tasks that they learned pre-operatively, such as how to operate the touchscreen, and they can remember many object–reward associations that they learned pre-operatively (Easton & Gaffan 2000*b*; Gaffan *et al.* 2001). This leads to the question of why the disconnection of the ascending pathway from the basal forebrain and midbrain to the temporal cortex has this marked impact on the acquisition of new memories. One possible answer is that some or all of the ascending influences are specifically required for the process of cortical plasticity, and are not as important for cortical information processing that does not require plasticity, such as the retrieval of old memories or the exercise of skills that were acquired pre-operatively. Another possible answer is simply that the acquisition of new memories is fundamentally a more fragile process than these other processes, as purely behavioural interventions, such as the requirement to perform a distracting concurrent task, affect acquisition more than retrieval (Naveh-Benjamin *et al.* 1998). These two answers are not mutually exclusive, however, and it is not necessary to decide between them in order to accept that the loss of these ascending influences impairs the acquisition of new memories more than the retrieval of old memories.

This new hypothesis of the origin of dense amnesia after temporal-lobe lesions has important implications for understanding human amnesia, particularly for the relationship between amnesia after discrete temporal-lobe lesions, amnesia in early stages of Alzheimer's disease, and amnesia in multi-infarct dementia (Mesulam 1995). However, my present focus is on its implications for localized memory systems. If temporal-lobe amnesia is ascribed to the interruption of ascending axons from the basal forebrain and midbrain, it is quite implausible to think that those axons constitute a memory system. A memory system must receive and store complex information, but the ascending axons from the basal forebrain and midbrain convey an arousal signal rather than complex information (Semba 1991; Easton & Gaffan 2000*a*).

To summarize the argument so far, we have seen that the effects of lesions in the cortical temporal areas that are thought to be the constituents of a putative temporal-lobe memory system, namely the hippocampal and the rhinal cortices, reveal two features that are difficult to reconcile with the idea that they constitute a memory system. The first difficulty is that in the monkey selective lesions in these cortical areas do not produce memory impairments as severe as those that are seen in human temporal-lobe amnesia, which were the original impetus for the hypothesis of memory systems itself. The second difficulty is that the effects of these lesions show that the cortical areas should be characterized as processing a certain kind of information, spatial information or object-identity information, rather than as being specialized for memory; and, in the case of object-identity information, it can clearly be seen that the impairment of this processing ability, after perirhinal lesions, is manifest in perceptual tasks that do not require new memory formation. Further, it is not possible to save the memory-systems hypothesis by extending the putative cortical memory system beyond the hippocampal and rhinal cortices into the lateral temporal-lobe cortex, lateral to the perirhinal and parahippocampal cortices, because the perceptual effects of a lesion in this area are even more obvious and severe than the perceptual effects of perirhinal cortex lesions.

The rival hypothesis is that memory function and perception are not separately localized in specific cortical areas. In medial temporal-lobe amnesia a widespread disruption of temporal cortical function, including the lateral temporal cortex as well as the rhinal and hippocampal cortex, is produced by the disconnection of the temporal cortex from the basal forebrain and midbrain. This disconnection produces dense anterograde amnesia because the acquisition of new memories is more vulnerable to the effects of the disconnection than are the other processes that the same cortical areas are involved in, such as perception, locomotion and memory retrieval.

4. SOME MEMORIES CANNOT BE ACQUIRED IN THE TEMPORAL LOBE

A further difficulty for the hypothesis of temporal-lobe memory storage can be seen in some properties of normal memory. The problem arises from the fact that the representation of complex visual scenes in the temporal lobes is divided at the vertical meridian of the visual field between the two hemispheres. When a monkey sees a single object that is presented against a large blank background, many neurons in the temporal lobe in both hemispheres respond to the object and signal its identity, even when the object is confined to one visual hemifield (Chelazzi *et al.* 1998). However, a single object presented against a large blank background is not a natural condition of object vision and memory. In an only slightly more naturalistic condition, when two objects are presented, with one object in each visual hemifield, the responses of the temporal cortex neurons are quite different. Now, neurons in the temporal lobe of each hemisphere respond only to the object that is in the visual hemifield contralateral to the hemisphere; their activity is not significantly affected by the object in the ipsilateral hemifield, even when the monkey is attending only to the object in the ipsilateral hemifield (Chelazzi *et al.* 1998). This poses a problem for understanding the memory of objects that are presented in this fashion, that is, in scenes having at least

