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Medial temporal and prefrontal function: Recent behavioural disconnection studies in the macaque monkey

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ABSTRACT

In the macaque monkey, disconnection syndromes can be produced experimentally either by selective section of axonal pathways or by crossed unilateral asymmetrical ablations. Behavioural investigation of the effects of these disconnections gives information that cannot be derived either from clinical studies or from the effects of bilateral symmetrical ablations in the monkey. Disconnection experiments are particularly suited to the study of the interactions between the components of widespread cortical networks. We propose that memory acquisition is dependent on plastic cortical changes that are widespread, rather than limited to the medial temporal lobe. Further, memory acquisition depends on cortical–subcortical interactions to a greater extent than memory retrieval does. Prefrontal cortex, we suggest, is specifically important in the representation of temporally complex events.

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1. Introduction

Lesions in the human brain frequently involve both the interruption of axons and the removal of neurons. In these circumstances it can be difficult to distinguish which kind of damage has given rise to which symptoms. One important use of disconnection studies in the macaque monkey is to test these alternatives experimentally. After training the animals to perform a behavioural test of the cognitive function of interest, the experimenter can produce a lesion that either removes neurons without damaging other neurons' axons, or cuts axons without removing neurons. An example of the former technique is neurotoxic lesions of hippocampus (Murray and Mishkin, 1998) while an example of the latter technique is section of the forebrain commissures (Eacott and Gaffan, 1989a, 1989b). Even when an axonal pathway cannot be sectioned without unwanted loss of adjacent neurons, the experimenter can compare an experimental group, having this axonal section combined with neuronal loss, with a control group which has the neuronal loss without the axonal section. An example is uncinate fascicle (for the anatomical description of the uncinate see Catani and Thiebaut de Schotten, 2008, this issue) section, which cannot be achieved without damaging the cortex in the superior temporal gyrus; here a control procedure, with superior temporal cortical damage but with the uncinate fascicle left intact, shows that this cortical damage has no effect on the visual tasks that are impaired by uncinate fascicle section (Eacott and Gaffan, 1992). These techniques for experimental investigation of the cognitive effects of axonal interruption are straightforwardly applicable to the elucidation of

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impairments that are seen clinically. An example of the fruitful interchange between clinical and experimental disconnection studies of this kind is in the explanation of visual hemi-neglect as arising from parietal leucotomy (Gaffan and Hornak, 1997; Thiebaut de Schotten et al., 2005; Gaffan, 2005; Doricchi et al., 2008, this issue; Thiebaut de Schotten et al., 2008, this issue) and callosotomy (Glickstein and Berlucchi, 2008, this issue; Doron and Gazzaniga, 2008, this issue).

A second technique of experimental disconnection in monkeys makes use of crossed unilateral asymmetrical ablations. This technique, introduced by Ettlinger (1959), capitalizes on the fact that, in the monkey, unilateral ablations by themselves, an ablation in one hemisphere leaving the same area in the opposite hemisphere intact, often lead to little or no cognitive impairment. (Those lesions that produce visual hemineglect in the monkey, as cited above, are an exception to this general rule, but that study showed that visual hemi-neglect is only produced in the monkey by certain specific leucotomies, not by unilateral cortical ablations.) Furthermore, connections between different telencephalic areas are predominantly ipsilateral. Consequently, crossed unilateral asymmetrical ablations, of one area in one hemisphere and of a different area in the opposite hemisphere, specifically and substantially impede the interaction between those two areas (see Fig. 1). This technique, unlike the technique of axonal section described above, is not directly comparable to any commonly arising clinical syndrome. Nonetheless it adds powerfully to the experimenter's ability to analyse interactions between areas. As we shall see, the cognitive impairment produced by disconnecting area A from area B by crossed unilateral asymmetrical ablations is usually less than the impairments produced by bilateral symmetrical ablations either of A or of B; disconnection of A from B impairs those tasks that require A–B interaction, but not those tasks that require both A and B but not their interaction (see also Catani and Mesualm, 2008a). Further, if the function of area B is well established, but that of area A is not, then the function of area A can be studied within the controlled scope of area B function by looking at their interaction. This allows elucidation of a specific part of area A's role that may be obscured by wider-ranging effects of bilateral lesions of that area. This aspect of the disconnection technique will be exemplified in Section 3 on disconnection of prefrontal cortex, a poorly understood area, from inferior temporal cortex, a well-understood area.

