PERGAMON

Neuroscience and Biobehavioral Reviews 25 (2001) 555–573

NEUROSCIENCE AND BIOBEHAVIORAL REVIEWS

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Review

# Exploring the neural bases of episodic and semantic memory: the role of structural and functional neuroimaging

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**Abstract**

Exploration of the neural bases of episodic and semantic memory is best pursued through the combined examination of the effects of identified lesions on memory and functional neuroimaging of both normal people and patients when they engage in memory processing of various kinds. Both structural and functional neuroimaging acquisition and analysis techniques have developed rapidly and will continue to do so. This review briefly outlines the history of neuroimaging as it impacts on memory research. Next, what has been learned so far from lesion-based research is outlined with emphasis on areas of disagreement as well as agreement. What has been learned from functional neuroimaging, particularly emission tomography and functional magnetic resonance imaging, is then discussed, and some stress is placed on topics where the interpretation of imaging studies has so far been unclear. Finally, how functional and structural imaging techniques can be optimally used to help resolve three areas of disagreement in the lesion literature will be discussed. These disagreements concern what the hippocampus and perirhinal cortex contribute to memory; whether any form of priming depends on the medial temporal lobes; and whether remote episodic as well as semantic memories cease to depend on the medial temporal lobes. Although the discussion will show the value of imaging techniques, it will also emphasize some of the limitations of current neuroimaging studies. © 2001 Published by Elsevier Science Ltd.

*Keywords:* Episodic memory; fMRI; Amnesia; Familiarity; Recollection

**Contents**



## 1. Introduction

A central aim of cognitive neuroscience is to identify the brain structures that mediate the ability of humans to encode, store and retrieve information about personally experienced episodes and facts of various kinds. Specification of how neurons in each of the critical regions interact to produce episodic and semantic memories depends on the use of computational models of neural networks. However, if these models are to be effective, they must be sufficiently constrained by both psychological and neuroanatomical knowledge. These constraints become stronger the more fully the central aim is achieved. The tighter the constraints become the fewer will be the number of possible networks that meet them so that the models' predictions will increasingly provide a basis for a heuristically valuable interplay between modelling and the steadily improving methods for identifying the critical neural structures underlying episodic and semantic memory.

Until around 1980, the neural bases of memory were explored almost entirely by systematic study of patients in whom brain damage had caused relatively selective deficits in episodic and/or semantic memory. This work had begun in the 1880s, but until the 1970s identification of the

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0149-7634/01/$ - see front matter © 2001 Published by Elsevier Science Ltd.
PII: S0149-7634(01)00034-3

location of the brain damage in patients with memory impairments could only be achieved in the rare cases where post-mortem analysis was possible or where there was neurosurgical information available (although this was not necessarily very accurate). If available, post-mortem histological analysis of patients' brains is still the method of choice. However, two caveats to this assertion are warranted. First, care needs to be taken that brain damage has not extended since memory was last tested so that the measured damage corresponds closely with the previously assessed memory impairment. Second, even now, critical histological measures may not be being made because there is insufficient theoretical understanding of the kinds of structural changes likely to cause memory deficits.

Computerized tomography (CT) in the 1970s provided the first opportunity to image where patients' brain damage was in life. The method was, however, relatively insensitive and, even if it identified damage in some structures, the precision was low and CT was unable to identify in which small structures relatively focal damage had occurred. For example, only post-mortem analysis succeeded in identifying neuronal damage in specific hypothalamic nuclei in two amnesic patients. Previous CT scans in the late 1970s had failed to identify any damage except some frontal lobe atrophy in one of the patients. At post-mortem, this patient was found to have less frontal lobe damage than the other patient in whom CT had failed to identify frontal lobe damage (see Ref. [45]). It was not until the emergence of magnetic resonance imaging (MRI) in the 1980s that structural imaging of the human brain improved to the extent that damage to relatively small structures (e.g. the hippocampus) could be identified with confidence. In the past two decades, there have been rapid technological developments with both structural imaging procedures, and this is particularly so with MRI. A variety of imaging sequences are now available with MRI, which allows different characteristics of tissue to be imaged thus providing a much fuller picture of both normal and damaged brain tissue than was available in the early 1980s.

By the end of the 1980s, positron emission tomography (PET) was beginning to be used in functional imaging studies of the brain activations that accompany specific psychological processes. These PET functional imaging studies measured blood flow changes as an indirect means of assessing the changes in neural activity. By 1991, functional MRI (fMRI) emerged as a method of indirectly monitoring changes in neural activity by measuring blood oxygen level dependent (BOLD) responses [7,59,85]. So, for the first time, it became possible, in healthy as well as brain-damaged people, to identify which brain regions change their level of activity when specific memory processes are engaged. However, although the spatial resolution was good, it was limited so that even now the precision of localization of activations should be assessed with care. Precision and accuracy of spatial localization is limited by physiological factors, by current machine limitations and problems with image acquisition (see Refs. [52,60]), as well as by aspects of current analysis procedures. Temporal resolution of activations is currently much worse (being well into the seconds range, far outside the millisecond (ms) range that is physiologically meaningful), although fMRI may have the ability under some conditions (e.g. high magnetic fields) to be sensitive to changes at least around 50–100 ms or so [52]. Only electroencephalographic (EEG) procedures have temporal resolution in the physiological range and these procedures will lack spatial resolution until agreed methods of identifying the source of signals that are picked up on the scalp are found.

The advent of powerful in vivo methods for imaging the structure and function of the healthy and damaged human brain has influenced memory research in two main ways. First, it has shifted lesion-based research away from mainly trying to see how memory breaks down and how different impairments dissociate from one another towards a serious attempt to identify what specific brain lesions cause different kinds of memory impairment. If damage to a specific brain structure results in a selective memory impairment, then this structure is likely to play a critical role in mediating the lost memory function in the normal brain. However, as will be discussed later, even this inference needs to be viewed with caution and should be supported by complementary sources of evidence.

Second, the neural bases of memory are now being explored not only with lesion-based research, but increasingly with functional neuroimaging approaches using PET, fMRI, event-related potential (ERP) and magnetoencephalography (MEG) in healthy and brain-damaged people. These approaches can be partially validated by the rare use of recording electrodes in the brains of certain classes of patient (e.g. temporal lobe epileptics) prior to surgery. All the functional neuroimaging techniques are, however, correlational so it remains important to provide additional evidence that activations related to a specific memory process reflect neural changes that are causally critical to the process rather than incidental changes. Such incidental neural changes could be critical for other processes that sometimes accompany the memory process in question. Lesion studies provide one source of additional evidence although the relevant selective damage may be extremely rare or even non-existent. More recently, transcranial magnetic stimulation (TMS), which causes a transient, but precisely timed electrophysiological disruption of normal neocortical activity over regions that can be reasonably spatially delimited, has become available [3,26]. This further source of additional evidence can not only establish where neuronal activity is causally necessary for a memory process, but also when within a range of a few ms, although it can only do this for neocortical structures, not deep ones such as the hippocampus.

The combined use of lesion-based and functional

neuroimaging approaches has advantages over the use of either approach alone. First, the two approaches provide independent evidence about the localization of specific memory processes. Second, the use of each approach can help the interpretation of what is found using the other approach. Third, each approach has its own strengths. For example, lesions are better at identifying whether normal activity in a structure is critical for a given memory process whereas functional imaging is much better at identifying the range of brain structures in which brain activity may be necessary for the normal performance of a given memory process. One benefit of functional neuroimaging's greater ability to identify the neural systems that subserve memory is that it can be used to guide the search for further kinds of selective lesion that may disrupt episodic and/or semantic memory. If such lesions can be identified, then it becomes possible not only to confirm that the structure is critical for the kind of memory in question, but also to specify more precisely the kind of memory the structure mediates. In turn, this would provide a focus for further functional neuroimaging research.