one object in each visual hemifield. Consider the case where an object, a constituent of a visual scene that contains other objects, is presented for learning in one visual hemifield but is subsequently presented for a recognition-memory test in the opposite hemifield. In the learning trial, neurons in only one temporal lobe respond to the object, and in the retention-test trial, neurons in only the other temporal lobe respond to the object. All proposals as to the neural basis of object memory assume that the memory of an object is stored as a modification in neurons that respond to the presentation of the object (Sakai & Miyashita 1991; Sakai *et al.* 1994; Bogasz *et al.* 2001), and indeed it is difficult to see how neurons that do not respond to the presentation of an object could either lay down or retrieve a memory of it. It thus follows, from the electrophysiological data, that in the case we are considering, where the target object in a scene is presented in opposite hemifields at learning and at the retention test, neurons in neither of the two temporal lobes have both the opportunity to lay down and also the opportunity to retrieve a memory of the target object. Therefore, if object memories are stored either exclusively or mainly as modifications of neurons within the temporal lobe, the memory of the object should either fail or suffer a substantial decrement in this case.

Hornak *et al.* (2002) performed an experiment to test this counter-intuitive prediction in normal human subjects. The subjects were asked to remember a set of objects that were always presented for learning in pairs with one object in each hemifield. At the subsequent retention test, each object that had been presented for learning was now presented again, together with a novel foil object in the opposite visual hemifield, and the subject indicated which of the two objects was the one that had been presented for learning. Between the acquisition presentation and the retention test, some of the objects changed their retinal position. The shift could be from one hemifield to the other ('horizontal shift') or a change of the same distance within a hemifield ('vertical shift'). Control objects were presented in the same retinal location at both acquisition and retention ('no change'). Further, these changes in retinal location, between the acquisition and the retention test, were produced in different ways in two different tasks: by keeping a single constant fixation point for the subject's eyes, and changing the position of the object on the display screen ('constant fixation') or by keeping the position of the object on the display screen the same, but changing the position of the subject's fixation point ('changing fixation'). The results with constant fixation confirmed the effect that one should expect if temporal-lobe neurons contribute to the storage of object memories: retention accuracy after horizontal shifts was less accurate (68.6% correct) than retention accuracy after vertical shifts (74.7% correct). The size of the effect, which was much less than a total failure of memory in the horizontal shift condition, suggests that temporal-lobe neurons store only part of the memory trace of the objects; nevertheless, the effect was highly reliable statistically, and to this extent confirms the prediction derived from the electrophysiological data. However, the results with changing fixation did not show that effect: retention accuracy after horizontal shifts was the same (73.1% correct) as after vertical shifts (71.0% correct). Though identical in terms of the retinal positions of objects in the various conditions, these two tasks are quite different from each other in the natural memory performances they resemble. In the task with constant fixation the subject repeatedly sees the same view of the apparatus from exactly the same fixation point, and memory in this task thus resembles the natural task of reconstructing in memory a complex scene in which one fixated only one object. The task with changing fixation requires the subject to fixate different positions in successive views, and memory in this task thus resembles the natural task of reconstructing in memory a complex scene that was inspected with successive saccades to different fixation points. The results from the task with changing fixation show that we do indeed possess the ability to store a memory of the scene that is not hemifield specific, a memory that cannot be stored in the temporal lobes.

These results imply that neuronal activity in the temporal lobe not only contributes to memory storage in the temporal lobe but also contributes to memory storage in extra-temporal cortical areas, in which a visual representation that is not hemifield specific must be stored. Thus, the severe visual memory impairment that is produced by medial temporal lesions is not to be explained by assuming that all visual memories are normally stored within the temporal lobe.