We next consider two specific areas, namely medial temporal cortex and prefrontal cortex, in which disconnection studies in macaque monkeys have made important recent advances; and in Section 4 we consider what general conclusions can be drawn from considering these two specific topics together.

2. Medial temporal function

The effects of cutting the fornix have been perhaps the most studied of all disconnection effects in the monkey. The role of the fornix in memory was a long-standing controversy in the

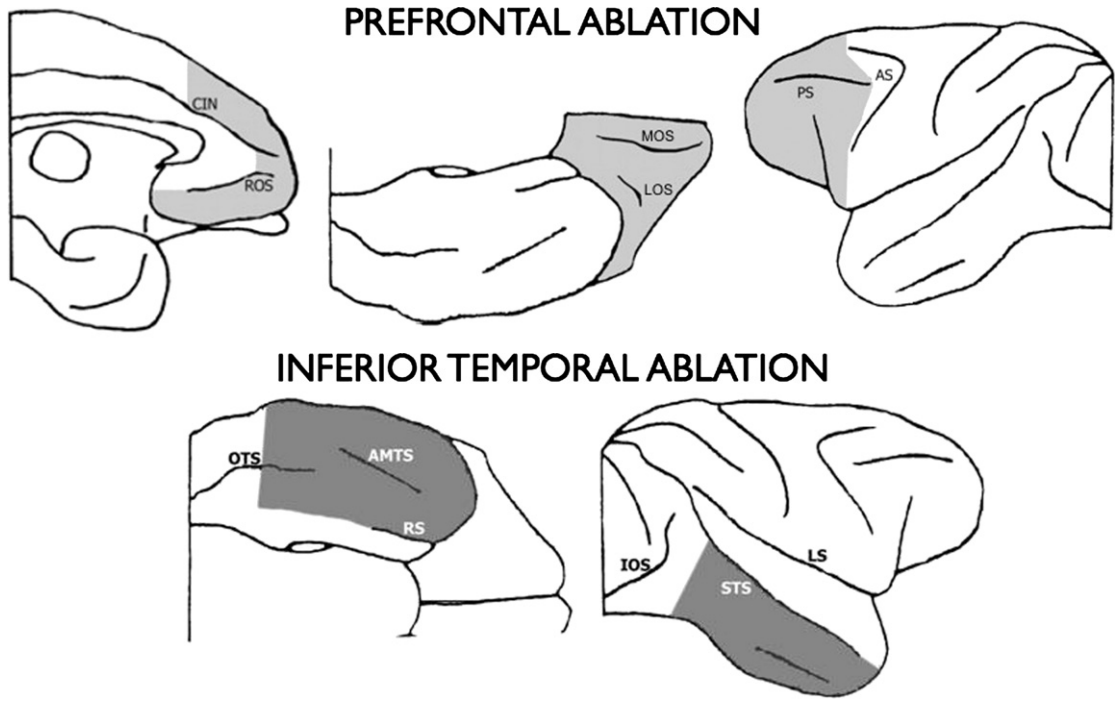


Fig. 1 – The surgical ablations in prefrontal–inferotemporal disconnection by crossed unilateral asymmetrical ablations, shown from lateral, ventral and medial views. The shaded areas indicate the areas of intended removal; the unilateral prefrontal ablation is shown in light grey and the unilateral inferior temporal ablation is shown in dark grey. The prefrontal ablation is shown in the left hemisphere and the inferotemporal ablation is shown in the right hemisphere. PS, principal sulcus; AS, arcuate sulcus; CIN, cingulate sulcus; ROS, rostral sulcus; MOS, medial orbital sulcus; LOS, lateral orbital sulcus; IOS, inferior occipital sulcus; STS, superior temporal sulcus; LS, lateral sulcus; OTS, occipito-temporal sulcus; AMTS, anterior middle temporal sulcus; RS, rhinal sulcus.