In the next section, we will briefly review what broadly accepted ideas have emerged about the neural bases of episodic and semantic memory from lesion-based studies (mainly of amnesia) and also indicate what are the areas of disagreement, what are the areas about which least is known, and, relatedly, what kinds of improved knowledge and theoretical development are most urgently needed from future research. Then we will briefly discuss what further knowledge about the neural bases of episodic and semantic memory has emerged in the past decade specifically from functional neuroimaging studies. The final section will consider how functional and structural imaging may help resolve some of the disagreements and fill some of the gaps in knowledge currently left by lesion-based research. This section will, however, also discuss some of the limitations and problems of current imaging procedures. It will illustrate, with selected examples, just how difficult it is to resolve certain theoretical issues. In particular, we will illustrate how neuroimaging studies need to take into account not only the present limitations of imaging, but also the complexity of the psychological and physiological processes responsible for human memory capabilities.

## 2. The neural bases of episodic and semantic memory: agreement, disagreement and needed developments

Most lesion-based evidence concerning the neural bases of episodic and semantic memory involves the examination of different kinds of patient with the organic amnesia syndrome and, more recently, examination of patients with semantic dementia. In the amnesia syndrome, patients may show preserved intelligence and short-term or working memory, but have, to varying levels of severity, two kinds of memory impairment. The most debilitating of these memory deficits is usually anterograde amnesia (AA), which involves an impaired ability to recall and recognize personal episodes and facts encountered after the onset of the brain damage responsible for the amnesia. Most amnesics show impairments in recalling and recognizing recently studied information after delays that may be only a few seconds long provided that the delay between study and test has been filled to prevent rehearsal. Retrograde amnesia (RA) is an impairment in recalling and recognizing personal episodes and facts encountered before the onset of amnesia. Memory for this pre-morbidly experienced information was clearly acquired normally, which is probably not the case with memory for post-morbidly encountered information. The overall severity of retrograde amnesia varies markedly across patients as does its temporal extent, i.e. some patients seem only to be impaired at recalling or recognizing memories acquired up to a few weeks or months prior to the onset of amnesia whereas other patients may be impaired at recalling and recognizing memories acquired up to decades prior to the onset of amnesia. The severity of AA does not correlate well with the severity of RA, and there is some evidence that AA and RA can occur in relative isolation although the vast majority of patients with the organic amnesia syndrome have some degree of both AA and RA (see Refs. [29,42]).

Lesions to any one of several brain regions can cause this syndrome. Thus, damage to the medial temporal lobes (MTLs), the midline diencephalon (MD), the basal forebrain, and perhaps the ventromedial frontal cortex can all cause organic amnesia (see Ref. [46]). These grey matter regions are all strongly interconnected with each other and there is increasingly strong evidence that damage to the fibre tracts, such as the fornix, which connect them can also produce amnesia [2]. There is also evidence that combined damage to the fornix, anterior temporal stem, and fibre tracts that run through or close to the amygdala can produce dense amnesia in monkeys (see Ref. [24]), and probably also does in humans. Finally, it is widely accepted that pre-frontal cortex (PFC) lesions in regions outside the ventromedial frontal cortex can disrupt memory although the memory impairments probably differ from those found in the organic amnesia syndrome. Many believe that some or all of the memory deficits caused by PFC lesions are secondary consequences of executive impairments, which lead to impoverishment of intentional encoding and retrieval processes. This, of course, carries the implication that the memory deficits of the organic amnesia syndrome are not caused by this kind of processing deficit.

In principle, organic amnesia could be caused by different kinds of deficit in encoding, storage, and/or retrieval. However, if encoding is interpreted as the representation of information at input, then there is no evidence that amnesia is caused by an encoding deficit. Many patients can represent and manipulate incoming information in mnemonically useful ways normally and at a normal rate (see Ref. [46]), but, despite this, they are very poor at

recalling or recognizing the information after even short filled delays. Nevertheless, it has been suggested that, at least in monkeys, perirhinal cortex lesions disrupt certain kinds of high-level integrative visual perception [55]. As there is clearly a marked overlap in the processes that underlie encoding and retrieval and there is no direct evidence that amnesics have deficits in effortful retrieval of the kind that some PFC lesions probably cause, very few researchers now believe that amnesia is caused by a retrieval deficit. Most researchers now believe that amnesia is caused by an inability to consolidate factual and episodic information normally into long-term memory although there is surprisingly little direct evidence for this view (see Ref. [48]).

Some guidance about what information is not consolidated normally into long-term memory and why consolidation might be disrupted in amnesia is provided by knowledge of the anatomical connections of the structures implicated in amnesia. For example, processed sensory and other kinds of information from many neocortical regions converges on the MTL, and particularly on the hippocampus (see Ref. [9]). So these regions are well placed to bind the components of complex representations together into long-term memory. The MTLs also send projections back into the neocortical regions from which they receive projections. This region is, therefore, well placed not only to consolidate and store associations between the components of complex memories, but also, when appropriate cues are provided, to reactivate the neocortical regions where these components may be represented and *stored* (see Ref. [48]). It may be significant, therefore, that combined damage to the fornix, anterior temporal stem, and fibre tracts that run through or close to the amygdala causes dense amnesia in monkeys [24]. These tracts project from the basal forebrain and midbrain to the MTLs and temporal neocortex and may mediate different kinds of chronic and phasic arousal-related modulations not only of the MTLs, but also of the neocortex. Such modulations are probably critical for consolidation and long-term storage in the modulated regions.

However, if the basal forebrain structures modulate consolidation in the MTLs and posterior neocortex in this way, then their functions are not identical to those of the MTLs. This raises the possibility not only that the different regions implicated in the amnesia syndrome may subserve somewhat different functions, but also that the different components of each region also subserve somewhat different functions from each other. But there is no consensus about whether large lesions of the MTLs, MD, basal forebrain, and ventromedial frontal cortex cause slightly different patterns of memory breakdown, and there is even less agreement about whether focal lesions to the components of each of these regions cause different functional deficits.

In particular, there is disagreement not only about how much more severely perirhinal cortex damage disrupts item recognition than hippocampal damage, but about whether it does so because it disturbs processes not affected by hippocampal damage (see Ref. [9]). Item recognition is believed to depend upon two kinds of memory: familiarity, which is the non-specific feeling that the item has been encountered before; and recollection, which involves the recall of something about an item (usually its contextual associates) that helps confirm it has been previously encountered. According to one view, hippocampal, like perirhinal cortex, lesions clearly disrupt item recognition as well as recall because they impair familiarity as well as recollection (see Refs. [41,66]) although perirhinal cortex lesions are more disruptive. According to the other view, hippocampal lesions cause at most only mild impairments of item recognition because, although they clearly impair recollection (and all kinds of recall), they do not impair familiarity (see Ref. [44]). Aggleton and Brown [1] have suggested that recollection is also disrupted by lesions of the fornix, which connects the hippocampus to the mammillary bodies and anterior thalamus in the MD, lesions of both of which also disrupt recollection. They have also suggested that item familiarity is disrupted by dorsomedial thalamic lesions to which the perirhinal cortex projects. However, it seems likely that the full specification of the brain systems that mediate recollection and familiarity will involve additional structures in the basal forebrain and frontal lobes, even if the structures specified by Aggleton and Brown are correct.

Very little is known in humans about the effects of lesions to specific thalamic nuclei, partly because lesions are rarely selective, but also because confident localization of damage to these small nuclei is at or beyond the resolution of current structural MRI techniques. These resolution problems are less severe with components of the MTL, but accurate measurement of extent and kind of damage is still a major problem, which contributes to the theoretical disagreements. For example, as Brown and Aggleton [9] point out there is uncertainty about the human equivalent of the functionally better understood monkey perirhinal cortex. There is also still very poor understanding of the precise effects on memory of different frontal cortex lesions in humans. This poor understanding is partly a result of the rarity of selective lesions and the early state of development of appropriate measurement techniques with structural MRI. A major cause of this second contributing factor is that there are few principled ways of determining what are likely to be the functionally meaningful regions of the frontal cortex (e.g. Brodmann areas are hard to identify because of a lack of markers with structural MRI and also their functional significance is uncertain). The evidence that ventromedial frontal cortex lesions in humans cause an organic amnesia syndrome is weak, and it is unclear whether the disruptive effects of frontal lesions on the control of the "consolidation modulations" that may be mediated in part by the basal forebrain [18] reflect a particular kind of disruption of executive functioning or relate to a different kind of functional deficit.