As originally pointed out by Horel (1978), a lesion in the white matter of the anterior medial temporal lobe, which can be either bilateral (Scoville & Milner 1957) or unilateral (Hornak *et al.* 1997), interrupts the uncinate fascicle, in which cortico-cortical axons transmit information between the temporal and prefrontal cortices. If the prefrontal cortex is an important site for the storage of extra-temporal memories, as § 5 suggests, then the interruption of this pathway could explain the impairment of extra-temporal as well as temporal memory storage in patients with these lesions.

5. FRONTAL AND OTHER CORTICAL PLASTICITY

Where could memories be stored outside the temporal lobe? One obvious candidate area is the prefrontal cortex. Ample evidence in non-human primates indicates that the prefrontal cortex is essential to normal memory function, not just in working memory but in a wide range of memory and learning functions (Gaffan & Harrison 1989*a*; Parker & Gaffan 1998*a*,*b*). Extensive but selective and bilaterally symmetrical prefrontal lesions, of the kind that are studied in these experiments with monkeys, are rarely if ever seen clinically. However, closely related evidence comes from bilaterally symmetrical lesions of one of the main thalamic nuclei related to the prefrontal cortex, MD. Lesions in MD produce memory impairment in both humans (Hodges & McCarthy 1993) and monkeys (Gaffan & Parker 2000), and it is likely that this results from disrupting the dense reciprocal connections between MD and the prefrontal cortex, rather than the very light projection that MD receives from the temporal lobe (Gaffan & Parker 2000). However, MD lesions in humans also produce impairments in a reasoning and fluency test that are also sensitive to frontal cortex damage (Hodges & McCarthy 1993), and in this respect the effects of MD lesions are different from temporal-lobe amnesia. Given this prefrontal involvement in the memory function, one

might expect that a syndrome resembling temporal-lobe amnesia would follow if the prefrontal cortex were deprived of the ascending influences that the prefrontal cortex, like the temporal cortex, receives from the basal forebrain and midbrain. In the monkey this disconnection can be produced by crossed unilateral lesions of the frontal cortex and the axons of the basal forebrain, and severe memory impairments are seen after this disconnection (Easton & Gaffan 2001; Easton *et al.* 2001). It is possible that basal forebrain axons ascending to the prefrontal cortex in the human brain pass through a bottleneck in the posterior ventromedial part of the frontal white matter, and that damage at this bottleneck is the explanation of the dense amnesia that can be produced by rupture of aneurysms of the anterior communicating artery in this region (Diamond *et al.* 1997).

There is ample evidence in monkeys to indicate that neurons in the prefrontal cortex adapt their activity in response to the demands of whatever task the animal is trained in (Duncan 2001). In the light of this evidence it may seem attractive to propose that this adaptive plasticity is the special defining feature of prefrontal cortex function. However, it is difficult to reconcile that proposal with the fact that other cortical areas adapt their activity in response to task demands in a similar way. This plasticity is seen not only in the temporal (Sakai & Miyashita 1991) and somatosensory cortex (Pascual Leone & Torres 1993) but even in the occipital cortex (Fiorentini *et al.* 1972; Schoups *et al.* 2001). For these reasons, frontal plasticity should not be thought of as being qualitatively different from other cortical plasticity. How, then, should the involvement of the prefrontal cortex in learning and memory be characterized? Many authors have commented on the difficulty of characterizing prefrontal cortex function in cognitive terms in any satisfactory manner (Wise *et al.* 1996; Duncan 2001; Gaffan 1994*b*). Temporal and frontal specialization of function, whether in memory or in any other cognitive domain, needs to considered within the broader context of the nature of the cortical localization of function, as discussed in § 6.