20th century (for anatomical description of the fornix see Catani and Thiebaut de Schotten, 2008, this issue). The fornix was central to the doctrine, widespread among clinical neurologists and most clearly expressed by Delay and Brion (1969), that amnesia was caused by any bilateral interruption of a hippocampus–fornix–mamillary system. This doctrine accounted parsimoniously both for human medial temporal amnesia, which it ascribed to hippocampal lesions, and for human diencephalic amnesia (see also Schmahmann and Pandya, 2008, this issue), which it ascribed to mamillary lesions. However, others contended that neither mamillary lesions (Victor et al., 1989) nor fornix section (Garcia-Bengochea and Friedman, 1987) caused any memory impairment in human patients. However, a careful review of the early clinical results strongly supported the doctrine that fornix transection in man caused memory impairment (Gaffan and Gaffan, 1991). In the monkey, fornix section was seen to lead to substantial memory impairments, not only in tasks that were overtly spatial (e.g., Buckley et al., 2008) but also in tasks that were not overtly spatial, including scene learning (Gaffan, 1994) and recency judgments (Charles et al., 2004). A further prediction of the Delay–Brion account was confirmed in the monkey by Parker and Gaffan (1997) who found that lesions of the mamillary nuclei caused memory impairments equally severe to those following fornix section, and that combined mamillary lesions and fornix section had no more severe effect than that of either alone. The culmination of the clinical side of this story was the study by Aggleton et al. (2000). These authors investigated a series of patients in whom colloid cysts had been surgically removed from the third ventricle, ventral to the fornix. The fornix had been sectioned bilaterally in some cases but not in others. Memory impairments were seen in the former but not in the latter group. One of the most convincing features of this study was that it included the assessment of a human version of a scene learning task that had been used to assess memory impairments in monkeys with fornix section; the measured severity of the impairment in patients with fornix section, compared to their control patients with colloid cyst removal and fornix intact, was almost identical in this task to the measured severity of the impairment in monkeys with fornix section, compared to their controls, in the same task (see Fig. 1 in Gaffan, 2002).

Although these results from patients and monkeys vindicate many elements of the Delay and Brion (1969) account of amnesia that account can by no means stand as a full explanation of all forms of organic amnesia. One reason is that the mediodorsal thalamic nucleus, the main rival to the mamillary bodies in the explanations of human diencephalic amnesia (Victor et al., 1989; Schmahmann and Pandya, 2008, this issue), does indeed have an important role in memory acquisition, in addition to the role of the mamillary nuclei, as we shall see in Section 3 on prefrontal function. Another reason is simply the relative severity of the learning impairment that is caused by discrete fornix lesions in man and monkey. Both patients and monkeys with fornix section, although substantially impaired in some kinds of learning task, can acquire new memories at or near normal levels in some other kinds of memory task (e.g., Charles et al., 2004; Mcmackin et al., 1995; Ross, 2008, this issue). The contrast here is with densely amnesic medial temporal patients such as HM, who is impaired in almost all kinds of new learning (Hood et al., 1999).

The prevailing view has been that this dense amnesia results from the removal of neurons in a putative medial temporal memory system which includes the hippocampus and the entorhinal and perirhinal cortex (Squire and Zola-Morgan, 1991). However, there are some objections to this explanation. First, removal of these neurons produces not only memory impairments but also perceptual impairments, both in patients and in monkeys (Murray et al., 2007), and non-mnemonic impairments of scene processing in patients (Hassabis et al., 2007). Second, removal of these neurons leaves some memory tasks unimpaired. Monkeys with removal of neurons in perirhinal cortex, the area mainly involved in object perception and memory in the medial temporal lobe, can learn object–reward associations at a normal rate in more than one version of this task (Buckley and Gaffan, 1997; Thornton et al., 1997) but HM is profoundly impaired in it (Hood et al., 1999). One alternative explanation, of a kind that was first put forward by Horel (1978), is that medial temporal amnesia results from axonal damage. The axons that normally run in the fornix are sectioned in HM, since these axons are part of the destroyed medial temporal tissue; in addition, removal of the amygdala and damage to the anterior temporal stem in HM (Corkin et al., 1997) cut many axonal pathways that connect temporal cortex reciprocally with prefrontal cortex and also with a number of subcortical structures such as the basal forebrain. Importantly, some of these severed connections are with cortex that is intact in HM, namely the lateral temporal cortex. Perhaps therefore it is this multiple disconnection that is the cause of dense anterograde amnesia (see also Ross, 2008, this issue).