There is also disagreement about whether the amnesia

syndrome has two characteristics, the presence of which would have important theoretical implications. First, although it is widely believed that many forms of conditioning and skill learning as well as certain forms of non-associative perceptual memory are preserved, it is not agreed whether priming is preserved. Priming is a form of memory for specific factual and episodic information, which depends on automatic retrieval processes, and need involve no feeling of familiarity for what is remembered. A widely held view is that priming depends on storage changes in the brain regions that represent the primed information, and that these changes ensure that when some or all of the information is next re-encoded that the representation is reactivated more fluently, i.e. more rapidly and perhaps more strongly (see Ref. [43]). This increased fluency of reactivation need not, however, lead to the feeling that the primed information is being remembered. If, as many believe, priming for all kinds of information is preserved, then it is hard to argue that amnesia arises from a failure to store any aspect of factual or episodic information for which priming can be demonstrated. However, some believe that all forms of priming are impaired [61] and the findings of a meta-analysis have suggested that although amnesics may show preserved priming for information that existed in memory prior to the study that triggered priming, they are impaired at priming for both item and associative information which was novel prior to the studying that triggered priming [25]. It is still not agreed, therefore, whether some or all forms of priming are impaired in amnesics with large lesions and if some forms of priming are impaired, which these are. Furthermore, it is also unclear whether amnesics with more focal lesions (e.g. of the hippocampus) showed preservation of kinds of priming that are impaired in patients with larger lesions (e.g. large parts of the MTL).

The other characteristic of amnesia, the existence of which is disputed, is related to RA. Many believe that memory for episodic as well as semantic information that was acquired longer before the onset of amnesia is less impaired (or even not impaired at all) compared to memories closer to the time of onset (e.g. Ref. [79]). This temporal gradient of RA should be found even in patients with total destruction of specific regions implicated in amnesia (e.g. the entire MTLs). However, this has never been universally believed and Nadel and Moscovitch [56] have recently argued that, in amnesics with large MTL lesions, there is no sparing of older episodic memories. These workers have proposed that, although factual memories, through a process of repetition and rehearsal, eventually cease to depend on the MTLs, but are stored and retrieved through neocortical processes, episodic memories remain dependent on the MTLs for as long as they last. With time and repetition, multiple versions of such memories are stored in a way that depends on increasing numbers of MTL neurons so that partial MTL damage may still impair older episodic memories less. But total MTL lesions should impair remote episodic memories as much as more recent ones. The evidence about whether remoter pre-morbid memories are equally or less impaired is very mixed. However, Teng and Squire [80] have reported that a 70 year old patient with almost total MTL destruction could recall as well as his classmates the routes learned 50 years earlier when he was at school, but was unable to recall the routes repeatedly experienced in his recent past.

It remains unproved whether the presence or absence of a temporal gradient in RA is relevant to the disputed theoretical claim that episodic as well as semantic memories are initially dependent on storage in the MTLs, but that storage transfers gradually to the neocortex. If the RA evidence is relevant to this claim, then transfer must go on for decades, which seems biologically implausible. If transfer exists, it may be more likely that it takes place over a period of weeks or months. If so, its properties may be revealed not by the very long temporal gradients of RA, but by patients who show an unusual form of AA. These patients may perform normally on memory tests for study-test delays that are up to 1 day or more long, but then, over a period of weeks, they show accelerated forgetting until eventually their memory is very impaired (e.g. Kapur et al. [33]). One possibility is that these patients are able to consolidate and initially store in the MTLs certain kinds of association that are relevant for both episodic and semantic memory. However, their brain damage and/or dysfunction prevent the transfer of these associative memories to neuronal assemblies in the posterior neocortex where the remembered information is represented.

Semantic dementia is another disorder, which may be relevant to the question of whether episodic and semantic memory storage transfers to the neocortex provided this process is postulated to occur in a time less than decades long. In this progressive disorder, patients show severe loss of previously very well known semantic memories. But although they cannot interpret new experiences as well as normal people, they initially have surprisingly good memory for personal episodes. However, there is some evidence that this good memory may not persist and that patients become very impaired at remembering episodes which are a year or so old. One possibility is that the term "semantic dementia" is a misnomer and that the patients can initially store facts and personally experienced episodes relatively well. However, they are unable to transfer the associations that are critical for these memories from the MTLs to the anterior temporal neocortex regions, which atrophy in the disorder.

In summary, although amnesia is very probably functionally heterogeneous, this has not been conclusively proved and there is certainly marked disagreement about the precise nature of this heterogeneity. It is critical that this issue is resolved because until then it will be extremely hard to determine *exactly* what memory functions each of the regions and sub-regions that are damaged in amnesics mediate in normal people. The degree and kind of functional heterogeneity in amnesia is also critical to the empirical

clarification of key issues such as what kinds of priming are preserved or impaired, and whether memories are less affected by the lesions that cause amnesia as they become increasingly old and more rehearsed. Clearly many lesions in the neocortex as well as the MTLs, MD, and basal forebrain impair the acquisition of episodic and semantic memories. But how all these regions that subserve these forms of complex memory interact with each other is still only vaguely understood. There is an urgent need to improve this knowledge.

## 3. What has functional neuroimaging revealed about episodic and semantic memory so far?

PET and fMRI have confirmed some of the findings that have emerged from lesion studies about the role of the MTL and PFC in episodic and factual memory (see Ref. [21,47] for reviews). These structures have commonly been found to activate during encoding of verbal and non-verbal kinds of information and also during the retrieval of these kinds of information. Functional neuroimaging has been much less successful at confirming the roles of the MD and basal forebrain in episodic and factual memory (see Ref. [47]). This is probably because only small structures in these regions are activated when memory processes are engaged so the activations usually lie at or just below the resolution of current technology.

Sceptics sometimes ask "What has functional neuroimaging revealed about episodic and semantic memory?" They want to know whether it has revealed anything about how the brain mediates these forms of memory that was not already known from lesion studies. This is a hard question to answer partly because there are no clear criteria for what is to count as significantly new. It is also the case that during the past decade neuroimaging techniques have been developing so the questions initially asked with the techniques were crude, not strongly hypothesis-driven, and often involved little more than attempts to confirm what lesion studies had already strongly suggested. Several relatively novel insights have nevertheless emerged.

First, posterior neocortical regions, which include the left and right parietal cortex as well as the precuneus, are commonly activated when retrieval of studied items, nearly always assessed in terms of recognition, is successful (see Refs. [16,28,51,69]). Furthermore, there is evidence that activation in these regions is greater when subjects correctly recognize studied items relative to when they fail to recognize them [71]. If these regions play a causal role in the successful retrieval of various kinds of factual and episodic memories, then one would expect that focal lesions in the appropriate parts of the parietal neocortex should impair these kinds of explicit memory. Similarly, TMS applied to these regions should slow recognition and/or impair its accuracy if the regions mediate memory processes. These possibilities remain to be tested, but such testing might be facilitated if functional neuroimaging could characterize more precisely what the underlying memory processes mediated by these regions may be. It has been argued that precuneus activations reflect the use of visual imagery during retrieval, a process that should be more intense when studied concrete words, compared to studied abstract words, are recognized [22]. However, left parietal and precuneus activations have also been found in subjects who encoded pictures of complex scenes more successfully into memory (see Ref. [53]). These parietal activations may, therefore, particularly accompany successful encoding as well as successful retrieval.

It is possible that certain kinds of visual (and perhaps other) representations are made when many kinds of information are encoded, and that the making of these representations improves memory for the information when this is later tested. Furthermore, the better the representations are made, the greater will be the activation of the relevant parietal neocortex regions. At retrieval, these representations are reactivated, particularly when retrieval is successful, and when this happens the parietal regions are strongly activated. A related possibility is that regions in the posterior neocortex, such as the precuneus, may actually store as well as represent certain kinds of information. These kinds of information could form the components, associations between which are stored in the MTL and make possible episodic and semantic memory. Whether some local associations are initially stored in the parts of the posterior neocortex in which the corresponding representations are made is an intriguing possibility, which needs to be tested (see Ref. [48]). An alternative possibility is that intra-item associations or associations represented within fairly small neocortical regions are stored within the MTL cortices, such as the perirhinal cortex. Most likely, storage occurs in both sets of sites, but exactly what is initially stored where is still largely unknown.