6. CORTICAL LOCALIZATION OF FUNCTION IS NOT ARBITRARY BUT HIERARCHICAL

The hypothesis we began from, namely that the function of the medial temporal cortex is memory, is an example of the products of a widespread style of hypothesis formation in cognitive neuroscience. In this style, the function of a cortical area can be anything that the theoretician's ingenuity can reconcile with a dataset. It can be an everyday mental function such as memory or emotion (Rolls 1999), or an invented function such as behavioural inhibition (Gray & McNaughton 2000), or an operationally defined process like recognition memory (Gaffan 1976). An alternative to this undisciplined theorization is the idea that cortical specialization of a function is hierarchically organized in a principled fashion.

The contrast between these two approaches can be illustrated in the prestriate visual cortex. Until recently, it was widely believed that the prestriate cortex contained a 'plethora of visual areas in each of which a relatively simple attribute of the visual image is analysed by the cells' (Cowey 1982, p. 7). According to this view, the attributes to which each area is devoted—colour, movement, depth, texture, and so on—can only be discovered empirically and separately, since the different areas function in parallel with each other. An alternative to this view has been developed by Lennie (1998). He proposes that, with the exception of movement information in optical flow analysis, information about these different attributes of a visual stimulus is kept together in all the visual areas—as seems to be required by the similar selectivities of neurons in the different areas to all of these attributes (fig. 4 in Lennie 1998). He explains the specialization of the different areas as serial stages in a hierarchical processing system. Each stage performs all the analysis that can be performed at that stage, given the information that is available in the input to that stage, and then passes the results on to higher stages for further processing.

The account of Lennie (1998) of visual function in the prestriate cortex is similar in many ways to an analysis of visual function in the temporal cortex that has been put forward by Murray & Bussey (1999) and Buckley & Gaffan (2000). This again relies on the idea of hierarchical processing. According to Murray & Bussey (1999) and Buckley & Gaffan (2000), simple object features such as colour are analysed in the modality-specific visual association cortex of the inferior temporal lobe lateral and posterior to the perirhinal cortex (area TE of von Bonin & Bailey (1947)); these features are then passed on to the perirhinal cortex, which analyses the conjunctions of object features, that is, the configuration of features that defines a unique object. Some of the evidence for this account, for example, is that colour-threshold tests and object-memory tests doubly dissociate the effects of lesions in area TE and in the perirhinal cortex (Buckley *et al.* 1997), and that colour-oddity judgements and simple-shape oddity judgements are not impaired by perirhinal lesions in the same way as oddity judgements based on object identity are, even when the colour- or shape-oddity judgements are made very difficult by choosing similar colours or shapes (Buckley *et al.* 2001). This hierarchical model of the perirhinal and inferior temporal cortex can be seen as an extension of the scheme of Lennie (1998) for the prestriate cortex. Similarly, the monkey's memory for objects presented in complex scenes depends on an interaction between the spatial information derived from the hippocampus and the object-identity information derived from the perirhinal cortex (Gaffan & Parker 1996), and this is again an extension of the hierarchical principle: object-in-place information in complex scenes must necessarily depend on prior extraction of information about places and object identities.

Another aspect of cortical localization brought out in the review of Lennie (1998) is the idea that cortical localization allows interactions between neurons within a specialized area to take place without needing long axons, which are expensive in terms of requiring space within the head. Thus, if evolution can 'know' in advance of an individual animal's experience that a group of neurons will need to interact with each other, it makes sense to put them into a specialized local area.

In these ways, the multiple double dissociations that ablation experiments have revealed in the temporal lobe, between the functions of area TE and the perirhinal cortex and the hippocampus-fornix (Gaffan 1994*a*; Buckley *et al.*

1997), should not be interpreted as evidence for a series of unrelated functional specializations, each of which has to be studied independently in its own right and with its own set of hypotheses and theories; rather, the functional specializations are derived from, and are fully explained by, the necessity of hierarchical organization, and of local grouping of neurons that need to interact with each other.