We have tested this idea experimentally in two ways, by axonal section and by crossed unilateral lesions. Surgical section through the amygdala and anterior temporal stem produced only mild learning impairments in monkeys, but when fornix section was added in the same monkeys they became profoundly impaired not only in scene learning but also in object–reward associative learning (Gaffan et al., 2001). One can achieve a similar disconnection in the visual modality by ablating the inferior temporal cortex unilaterally, thus removing the route by which visual object-identity information reaches the temporal lobe on that side, and in the other hemisphere making a unilateral lesion of the basal forebrain or the medial forebrain bundle combined with unilateral fornix section. Each of these unilateral lesions alone had little effect on monkeys' ability to acquire new memories, but their combination, thus completing the disconnection, had a devastating effect on new learning (Easton and Gaffan, 2001; Easton et al., 2001, 2002). These results show that disconnection of the temporal lobe from subcortical interactions produces severe anterograde amnesia in the monkey even when the neurons of the putative medial temporal lobe memory system are intact. They suggest that all temporal cortex, including the temporal cortex lateral to the putative medial temporal memory system, takes part in memory acquisition as well as in perception, and that memory acquisition requires cortical–subcortical interaction.

An interesting corollary concerns anterograde and retrograde amnesic effects. In the monkey one can measure retrograde amnesia by a one-trial postoperative retrieval test of each of many independent preoperatively acquired memories.

This measure of retrograde amnesia is uncontaminated by postoperative re-learning. In several experiments fornix section produced more severe anterograde than retrograde amnesia, that is, either no retrograde impairment or only a very mild retrograde impairment by comparison to the memory acquisition impairment with the same stimulus material (Buckley et al., 2008). Removal of perirhinal and entorhinal cortex, on the other hand, produced more severe retrograde than anterograde amnesia (Thornton et al., 1997). A similar effect was seen after removal of inferior temporal cortex lateral to perirhinal cortex (Dean and Weiskrantz, 1974; Fig. 2). These results are consistent with the idea that subcortical interactions of temporal cortex are specifically necessary for memory acquisition, and that once a memory has been acquired it is stored in cortex. Thus, cortical–subcortical disconnection impairs memory acquisition more severely than it impairs the retrieval of preoperatively acquired memories, while removal of cortical neurons impairs the retrieval of preoperatively acquired memories more severely than it impairs memory acquisition. Though anterograde and retrograde amnesic effects of selective neurotoxic removal of hippocampal neurons (which are also cortical) have not yet been compared in the monkey using the method of one-trial postoperative retrieval, similar rat experiments point to a greater retrograde than anterograde effect of these removals (Sutherland et al., 2001). It will be important for future monkey experiments to compare the anterograde and retrograde effects of selective removal of hippocampal neurons in the monkey.

3. Prefrontal function

Disconnection results from prefrontal cortex have produced, as it turns out, some interesting parallels with those on temporal cortex. However, the starting points of these two sets of experiments were quite different. Symmetrical bilateral prefrontal ablations in monkeys produce severe impairments in a very wide variety of cognitive tasks. This suggests that prefrontal cortex as a whole subserves some very general and very important cognitive function, but at the same time makes it difficult to guess what precisely that function might be. One way to try to overcome this difficulty is to make small ablations within restricted subdivisions of prefrontal cortex, hoping to find several subdivisions each with a more specific function. However, we know of only two studies that have reported double dissociations of function between areas within prefrontal cortex (Butter, 1969; M.G. Baxter, unpublished observations). Disconnection offers a different and complementary approach. Unilateral prefrontal ablations, even the removal of the whole of prefrontal cortex in one hemisphere, have little behavioural effect in macaque monkeys, as is shown in many of the experiments cited below. This means that, if one makes a unilateral prefrontal ablation in one hemisphere and a unilateral inferior temporal ablation in the other hemisphere, one can expect that the remaining intact prefrontal cortex, in the hemisphere with the inferior temporal ablation, will be able to perform its normal duties adequately so long as they do not require interaction with visual object-identity information (which is represented in inferior temporal cortex). Therefore, if the unknown, general and important cognitive function of prefrontal cortex, say X, is required to be applied in a certain task to, say, the reward outcomes in the task, then one can expect this process to be unaffected by the disconnection from inferior temporal cortex. Knowing that X is impeded only specifically in its interaction with visual object-identity means that one can manipulate the role of visual identity in various cognitive tasks, to discover when disconnection impairs or does not impair them, and thus to make more specific statements about X.