Second, both encoding and retrieval have been related to a surprisingly large number of activations of different parts of the PFC (see Ref. [21]). The implication is that more PFC regions are implicated in episodic and semantic memory than lesion research has suggested. Activations have been reported in both hemispheres and at ventrolateral PFC, dorsolateral PFC, and frontal polar sites, but it has proved hard to specify to what processes these activations correspond. An early attempt to summarize the pattern of activations was the HERA account [83]. According to this account, episodic encoding processes tend to activate the left PFC more than the right whereas episodic retrieval processes tend to activate right PFC structures more. Subsequent work has indicated that lateralisation of memory-related activations may not depend not so much on whether encoding or retrieval are primarily being engaged, but more on whether verbal or hard-to-verbalize materials are being processed (see Ref. [35]) and whether this processing relates primarily to encoding or retrieval may not matter. Nolde et al. [58] have also argued that

extent of left PFC activations during retrieval probably increases as the executive demands of retrieval increase. For example, Yes/No recognition increases left-sided activation relative to forced choice recognition and the same applies when free recall is compared with cued recall, or when more complex kinds of information, such as the temporal location or source of items, have to be retrieved. Similar studies need to be made to identify the PFC regions that are activated when encoding calls on executive functions to differing degrees.

A host of studies indicate that the PFC is activated during working memory as well as long-term memory tasks, and during non-memory as well as memory tasks (see Ref. [21]). Interpretation of what processes the PFC is mediating, and analysis of what these processes are contributing to long-term memory, can only be achieved by focusing on specific regions as well as the hemisphere in which these regions lie. In a preliminary attempt to do this, Fletcher and Henson [21] have suggested that the ventrolateral PFC is particularly concerned with the updating and maintenance of information, the dorsolateral PFC is particularly concerned with selecting, manipulating and monitoring information that information, and the lateral parts of the frontal pole are concerned with selecting what processes to engage or what sub-goals to try and achieve. Clearly, all these processes are likely to be engaged in both the encoding and retrieval of complex episodic and factual memories, but to differing degrees depending on the precise demands of the memory tasks in which subjects are engaged. It also needs to be determined to what degree activity in these regions (both intra- as well as inter-hemispherically) relates to the kinds of information being processed. Finally, it remains possible that that some PFC regions, such as the orbitofrontal cortex, play a role in memory that is not related to executive function as was considered in the previous section.

Third, event-related fMRI (see Refs. [32,67]) has made it possible to identify whether activations related to encoding that produces successful recognition or recall differ from activations related to encoding that fails to produce later successful explicit memory. The first studies of this kind [8,88] found that activations in the MTL and PFC were greater when encoding led to later recognition of either complex pictures or words. Similar studies had previously shown that, when encoding led to later successful recall as well as recognition, it was associated with enhanced positivity of a relatively late component of subjects' ERPs (e.g. Ref. [62]). These ERP studies suggested that one or more processes, which begin a few 100 ms after new information is presented, lead to better later explicit memory. The precise localization of this or these processes is, however, hard to achieve using scalp recordings alone and ERPs are probably unable to detect signals generated from deep structures such as the MTLs. Localization depends on the use of emission tomography or fMRI. Although event-related fMRI is the only non-invasive technique that can identify accurately the neural correlates of specific memory events, emission tomography can identify whether individual activations correlate with the level of explicit memory shown by subjects. It was indicated above that Montaldi et al. ([53]; and see Ref. [47]) found that individuals, who showed better explicit memory for complex scene pictures, showed greater parietal region activations. These individuals also showed more left medial PFC and MTL activations than individuals with less good memory.

If greater activation in a structure usually indicates that it is working more efficiently, then what processes might be being more efficiently mediated by the structures that are more active when encoding leads to better later explicit memory? There are two obvious broad kinds of possibility. The processes could relate to the representation of rich kinds of information during encoding. When information is processed at encoding it is generally analysed perceptually, interpreted, and related to other information in memory. The richness of what is represented, provided it is stored in long-term memory, determines how well the target information can be later recalled and recognized. PFC regions might be more active because they are mediating executive processes more effectively, and these processes help drive which kinds of information are represented in the posterior neocortex. Posterior neocortical structures may be more active when they are representing specific kinds of information in a more *distinct* manner. The other possibility is that the processes mediate the initial consolidation of some or all of what is represented into long-term memory. Most workers believe that this initial consolidation continues for minutes, hours or even longer. However, the time window of functional neuroimaging lies between a few seconds and perhaps 1 or 2 min (e.g. see Ref. [34]). The intensity with which this process occurs, therefore, should not be possible to visualize directly by current non-invasive imaging procedures. Even though this is probably true, it may nevertheless also be true that the intensity with which the processes underlying consolidation occur is largely determined by what happens within a second or so of the initial representation of encoded information. If so, the level of activation in structures, such as the MTLs, could directly reflect how strongly consolidation processes are engaged, and consequently predict how good later memory will be. It is, of course, possible that activation in some structures reflects not only how distinct is the representation that they are mediating, but also how strongly the representation's consolidation is being triggered.

Fourth, although direct functional neuroimaging comparisons of recall and recognition [12] have so far failed to identify convincingly the distinct, but partially overlapping neural networks, which are likely to underlie these two forms of memory, there has been rather more success in identifying the neural bases of recollection and familiarity [19,28]. The lesion literature has yielded conflicting evidence about the neural bases of recollection, recall, and familiarity. Nevertheless, a strong strand of research

suggests that PFC lesions usually disrupt intentional recall much more than intentional recognition (see Ref. [42]). This is plausible because recall should involve more search processes than does recognition if it is accepted that recognition depends on familiarity as well as the kind of recall, known as recollection [31,40]. Also, the search processes may be of a different kind because recollection always starts with the target or foil information as a cue whereas recall can either be the same or involve cues only loosely associated with the target, e.g. context or related items. There is also conflict in the lesion literature about whether different parts of the MTLs are primarily responsible for familiarity and recollection, and correspondingly for familiarity and recall (e.g. 1, 41). Specifically, it is unclear whether the hippocampus is critical for the mediation of feelings of item familiarity as well as recollection (and, more generally, of recall) or whether it is merely critical for recollection (and, more generally, recall).

Functional neuroimaging, using the remember/know procedure [82], has suggested that the PFC regions activated when subjects successfully recollect or feel that something is familiar are not identical although they overlap. Henson et al. [28] used an event-related fMRI study to show that normal subjects have enhanced activations in left PFC and parietal neocortex sites when studied words are recollected or found to be familiar relative to when unstudied words are correctly rejected. However, recollection of words produced more activation in the left anterior PFC as well as in the left parietal neocortex and posterior cingulate region than did finding words to be familiar. In contrast, when studied words were found to be familiar there was greater activation in the right lateral and medial PFC than when words were recollected. It would be surprising if some PFC regions were directly involved in mediating feelings of familiarity at retrieval whether or not these regions also mediate recollection (recall). However, as the authors suggest, the PFC regions that activate most when subjects find studied words to be familiar may not be concerned with production of feelings of familiarity. Their activation may be related to the extra monitoring of the probably less confident recognition that is found for items that are familiar, but for which confirmatory evidence is not recollected. Without somehow controlling for level of confidence, it is hard to be sure that activations reflect the neural mechanisms that produce the feeling of familiarity itself rather than the monitoring that confirms whether the item truly came from a recently studied list.

Nevertheless, unless future studies that control for differences in confidence show otherwise, it remains possible that there are some PFC regions that are primarily or solely involved in producing recollection and other PFC regions that are primarily or solely involved in producing feelings of familiarity. If correct, this would suggest that the implications of the strong strand of the lesion literature are not entirely correct. The functional neuroimaging findings would suggest that recall should be worse affected than recognition by lesions in PFC regions activated most by recollection. This is because recollection is either a subtype of recall or equivalent to it and because recognition can also be supported by familiarity, which is at least partially mediated by distinct PFC regions. In contrast, recognition should be more disrupted than recall by lesions of those PFC regions that are selectively activated by feelings of familiarity.