7. PREFRONTAL CORTICAL FUNCTION IN A HIERARCHICAL SCHEME

This hierarchical approach can be naturally extended to the prefrontal cortex, which appears to be the apex of the hierarchy, in the sense that this cortical area is the furthest removed from the periphery (Jones & Powell 1970). However, this is not all there is to say about the position of the prefrontal cortex within a scheme of hierarchically organized cortical areas.

One of the most surprising aspects of prefrontal function is the absence of clear functional subdivisions within such a large area of cortex. Cytoarchitectonic subdivision of areas within the prefrontal cortex is contentious; unlike the divisions of the frontal cortex outside the prefrontal cortex, where the divisions are clear and widely agreed, within the prefrontal cortex the cytoarchitectonic areas are unclear, and the areas delineated by different investigators bear almost no similarity to each other (Akert 1964). Due to the fact that these areas are not universally agreed anatomical entities such as the striate cortex or the hippocampus, one should not have a strong expectation based on simply cytoarchitectural grounds that they must really be functionally different from each other. Differences between the electrophysiological properties or the haemodynamic responses of different areas would suggest such functional subdivisions, and some such differences have been observed, but they are neither consistent from study to study nor strong (Duncan 2001).

The absolute proof of such functional subdivisions could come only from double dissociations between the effects of different lesions within the prefrontal cortex. In spite of many ablation experiments in the macaque monkey designed to look for such double dissociations, I know of only one possible success, that of Butter (1969). However, Butter himself in this paper did not interpret his data as being strong evidence for specialization within the prefrontal cortex but quite the reverse. His experiment, with three different cognitive tasks and six different lesions within the prefrontal cortex, tested for a total of 45 different possible double dissociations, one for each pair of tasks and pair of lesions; however, he discovered only one. In assessing double dissociations it is important to distinguish between the prefrontal cortex and other cortical areas that are in the frontal lobe but are not prefrontal, and are not removed from the periphery but close to inputs and outputs; these include motor areas such as the frontal eye fields, the premotor and supplementary motor cortex, and several cingulate motor areas, and also the anterior olfactory nucleus on the posterior-medial part of the orbital surface—which was one of the lesions in the only double dissociation of Butter (1969). Thus, studies in macaques reporting double dissociations within the frontal cortex, but not within the prefrontal cortex, are not relevant to the issue of specialization within prefrontal cortex function, however valuable in themselves they are (figs 11 and 12 in Petrides 1987). In the marmoset, however, the extent of the prefrontal, as opposed to the other frontal, cortex is not completely clear (Peden & von Bonin 1947; Garey 1994; Preuss 1995; Wallis *et al.* 2001). Finally, while the evidence for subdivided function is weak, the evidence for parallel function within macaque prefrontal cortex is strong. Parker & Gaffan (1998*b*) found that complete removal of the prefrontal cortex in the monkey produced a devastating impairment in even the simplest possible learning task, the acquisition of a single object–reward association, but that even the acquisition of multiple concurrent object–reward associations was not significantly impaired by removal of the ventral half of the prefrontal cortex. This result shows that the dorsal half of the prefrontal cortex is able to substitute fully for the ventral half in this task, even though objects and rewards are thought to be preferentially processed in the ventral half. In this way, it seems that the commonality of function between different parts of the prefrontal cortex is more important than minor differences between areas.

One response to this whole state of affairs is to hope that if only the cytoarchitectural divisions were drawn just right, and the lesions and experimental tasks were designed just right, then ablation experiments in macaque monkeys would reveal many double dissociations within the prefrontal cortex; this is the approach taken by Passingham (1993). I think it is more realistic to conclude that the apparent lack of strong heterogeneity of function within the very large area of prefrontal cortex is telling us something important about the function of this cortex. What it may indicate is that, after a certain level of processing has been achieved, the hierarchical system of localized function is no longer appropriate. The two advantages of this scheme that were identified in § 6 were that: information can be analysed in a certain hierarchical order that can be predicted in advance; and interactions within a subset of neurons that can be predicted in advance to require such interactions can take place locally without requiring long axons. However, some types of information analysis that an individual may benefit from are not predictable in advance. To support unpredictable processing demands it is necessary to abandon local grouping after a certain stage and allow neurons to interact at random. It is unsurprising in this context that it is the animals of highly intelligent and adaptable species—humans, apes and Old World monkeys—that alone possess a large area of prefrontal cortex (Preuss 1995). Certainly this would also explain why conditional discrimination tasks, in which animals learn quite arbitrary rules, are so sensitive to the effects of prefrontal cortex lesions in macaques. According to this view the prefrontal cortex is not just the apex of a hierarchy of specialized cortical areas, but also the level at which the principle of hierarchically organized localized specialization of function is discarded. This explains why the prefrontal cortex occupies such a large area without strongly differentiated functional subdivisions.