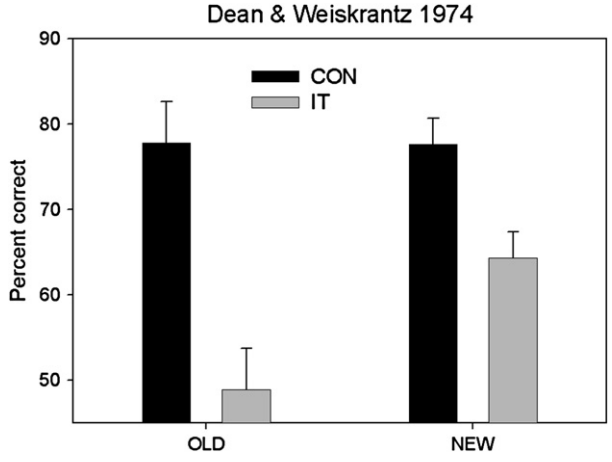


Fig. 2 – Data re-drawn from Dean and Weiskrantz (1974). Monkeys were trained in object–reward associations preoperatively, either remained as controls or received partial ablations of inferior temporal cortex not including the perirhinal cortex, and had a postoperative one-trial test of the preoperatively acquired discriminations followed by a test of new learning. The effect of the ablation was more severe in retrieval of the old problems than in learning of the new problems ($F = 9.330$, $df = 1.4$, $p = .038$).

The data from experiments of this kind can be summarized quite briefly. Concurrent object–reward association learning is unimpaired by prefrontal–inferotemporal disconnection, even though it is impaired by bilateral symmetrical ablations of either prefrontal or inferior temporal cortex (Parker and Gaffan, 1998b; Gaffan et al., 2002). The same is true of concurrent reversal learning (Wilson and Gaffan, 2008). One class of tasks that are impaired by prefrontal–inferotemporal disconnection is that of conditional discriminations. In these tasks an instruction cue, varying from trial to trial, informs the animal which choice is to be rewarded on that trial. These tasks can employ visual instruction cues and a nonvisual choice, or nonvisual instruction cues and a visual choice, or instruction cues and choices that are both visual. All these three kinds of conditional learning are impaired by prefrontal–inferotemporal disconnection, either with uncinate fascicle section or with crossed unilateral ablations (Gutnikov et al., 1997; Parker and Gaffan, 1998b; Bussey et al., 2002).

A second class of tasks that are impaired consists of tasks that require integration of visual information across successive trials. An example is delayed matching-to-sample (Parker and Gaffan, 1998a). The presentation of the sample object in this task informs the animal that the next trial will have that object as the rewarded choice. Delayed matching-to-sample was impaired both by crossed unilateral temporal and

prefrontal ablations (Parker and Gaffan, 1998a) and by uncinate fascicle section (Gaffan and Eacott, 1995). Gaffan and Eacott (1995) tested control monkeys and monkeys with uncinate fascicle section pre and postoperatively in two versions of delayed matching-to-sample, one with trial-unique stimuli and the other with a small repeating set of stimuli drawn from the same population as the trial-unique stimuli. Their hypothesis was that uncinate fascicle section would impair one of these tasks but not the other, and they analysed the results from the two tasks separately. In these separate analyses neither task showed a significant difference between the groups, although on average in both tasks the group with uncinate fascicle section was impaired, relative to the control group. However, our present understanding of temporal–frontal disconnection effects would predict, instead, that these two tasks would be equally impaired by uncinate fascicle section. When Gaffan and Eacott's results from their two tasks are reanalysed together in a factorial analysis of Group (control and uncinate fascicle section), Stage of surgery (pre and postoperative), and Task (trial-unique and small-set matching) they show a significant interaction of Group with Stage ($F = 8.895$, $df = 1.5$, $p = .031$) and no interaction of Task by Group by Stage ($F < 1$). Thus, the results of Gaffan and Eacott (1995) are consistent with our present understanding of temporal–frontal disconnection effects.