The study of Henson and his colleagues did not find that either recollection or familiarity activated the MTLs more than did correctly identifying unstudied words as new. The absence of an MTL effect could be related to a counterbalancing encoding activation that may have occurred incidentally when the new words were presented (see Ref. [74]). However, such an effect could only have been identified if a low-level baseline comparison had been used. Such a low-level baseline was used by Eldridge et al. [19], who have used the remember/know procedure with event-related fMRI to compare the hippocampal activation produced when words are recognized and recollected with that produced when words are recognized, but only found to be familiar. Using a regions of interest approach that was focused on the hippocampus, it was found that recollecting words produced more hippocampal activation than not only the fixation baseline, but also finding words to be familiar, but not recollecting anything about them. More strikingly, Eldridge and her colleagues found that the words that were felt only to be familiar were not associated with any measurable hippocampal activation at all. This study, therefore, seems to be indicating that familiarity does not involve the hippocampus.

Opponents of this view do not have to accept the apparent implication that this study's results are inconsistent with their belief. One reason for this is the difficulty of being sure that there was not a significant level of hippocampal activation associated with encoding that may have occurred incidentally whilst they were fixating. For example, subjects may have engaged in irrelevant thoughts whilst fixating and been able later to remember that they had had these thoughts in the context of the scanner. As already discussed, there is evidence that such encoding activates the MTL and probably the hippocampus (e.g. Ref. [8,89]). If there was such activation, then it could have concealed hippocampal activity that reflected the role of this structure in mediating feelings of word familiarity. Another concern is that the familiarity felt by the subjects was rather weak and that stronger feelings of familiarity might have activated the hippocampus significantly.

Criticisms like these have bedevilled many of the inferences drawn from functional neuroimaging studies that have explored the neural correlates of encoding and retrieval, novelty, priming, and the possible differences between the neural bases of episodic and semantic memories acquired recently or a long time ago. With these studies, therefore, it is even less clear what novel findings that extend beyond what has been learned from lesion studies can be made with

confidence. One controversial claim relates to a possible difference in the neural bases of encoding and retrieval processes. Lepage et al. [37] argued, on the basis of a meta-analysis with PET studies of encoding and retrieval, that encoding activates more anterior regions of the MTLs than does retrieval. But, on the basis of another meta-analysis of fMRI as well as additional PET studies, Schacter and Wagner [75] concluded that encoding activations are not as anterior in the MTL as the analysis of Lepage et al. [37] suggested. They found that fMRI encoding activations were almost exclusively in the posterior MTL whereas some PET encoding activations were found in the posterior MTL and others were found in the anterior MTL.

A major problem with comparing encoding and retrieval activations is that very few studies have compared encoding and retrieval directly in the same subjects so that different effects could be related to irrelevant incidental factors that are not controlled for in such comparisons. One factor that is difficult to match even within studies that directly compare encoding and retrieval is the information being processed during encoding and retrieval. It is not necessarily sufficient to match the kinds of materials that subjects encode or retrieve because subjects may relate these materials to information in their own memory during encoding, and retrieve such associated information during retrieval. So the nominal stimuli may be matched, but the subjectively processed information may not be.

Nevertheless, Schacter et al. [74] have made a careful comparison, using PET, of the encoding and retrieval of drawings of novel three-dimensional shapes. Encoding of both new and previously studied shapes was compared with the attempted recognition of new and studied shapes. Two baseline tasks were also used: passive fixation and passive viewing of shapes (subjects were instructed not to memorize the shapes). Encoding of studied shapes may yield some activation that relates to incidental recognition of the shapes and attempted recognition of new drawings may yield some activation that relates to encoding that is likely to be greater for shapes perceived as novel. So, Schacter and his colleagues placed particular emphasis on the comparison of the encoding of new shapes and the attempted retrieval of old shapes. Relative to the low level baseline conditions, encoding and retrieval whether of new or studied shapes were related to similar activations of the MTL that lay in the more posterior regions. These activational effects were greater when subjects encoded new shapes than when they retrieved studied shapes.

If the MTL stores certain kinds of information at least initially, then there is no reason to expect that putting a given kind of information into long-term storage should involve activity of different neurons than successfully retrieving the *same* information from memory. It is more plausible to argue, however, that different kinds of information may be stored in different stretches of the longitudinal extent of the MTL (and hippocampus in particular). It is known that the perirhinal and parahippocampal cortices receive different neocortical inputs and project to different regions of the longitudinal extent of the hippocampus. Therefore, although these hippocampal regions are interconnected, it is possible that different information is stored in distinct, if overlapping hippocampal regions. If this is so, then encoding and retrieval of different information might explain why encoding and retrieval have sometimes been found to activate different regions of the longitudinal extent of the hippocampus. For example, Dolan and Fletcher [15], in an fMRI study of the neural correlates of the learning of grammatical correct sequences of letters, argued that encoding of novel letter sequences activated the left anterior MTL whereas retrieval of familiar sequences activated the left posterior MTL. However, as Schacter and his colleagues [74] point out, the subjects had to encode the relationships between the individual letters in a string when the string was novel. When it was familiar, such encoding may no longer have been necessary and the string might have been treated as a single item. This interpretation carries the implication that inter-item associations are stored in the anterior end of the MTL whereas item information is stored more posteriorly.

However, there is nothing in the lesion literature to support this suggestion. Furthermore, a study by Small et al. [76] implies that although the encoding into memory of different kinds of information may activate different stretches of the longitudinal extent of the hippocampus, the pattern of activations does not correspond to the pattern proposed by Schacter and his colleagues. Small and his colleagues claimed, on the basis of an fMRI study, that whereas encoding faces individually mainly activated posterior regions of the hippocampus, encoding names individually mainly activated *anterior* regions of the hippocampus, and encoding associations between faces and names did not simply cause a summation of the two kinds of item encoding activation, but activated the *body* of the hippocampus. Interestingly, it was also found that the body of the hippocampus was activated when subjects recalled the name associated with a face when the face acted as a cue. However, the anatomical evidence does not provide strong support for the views of either Schacter or Small and their colleagues. There are reasons for being cautious about the level of precision that can be claimed for the localization of the BOLD response, particularly in the inferior medial temporal regions that include the hippocampus and perirhinal cortex. If different parts of the longitudinal extent of the hippocampus are primarily responsible for storing different kinds of information, then selective lesions of these regions should cause information-specific memory deficits in humans as well as non-human primates.

Novelty-related activations in memory tasks have been extensively explored in functional neuroimaging studies (see Refs. [11,47,84] for reviews) and there is no doubt that novelty is often related to activations in a variety of brain structures, including the MTLs. However, it is still very poorly understood what processes produce these

activations, and under exactly what conditions they occur. When novel information is presented, subjects often consciously detect that the information is novel in some sense (never experienced before, not experienced before in this context, odd in this context). But studies have rarely tried to monitor the extent to which such conscious novelty detection has occurred. If conscious novelty detection occurs, then often some kind of arousal response may be triggered. This may be detected either in terms of autonomic or EEG/ERP responses or behaviourally. This has never been done to our knowledge in neuroimaging studies. In lesion studies, it has been done, but with results that are not entirely clear. On the one hand, in humans, Knight [36] found that MTL lesions, which he described as hippocampal lesions, disrupted the autonomic and ERP correlates of the arousal triggered by the conscious detection of novelty. On the other hand, Parker et al. [63] found that monkeys with fornix lesions (which partially disconnect the hippocampus) showed a normal Von Restorff effect (an improvement of subsequent memory for certain items that are detected as odd in a given context) whereas lesions that disconnected the perirhinal cortex from the PFC disrupted the effect. There is a possible reconciliation of these apparently discrepant results. Honey et al. [30] found that rats with hippocampal lesions responded normally when stimuli were changed, but did not do so when stimuli were rearranged. This suggests that hippocampal lesions may disrupt the alerting response that is triggered by the detection of novel associations (rearranged stimulus combinations), but have no effect on the alerting response that is triggered by the detection of novel items. Perirhinal cortex as well as PFC lesions may disrupt the alerting triggered by the detection of novel items.