8. RULES OF CORTICAL AND SUBCORTICAL PLASTICITY

As noted in § 5, electrophysiological studies of the prefrontal cortex show that neurons in the prefrontal cortex

adapt their activity flexibly to task demands. More specifically, Chen *et al.* (2001) have suggested that prefrontal neurons change in response to instrumental training, that is, their activity is shaped by rewards and punishments. Before considering this proposal further, note that it applies equally to cortical plasticity outside the prefrontal cortex, as well as to the prefrontal cortex. A recent experiment by Schoups *et al.* (2001) in the striate cortex shows this very clearly. These authors trained monkeys to discriminate between lines of two orientations that were near to 45° (*ca.* 44–46°). The effect of training was to change the orientation tuning curves in those striate-cortex neurons in which the peak sensitivity was 12–20° removed from 45°, either clockwise or anticlockwise. These neurons had the steepest slope of their orientation tuning curve at 45° and were therefore best able to make fine discriminations among orientations near to 45°, as the task demanded; and the effect of training was that the slope of the tuning curve of these neurons at this steepest point became steeper, thus improving the monkey's discriminative ability in the trained task. Many other examples of perceptual learning in the cortex can be explained by the simple assumption that trained stimuli expand their representation in the cortex; this could explain, for example, the expanded finger representation in the cortex in Braille readers (Pascual Leone & Torres 1993), and several other kinds of perceptual learning (reviewed by Gaffan 1996). However, such an explanation cannot apply to the experiment by Schoups *et al.* (2001), as these authors emphasize; the trained stimuli did not expand their cortical representation, and the cortical change resulting from training was not an expanded representation but an alteration in tuning curves. Rather, it appears necessary to explain their results as showing instrumental training effects, similar to those in the prefrontal cortex that Chen *et al.* (2001) discuss; the striate neurons changed in such a way as to maximize rewards.

This idea of instrumental training of cortical neurons is unfamiliar, but it is not difficult in principle to see how such training effects could occur. The idea of instrumental reinforcement is that an association is strengthened when reinforcement follows, even though reinforcement is not itself a term in the strengthened association—reinforcement is neither the retrieval cue for the association, nor the information recalled by the association (Sutton & Barto 1998). Translating this into neural terms to apply instrumental learning to cortical neurons, the necessary assumption is that reward delivery sends a neuromodulatory signal to cortical neurons, that is, a signal that does not directly elicit action potentials. Then the synapses that have been active before reward delivery, corresponding to the associations in psychological terms, need to be strengthened. The result is not that the neurons come to signal reward but that their activity comes to perform whatever function maximizes the probability of reward delivery subsequent to that activity.

Of course, the range of functions available to striate-cortex neurons is far narrower than the range of functions available to prefrontal cortex neurons, because of the restricted kind of information that is available presynaptically to striate neurons. Further, the changes observed by Schoups *et al.* (2001) were not necessarily only the direct effects of changes within the neurons that showed the changed tuning curves, but could possibly reflect a secondary effect of changes in other neurons; however, the same qualification applies to changes in the responses of the prefrontal neurons. Subject to these qualifications, the basic idea of synaptic weights being strengthened by instrumental reinforcement is necessary to explain the results from the striate cortex by Schoups *et al.* (2001) just as much as to explain the examples from the frontal cortex discussed by Duncan (2001) and Chen *et al.* (2001). The rules of cortical plasticity could be much more complicated than any of the possibilities I have discussed, but it is hard to see that a simpler idea could explain these results.