Another example of a task requiring integration of visual information across trials is object discrimination learning set. Here the animal uses one choice trial with a particular pair of objects as the source of an instruction as to what choice to make on the immediately following trial with the same objects. That this is a different process from object–reward association learning is shown by the fact that monkeys develop discrimination learning set only when the successive trials with each pair of objects follow immediately upon each other, not when they are separated by a long delay (Murray and Gaffan, 2006). Monkeys that have developed a discrimination learning set do not lose the ability to learn object–reward associations after prefrontal–inferotemporal disconnection, but they lose the learning set, reverting to the slow learning that they showed before developing learning set (see Fig. 4 in Browning et al., 2007).

The above set of results suggests the following hypothesis. In the unimpaired tasks, concurrent object–reward association learning and concurrent reversal learning, what the animal needs to know about each object is a simple two-term association: each object is either associated with reward, or with no reward. In the impaired tasks the animal needs to know a more complex, temporally extended association with each object, involving three or more terms: for example, in a conditional task the sequences cue1–object A–reward, cue2–object B–reward, cue1–object B–no reward, cue2–object A–no reward; or in a task requiring integration across trials similar complex events such as sample1–object 9–no reward. So one can hypothesize that prefrontal involvement in processing visual object-identity information is required whenever the monkey learns about visual objects as terms in temporally complex events, involving at least three items, but not when the monkey learns about visual objects only as terms in temporally simpler events, involving only two items.

To test this idea Browning and Gaffan (2008a) used a variant of concurrent object–reward association learning. The monkeys made choices between visually presented objects on a touch screen, and in one condition the objects presented for choice were each the first item of some two-object serial compound event. Thus, given a choice between objects A and C, the monkey if it chose A would see A replaced by B for 2 sec, then a reward; and if it chose C would see C replaced by D for 2 sec, then no reward. In previous experiments with normal monkeys, tests of mediated generalization showed that normal monkeys learn such a task by associating the two objects A and B with each other, and the resulting serial visual compound with reward (Gaffan and Dickinson, 2008). This is despite the fact that, operationally, the task does not require the monkey to learn to choose the second object, B, in order to obtain reward. Since this is a three-term association one would expect that prefrontal–inferotemporal disconnection would impair the learning of it, and this was what Browning and Gaffan observed. In a control task, single objects were associated with either reward or no reward, but with an unfilled delay between object choice and reward outcome; this task, which was more difficult for normal monkeys than the serial compound task, was learned without impairment by the animals with prefrontal–inferotemporal disconnection. These results give strong support to the idea that prefrontal–inferotemporal interaction is specifically required for the representation of temporally complex events involving visual objects.

The very broad effects of bilateral ablations of prefrontal cortex in the monkey, together with similar evidence from human neuroscience, have led to the characterization of prefrontal cortex function in terms of general cognitive abilities such as response to cognitive demand (Duncan and Owen, 2000), executive cognitive control (Miller and Cohen, 2001) or behavioural inhibition (Aron et al., 2004; Sakagami et al., 2006). Instead, the results from disconnection studies suggest that the effects of bilateral prefrontal lesions are broad because all cognitive tasks require some form of temporally complex representation. The advantage of the disconnection technique is that it can assess whether there is a need for one particular type of temporally complex representations, namely those that necessarily involve visual objects. Where that type is not needed, as in the unfilled delay or the concurrent reversal tasks, no impairment is produced by the disconnection even though those tasks require fluid intelligence, working memory, or behavioural inhibition to the same extent that the serial compound task does.

This characterization of prefrontal function in the representation of some specific kinds of information, namely temporally complex information, makes it easy to see that the acquisition of such representations, that is, memories of temporally complex events, requires the prefrontal cortex as much as the temporal cortex. This contrasts with the conventional view that all memories are acquired in the temporal lobe.