The arousal produced by the conscious detection of novelty may improve subsequent memory either because the arousal upregulates consolidation or because it triggers more elaborate and distinctive representations to be made of the novel material, or both. Novelty-related activations may, therefore, be caused by conscious detection of novelty, the arousal that this triggers, and/or the more elaborative encoding that this may produce. All these processes need to be carefully monitored. In an event-related fMRI study, we have found that when novelty of complex scenes was consciously detected, but some care was taken to minimize any arousal response and additional encoding, that activations were *not* found in the MTLs [54]. Indeed, the only activation found was a small one in the parietal neocortex. If our finding is replicable, it suggests that novelty-related MTL activations are produced by the triggering of an arousal response or the extra encoding that often ensues.

Like novelty-related neural responses, the neural responses associated with priming have also been extensively explored with PET and fMRI. Most frequently, relative to novel presentation of items, it has been claimed that priming is related to decreased activation of neocortical regions. Most often, deactivations have been found in the posterior neocortex, particularly with perceptual priming tasks that involve visual stimuli or in PFC regions, particularly with tasks that involve conceptual priming (see Refs. [72,73]). This is consistent with the proposal that priming is a form of memory for complex information in which memory storage changes occur in the neocortical sites where the primed information is represented. The storage changes allow the information to be accessed or re-represented more fluently, but by themselves do not lead to a feeling of familiarity when the primed information is reactivated in this way. Wiggs and Martin [90] have argued, partly on the basis of single unit recording studies in monkeys (see Ref. [9]), that with stimulus repetition, sparser, but more specific, neural representations are created in which fewer neurons are activated, but these neurons form a tighter and more efficient network. Rugg et al. [68] have reported that the ERP to studied visually presented words showed an enhanced positivity between 300 and 500 ms for repeated words relative to novel words that were correctly judged to be novel. This enhanced positivity was the same size in posterior electrode sites for recognized and unrecognised studied words, which suggests that it may relate to behavioural priming. If this is correct, the result is consistent with Wiggs and Martin's view. It is plausible that the greater synchrony of firing of neurons in the posterior neocortex that triggers enhanced positivity could be a direct result of the tighter and sparser neural representation that priming produces, and enables the primed representation to be more efficiently reactivated.

Although plausible, however, the evidence supporting the sparser encoding hypothesis of priming is still weak and indirect. With respect to the cortical deactivations that have often been reported to accompany priming, there may be kinds of priming for which these are not found. In an elegant study, Henson et al. [27] found that although repetition of famous faces and known visual symbols was associated with deactivation in the right fusiform region, activations were found when unknown faces and symbols were repeated and these activations occurred even when the previously unknown stimuli had been repeated several times. Henson and his colleagues suggested that priming of information that already has a representation in memory leads to deactivations whereas, when a completely new memory has to be created activations are found. What this implies in relation to Wiggs and Martin's hypothesis is unclear, but the implications for storage of activations compared to deactivations are presumably different. Van Turennout et al. [86] found both activations and deactivations in a priming task that involved naming of object pictures that were repeated either after a short delay of 30 s or after a long delay of 3 days. Deactivations were found in posterior neocortical regions at both delays. These deactivations were probably related to a perceptual priming effect because they were found with nonsense objects as well as nameable ones. There were also deactivations in the inferior PFC (in Broca's area) and accompanying

activations in the left insular that took 3 days to develop. As these effects were only found for nameable pictures, van Turennout and her colleagues related them to reorganization of the neural systems that represent lexical (and perhaps semantic) information. It is unclear what this study implies about the occurrence of priming activations compared to deactivations. Although the objects depicted and their names were highly familiar, as the authors pointed out, the pictures of them were novel. It could be, therefore, that the account of Henson and his colleagues is too simple and that both activations and deactivations are associated with the priming of previously novel information.

Van Turennout et al. [86] pointed out that some of the changes they observed could have been related to explicit memory processes such as recollection. This is because their study, like most studies of priming, compared the first time stimuli were presented with the second time they were presented. Many priming studies using PET and fMRI have been confounded in this way. Indeed, to our knowledge, no published study has explored priming in an event-related manner so as to control whether priming has occurred behaviourally and also to examine whether primed information has or has not been recognized. The ideal comparison would be between repeated and primed information and repeated, but unprimed information. If recognition is measured, then it becomes possible to determine whether priming in the context of recognition produces different effects from priming in the context of non-recognition. Many regard priming as unintentional retrieval with enhanced fluency, but without recognition or recall. However, the relationship of enhanced fluency to explicit memory remains unresolved. Priming may be: (1) completely unrelated to explicit memory as many believe, (2) it could be directly related to explicit memory in which case stronger priming effects should be found when it is accompanied by explicit memory, or (3) priming accompanied by explicit memory could involve qualitatively different neural processes from priming that is not accompanied by explicit memory.

Donaldson et al. [16] have attempted to explore these ideas in a different way. They compared conceptual priming, using a task in which subjects had to classify words as abstract or concrete as rapidly as possible, and explicit memory, using a task in which subjects had to decide whether such words had been studied or not (i.e. recognition). It has been argued by some that conceptual priming may activate the familiarity process, which is one of the two processes that support item recognition. Donaldson and his colleagues argued that if this was the case, then familiarity should activate not only the structures usually involved in recognition, but should also deactivate the structures usually deactivated by conceptual priming. However, although recognition was associated with the usual activations of structures, such as the lateral parietal and anterior frontal neocortex, it produced no effect of any kind on structures, such as the left temporal neocortex and dorsal inferior frontal gyrus, usually deactivated in conceptual priming. Furthermore, this effect was similar for rapid as well as slower recognition responses. This suggests that even when recognition was rapid and depended primarily on familiarity, no effect was found in the neocortical regions important in conceptual priming. The study is not conclusive however. First, it is extremely hard to be sure that what is retrieved in conceptual (and for that matter perceptual) priming and familiarity-related recognition is the same information even if priming and recognition are of the same stimuli. Second, conceptual priming was found to produce activations in the "recognition network" that were highly similar to those associated with recognition. Although these activations were probably related to incidental recognition of primed words, this needs to be shown directly. Furthermore, as was indicated in the previous paragraph, different structures may be affected depending on whether behavioural priming does or does not occur in the presence of recognition. Indeed, in preliminary work [78], we found that conceptual priming in the absence of recognition was related to more activations as well as deactivations in more brain structures than was priming that occurred in the presence of recognition. A completely convincing refutation of the view that conceptual priming is essential for familiarity-related recognition may, therefore, require the demonstration that such recognition does not modulate *any part* of the neural network that is *critical* for the normal conceptual priming of the *same* information.

One way to circumvent the problem of confounding measures of priming with explicit memory in functional neuroimaging studies is to prevent subjects from having any explicit memory for primed stimuli by presenting them subliminally through the use of a masking procedure prior to scanning. This procedure should mean that subjects are never aware of the repeated stimuli so subjects feel that both repeated and unrepeated stimuli are novel. Two PET studies have used this procedure. In one, Elliot and Dolan [20] reported that repeated Kanji ideograms activated the right parahippocampal cortex less than Kanji ideograms being presented for the first time. In contrast, Beauregard et al. [6] reported the opposite effect for words. They claimed that repeated words activated the right anterior hippocampal area more than words being presented for the first time. Several comments on these interesting studies are warranted. First, contrary to Donaldson et al. [16] and other functional neuroimaging studies of priming (see Refs. [47,72]) these studies suggest that the MTLs are involved in priming both for information that was novel prior to study (ideograms) and information that was familiar prior to study (words). If replicable, it could be argued that these results depend on examining priming when it does not occur in the context of explicit memory, and is also not confounded with explicit memory. Second, however, it could be argued that the MTL effects reflect the fact that subjects not only fail to recognize primed stimuli, but also are not even aware of

primed stimuli at the time of study. In other words, the kind of priming involved is different from the standard kind. The issue can be addressed by determining whether by using a standard priming procedure and examining whether unrecognised primed stimuli produce different MTL effects from unrecognised and unprimed stimuli. Nevertheless, the MTL effects are uncomfortable for those who believe that no kind of priming is disrupted by MTL lesions. Third, perhaps supportive of the notion that a different kind of priming was involved in the two PET studies, the pattern of activation and deactivation reported is the opposite of that suggested by the study of Henson et al. [27] although not necessarily that of van Turennout et al. [86]. This emphasises the need to identify not only the principles which determine whether priming is associated with activations or deactivations in specific structures, but also what these changes imply about the processes that underlie priming. Fourth, confidence in the results cannot be high because behavioural priming, novelty detection, attentional level, and encoding were not controlled or monitored. If such control is to be possible, event-related procedures have to be used. As will be briefly discussed in the next section, confident identification of priming effects may mean that even these control procedures are not sufficient.