A modification of this proposal needs to be made, however, in order to accommodate the memory of aversive events. If instrumental learning were the only principle of memory formation, punishment would have to induce forgetting. To avoid this implausible consequence, it is preferable to assume that the neuromodulatory signal is not generated only by reward but by any event of significance to the animal, whether rewarding or aversive. This signal could correspond to the cortical arousal signal that is carried by the ascending influences from the basal forebrain and midbrain, discussed in § 3. Thus, the simplest hypothesis of a rule for cortical plasticity consistent with the observations I have discussed is that the activity of cortical neurons comes to perform whatever function maximizes the probability of cortical arousal subsequent to that activity.

Memory performance, such as the ability to recognize an object that has been seen before, could be a by-product of the synaptic changes that are generated by such a mechanism when an object is encountered and elicits some cortical arousal. If that is the only mechanism of cortical plasticity, however, it will not account for instrumental learning in the traditional sense, that is, the fact that animals learn to produce rewards and do not learn to produce punishments. Thus, a different kind of plasticity will be required subcortically to instantiate instrumental learning itself. Waelti *et al.* (2001) suggest that dopaminergic neurons, many of which project into the basal ganglia, provide teaching signals for associative learning: this could support a mechanism for reward-guided instrumental learning in the basal ganglia. This putative subcortical mechanism of instrumental learning receives the output of the cortex, however, so the memory functions provided by the cortex will be available to guide instrumental action. On the basis of monkeys' memory performance in a win–shift, lose–stay task, I proposed (Gaffan 1985) that rewards have two effects on plasticity in the brain: they lay down memories and also, independently, shape instrumental action. The present hypothesis extends this earlier hypothesis by supposing that memories are in the cortex and instrumental habits are in the basal ganglia. This is reminiscent of the proposal by Mishkin & Petri (1984) that habit learning is in the basal ganglia. However, unlike Mishkin & Petri (1984), I do not think that when a monkey learns some new object discrimination for food reward, a new habit is laid down in the basal ganglia. Rather, I propose that neurons in the basal ganglia acquire, in many such experiences with different objects, the habit of approaching those objects that evoke the memory of food reward, and the new discrimination is acquired by a cortical change as the new object becomes associated in memory with food.

9. CONCLUSION

I have drawn attention to some implications of the concept of memory systems that are not supported by the evidence. These include the idea that memories are stored exclusively in the putative memory systems, and the idea that the function of the putative memory systems is best characterized as memory. However, the concept of memory systems is in many ways attractive and useful. It enables electrophysiological, neuroanatomical and cognitive studies to proclaim their clear relevance, which I do not doubt, to those problems of memory disorder that are such a prominent part of many brain diseases; and, for similar reasons, it allows the general drift of a research program to be conveyed instantly to a lay audience. In view of these advantages of the concept it might be thought churlish to insist on the falsity of its implications; after all, if medial temporal lesions produce amnesia, as they certainly do, then is this not sufficient in itself to justify the concept of a medial temporal memory system or systems in some sense, even if in detail some of the apparent implications of that idea have to be subsequently modified? Against this tolerant view it is necessary to show not simply that some implications of the concept are in conflict with the evidence but that the concept itself is harmful. This review has identified two ways in which the concept of memory systems impedes progress. In the study of cortical localization of function, it is a prominent instantiation of the idea that the functions of cortical areas can be characterized intuitively and in a haphazard and piecemeal fashion, and it thus stands in the way of a systematic hierarchical explanation of functional localization and its breakdown in the prefrontal cortex. Additionally, in the study of cortical plasticity, it stands in the way of the simple hypothesis that all cortical areas have the same rules of plasticity.

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GLOSSARY

ACH: acetylcholine
AM: amygdala
FX: fornix
MD: mediodorsal thalamic nucleus
TS: temporal stem