The object-in-place scene learning task (Gaffan, 1994), which was discussed briefly above in the context of human amnesia (Aggleton et al., 2000), allows us to compare the mechanisms of memory acquisition in prefrontal and temporal cortex. In this task, standard two-choice concurrent object discriminations are made easier for the monkey by placing each pair of objects within a unique, computer-generated

background scene that always appears with those particular objects and is never repeated with any other objects. The monkeys' learning curve in this task is much faster than that of monkeys performing a similar concurrent discrimination task without the assistance of the scenes. We have used this task as a monkey analogue of human episodic memory, because it is very rapidly learned, and it sets associative learning in a spatial and temporal context. This task requires the association together of not only a reward event but also both a foreground object and the elements of the background scene, which are perceived in successive visual fixations. As such it requires a multiple-term association and the processing of a temporally complex event, and should therefore be dependent on prefrontal–inferotemporal interaction, as confirmed by Browning et al. (2005).

Mitchell and Gaffan (2008) made selective lesions of the medial part of the mediodorsal thalamic nucleus, which is heavily interconnected with prefrontal cortex, and tested these monkeys for anterograde and retrograde amnesic effects with scenes, using a one-trial postoperative test of preoperatively acquired scenes. The result was like that from fornix section (Gaffan, 1994): mediodorsal thalamic lesions produced an anterograde amnesic effect but no retrograde amnesic effect. Clearly, therefore, the effects of mediodorsal thalamic lesions on new learning cannot be ascribed to a broad deficit in cognitive control or any other of the broad functions that have been attributed to prefrontal cortex, since such a deficit would be reflected also in a retrieval deficit with preoperatively acquired scenes, which was not observed (Mitchell and Gaffan, 2008). Rather, the disconnection of cortical–subcortical interaction produces more severe anterograde than retrograde amnesia both in the case of prefrontal cortex and in the case of temporal cortex. As we have seen above, cortical removals produce the opposite pattern, a more severe retrograde than anterograde effect. This generalization extends to cortical removals of prefrontal cortex in prefrontal–inferotemporal disconnection by crossed unilateral removals (Browning and Gaffan, 2008b).

It might be objected that the effects of bilateral symmetrical prefrontal cortical removals have not yet been tested in the one-trial test of retrograde amnesia, and could conceivably (unlike bilateral symmetrical temporal cortical removals, as noted above) produce more severe anterograde than retrograde effects. However, these results from one-trial tests are supported by results from a more conventional paradigm in which a difficult strategy task, learned to criterion preoperatively, is tested postoperatively in multiple trials. Mediodorsal thalamic lesions did not impair the postoperative performance of the preoperatively trained strategy task (Mitchell et al., 2007) but bilateral symmetrical prefrontal cortical removals did (M.G. Baxter, unpublished observations). These results strongly suggest that bilateral symmetrical removals of prefrontal cortex, like those of temporal cortex and unlike mediodorsal thalamic lesions, produce powerful retrograde amnesic effects. Of course, it will be important for future experiments to test not only bilateral symmetrical selective hippocampal removals but also bilateral symmetrical prefrontal removals in the one-trial retrieval test and in comparable new postoperative learning. The existing data, however, strongly supports the generalization that, both for temporal and for prefrontal cortex, cortical–subcortical disconnection impairs memory acquisition more severely than it impairs the retrieval of preoperatively acquired memories, while removal of cortical neurons impairs the retrieval of preoperatively acquired memories more severely than it impairs memory acquisition.

4. Conclusion

The search for localization of function, which in the monkey ablation literature has taken the form of looking for double dissociations between the effects of bilaterally symmetrical lesions in different areas or structures, has produced much information of great value. However, this paradigm is in danger of impeding progress, if its success is taken to indicate that no other kind of approach to understand brain function by ablation effects is required or even legitimate. No-one doubts that the effects of bilateral symmetric ablations in the prefrontal cortex can be reliably distinguished, using appropriate behavioural tasks, from the effects of bilateral symmetric ablations in the temporal cortex. This is by no means incompatible, however, with the idea that brain lesion effects, even the effects of bilaterally symmetrical lesions, are best understood as interruptions or disconnections of information flow in distributed networks (Geschwind, 1965; Catani and Ffytche, 2005; Catani and Mesualm, 2008a,b, this issue). Disconnection experiments are particularly suited to the investigation of the interactions between the components of such widespread networks.

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