There have been several fMRI studies, that have compared the activations associated with the retrieval of more recently acquired and more remotely acquired memories. These studies have usually focused on episodic memory and have had mixed results [13,38,49,50,57,70]. If episodic memories transfer from the MTLs to the neocortex, and the MTLs cease to act as an episodic storage site with the passage of time and with rehearsal, then retrieving remote memories should activate the MTLs less, if at all. Some studies have found this, but others have not. Indeed, Maguire (in press) even found some evidence that retrieving episodic memories activated the MTLs slightly more as the memories became older. This is compatible with the view that, with repetition, storage of episodic memories involves a steadily increasing number of MTL neurons (see Ref. [56]).

One reason why the studies do not agree could be that they have set the values of the factors that determine whether transfer occurs at different levels. For example, the age of recent and remote memories across the studies varies from 1 week to several years for recent memories, a few years to decades for remote memories, and a similar variability probably applies to the amount of repetition and rehearsal that the recent and remote memories have undergone. Another reason why the studies may differ is more worrying. It is that various confounding factors have not been controlled in some or all of the studies. Such confounds could conceal a genuine or create an artefactual reduction in MTL activation when remote, rather than recent, episodic memories are retrieved. What these confounds may be and ways to deal with them will be discussed in the next section.

## 4. Can structural and functional neuroimaging resolve the disagreements arising from the lesion literature? Problems, limitations and hopes

In this section, we will pick three claims concerning episodic and semantic memory about which the lesion literature has so far failed to produce agreement: whether the hippocampus subserves different memory functions from the MTL cortices, and, in particular, the perirhinal cortex; whether some or all kinds of priming (enhanced fluency of processing of studied information) are critically dependent on the MTLs, including the hippocampus; and whether episodic as well as semantic memory storage initially involves the MTLs, but later transfers to the neocortex.

First, some patients with relatively selective hippocampal lesions show clearly impaired item recognition as well as recall [41] whereas others show clearly impaired recall, but item recognition is certainly less impaired and possibly not impaired at all (e.g. Ref. [44]). A plausible interpretation of this difference is that in some of these patients there is a deficit in item familiarity memory as well as recollection whereas in others only recollection is impaired. Unless one believes that the brain is organized in radically different ways in normal people such that, in some, the hippocampus plays a critical role in item familiarity memory whereas, in others, it does not, then there have to be differences between the patients in the nature of the brain disruption or the nature of the adjustments that have been made to damage. Until it is known what these differences are, it will not be possible to identify what role, if any, the hippocampus plays in familiarity memory.

If the patients who show relatively preserved item recognition have re-organized their brains so that non-hippocampal structures have taken over the hippocampus' hypothetically critical role in mediating item familiarity memory, then fMRI studies should have the ability to reveal that such re-organization has occurred. Maguire et al. [39] have reported that patient Jon activated the same brain regions as normal subjects when he recollected specific episodes from his past. However, using structural equation modelling, they have claimed that, during recollection, the effective connectivity between the MTL and other regions was different in Jon from what it was in normal people. Whereas normal people showed increased connectivity between the hippocampus and parahippocampal cortex when they recollected episodes, Jon showed increased connectivity between the hippocampus and retrosplenial cortex, and between the retrosplenial cortex and the medial frontal cortex. As Jon is very impaired at recollection and could only recall very few personal experiences, however, even if these results are reliable, they do not mean that Jon's brain has re-organized his brain functions so as to mediate recollection (and, by implication, item recognition) more efficiently.

It is far more important to know whether Jon has re-organized the brain processes that mediate item familiarity,

particularly because some evidence indicates that this may be preserved. Thus, Duezel et al. [17] have shown that Jon's recognition of studied words was not accompanied by the ERP index of recollection (an increase in the late positive component between 500 and 700 ms), but showed the normal decrease in the N400 effect. This decrease has been linked to item familiarity. Nevertheless, the approach adopted by Maguire and her colleagues is clearly the right one to use in order to identify whether re-organization of either recollection or familiarity has occurred. The study also implies that re-organization could involve altered connectivity patterns between previously involved structures as well as brain structures not previously involved in mediating familiarity or recollection. If fMRI indicates that a patient activates neocortical regions not activated in normal people when items are recognized without being recollected (i.e. found familiar), this does not prove that the activation underlies the patient's preserved familiarity. To do this, TMS could be used to identify not only whether normal activity within a specific neocortical region is critical for familiarity, but also, if it is critical, how long after stimulus presentation it occurs. If fMRI identifies deeper structures that seem to be involved in re-organization, proving that they are critical for a patient's relatively normal item familiarity memory will be much harder. It is extremely unlikely that patients will suffer a second lesion that focally damages such a candidate site. However, item recognition and the ERPs that are associated with relatively preserved recognition (see Ref. [17]) could be recorded in lesioned monkeys. In this way, it may be possible to identify the status of familiarity in monkeys with hippocampal lesions both before and after the site that may be involved in re-organization is lesioned.

No patient with relatively selective hippocampal damage has total destruction of this structure so the continued functioning of the residuum of this structure may be sufficient to mediate relatively normal item recognition. One might expect that the greater is the volume of residual hippocampus, the better will be item recognition in a patient. If this is happening, then the hippocampus should be activated when patients engage in successful recognition. As indicated in the previous paragraph, Maguire et al. [39] have reported that Jon's residual hippocampus (around 50% of the volume of a normal hippocampus for a person of his age) was activated when he recollected personal experiences.

Before discussing the problems with confidently localizing activations to the hippocampus rather than the adjacent MTL cortices, two further important points need to be made. The first is that, given the severity of Jon's recollection impairment, it is far more important to show that his or other similar patients do or do not show hippocampal activations when engaged in successful item recognition that is not accompanied by recollection (perhaps identified through the use of the remember/know procedure). Such recognition must depend on the patients' probably preserved familiarity memory.

The second point is that both in monkeys and in humans there is no evidence that as damage to the hippocampus increases the more impaired item recognition becomes. In fact, there is currently a dispute, concerning the more extensive monkey hippocampal lesion literature, about whether as hippocampal destruction increases item recognition actually improves [4,5,91]. If this does happen, one possible reason is that residual hippocampal tissue is abnormal and projects abnormal signals to neighbouring structures, such as the perirhinal cortex, that are involved in item recognition, Such disruptive signals, which should impair functioning in structures that receive them, are likely to be far greater when there is more residual, but abnormal, hippocampus. If this is happening, then it should be possible to detect abnormal levels of activation in patients with hippocampal lesions and clearly impaired item recognition, when they encode information into memory or engage in subsequent recognition of the encoded information. The negative relationship which Baxter and Murray [4,5] have argued exists between extent of hippocampal damage and item recognition does not take into account precisely which hippocampal regions are damaged and to what extent. Nevertheless, whatever the exact damage is, if patients with clear item recognition deficits show abnormal activations in extra-hippocampal structures, such as the perirhinal cortex, this could underlie their poor performance.

Identification of whether residual hippocampus rather than adjacent MTL cortices is activated in patients with relatively selective hippocampal lesions when they perform tasks that depend on recollection or familiarity requires that current techniques have sufficient spatial resolution and accuracy. This is less certain than often seems to be supposed. The physiological limits of the BOLD response allow a clear distinction to be made between hippocampal and adjacent MTL cortex effects. However, it needs to be remembered that these limits are not currently approached. Limitations of most available MRI systems constrain the sensitivity and resolution of image acquisition. Furthermore, image analysis techniques usually reduce spatial resolution through the use of smoothing procedures, and accuracy of localization of the BOLD signal is reduced by co-registration procedures.

These limitations are further compounded by susceptibility artefact problems in the MTL. Although fMRI has better spatial resolution than PET in most brain regions, there is reduction of the BOLD signal to noise ratio in the MTL region because of susceptible artefacts, which may also cause signals to be wrongly localized. These effects are more marked in anterior and inferior parts of the MTL so that it has proved very difficult to detect activations from the perirhinal cortex with fMRI. Preliminary work by Strange et al. [80] suggests that perirhinal cortex activations may be detected when a procedure that minimizes frontal-occipital wrap-around and possible Nyquist ghosting is

used. Interestingly, Strange and his colleagues found that word encoding which led to better subsequent recall of studied words produced more perirhinal cortex, but not posterior MTL cortex activation, unlike earlier studies [8,89]. However, further work needs to be done to determine whether this difference occurred because the new acquisition procedure truly increases sensitivity in the perirhinal cortex region. An alternative possibility is that appropriate encoding comparisons can be found to activate the perirhinal cortex even when special acquisition procedures are not used. Indeed, in another preliminary study that did not use special procedures, Pihlajamaki et al. [64] have reported that associative encoding of pairs of pictures activated the posterior perirhinal cortex. It remains possible, however, that they would also have found activation in the anterior perirhinal cortex if they had used the procedure of Strange and his colleagues.

Given the theoretical importance of distinguishing between activations in a patient's hippocampus and adjacent MTL cortices, it behoves people to be extremely cautious in making claims even if all currently available precautions have been used to ensure that the BOLD signal has been sensitively and accurately located with maximum spatial resolution. A study by Fransson et al. [23] highlights the need for caution. Fransson and his colleagues examined where in the MTLs encoding of scene-face associations produced activations. There are strong theoretical reasons to believe that such encoding should activate the hippocampus. These experimenters scanned with an in plane resolution of $2 \times 2$ mm and a section thickness of 1 mm to provide excellent spatial resolution and reduce susceptibility artefacts. Analysis involved no spatial smoothing and technical attempts were made to exclude direct vascular flow-related artefacts. When this was done, activation was found in posterior MTL cortex, but not in the hippocampus. Clearly, fMRI work with patients who have relatively selective hippocampal lesions must use the best techniques currently available to localize BOLD signals with the greatest accuracy and precision so that signals emerging from structures lying within millimetres of each other can be more confidently discriminated. These techniques are rarely used because they are time consuming. The hope is that improvements will be made over the next few years, which will make processing faster as well as improving accuracy.

A further possible difference between patients with relatively selective hippocampal lesions is that those with clearly impaired item recognition have extra-hippocampal damage, undetected by conventional structural MRI procedures, that is causing most or all of this memory impairment. An argument against this possibility is that even when some of these patients have come to post-mortem, damage that could clearly have caused their poor item recognition has not been identified (e.g. Refs. [87,92]). However, although post-mortem histological analysis must be the method of choice over contemporary structural MRI because of its superior spatial resolution, it is unknown what kinds of structural impairment may contribute to inefficient functioning of apparently normal structures. Perhaps relatedly, post-mortem analyses have usually failed to measure potentially important tissue characteristics, such as neuronal numbers. Both in vivo and post-mortem analyses need to become more systematic. New developments should help this process. For example, functional neuroimaging may have the potential to reveal whether a small region is working sub-optimally. Small et al. [77] have claimed that an fMRI technique developed to be sensitive to static neuronal function (rather than dynamic, task-related changes) is capable of identifying changes in different hippocampal regions. For example, they reported that the strength of the BOLD response in the subiculum correlated with elderly subjects' performance on a standardized memory test. Structural MRI has, until recently, mainly relied on what skilled neuroradiologists can identify and on manual volumetric measurement of a few structures, such as the hippocampus and amygdala, for which boundary markers can be most easily identified. However, T2 relaxometry, diffusion tensor imaging, and chemical shift imaging may be usable to identify abnormalities in small brain regions that are not detectable with T1 weighted images. Abnormalities in the different receptors of various transmitters could be contributing to dysfunction in regions that appear relatively normal on some or all structural scans, but these abnormalities should become increasingly accessible to improving emission tomographic techniques.

In summary, resolving why memory performance varies so markedly across different patients' with relatively selective hippocampal lesions depends on improvements in structural and functional imaging techniques as well as on accessing sufficient numbers of these rare patients. It also depends on assessing these patients' memory with appropriate memory measures that tap the underlying processes mediated by the hippocampus and/or adjacent MTL cortices. This last point is relevant to the controversial claim that the hippocampus is not critical for the acquisition of semantic memories [87] although it may appear to be so because the initial acquisition of factual memories is facilitated by the storage of the learning episodes in which the facts appeared. Disproof of the claim depends on showing that the hippocampus is necessary for the acquisition of semantic memory even when retrieval of the episode in which it appeared is not used. This condition may be satisfied when hippocampal patients show significantly impaired recall of factual memories that were acquired in a single episode although neither the patients nor their control subjects show any sign of context dependent forgetting. The absence of context dependent forgetting is an indication that the context associated with initial acquisition of the factual memories is not being retrieved to facilitate factual recall. In other words, episodic memory is not being used to facilitate semantic memory. The issue could be explored not only by studying hippocampal patients in this way, but also

by functional neuroimaging of patients and normal people when they show recall of facts, learned in a single context, without showing context-dependent forgetting.

Determining whether certain forms of priming are critically dependent on the MTLs' mediation only requires that structural and functional neuroimaging techniques are pushed to their limits when the aim is to identify which MTL regions are critical. But such specificity is not currently required because it is still not known whether amnesia, and, more specifically, MTL lesions, disrupt any kinds of priming. The process of determination is difficult because many psychological processes need to be controlled in order to identify the neural correlates of priming, i.e. enhanced fluency of processing, not necessarily related to recognition or recall of the primed information, that results from a memory storage change. In the previous section, we argued that the activations produced by behaviourally primed and unprimed stimuli can only be accurately compared when event-related procedures are used. Such procedures ensure that primed and unprimed stimuli can be matched with respect to whether the stimuli are explicitly remembered or not. However, even if primed and unprimed stimuli are unrecognised, interpretative problems still remain.

First, there is a problem with assessing priming and recognition together on a stimulus by stimulus basis because priming measures can be affected by recognition. This problem was illustrated by a study of the behavioural correlates of a priming task in which subjects had to categorize object drawings as representing animate or inanimate things as quickly as possible [65]. Subjects failed to show speeded responses when items were repeated if their speeded judgements were followed shortly afterwards by the judgement that the object picture had been seen a week earlier. However, when speeded judgements were followed by non-recognition of the pictures, priming was still found. The only way to deal with this problem requires that initially only priming judgements about repeated and novel stimuli can be imaged, after which subjects are imaged whilst making recognition judgements about the same stimuli [78]. The recognition judgement made, however, is likely to involve recollection and even "unrecognised" stimuli may be felt to be familiar. Future studies may need to employ more than one procedure to deal with this problem. For example, the procedure of Spencer and his colleagues may be followed in some subjects whereas two other procedures are also used with other subjects. One group can make priming judgements followed by recognition judgements one stimulus at a time. A second group can make priming judgements followed by familiarity judgements one stimulus at a time. These procedures may only allow priming in the context of non-recognition to be examined, but allow experimenters to determine whether different procedures, dependent on different assumptions, yield the same results.

Second, it may be important to know how confident subjects are about their judgements of recognition and non-recognition of stimuli. This is because it might be argued that confidence in these judgements could influence the level of activation of some parts of the MTLs. Confidence could be measured indirectly in terms of how quickly subjects make their judgements or directly, in terms of subjects' confidence ratings in their judgements.

Third, primed stimuli may be associated with less activation of parts of the MTLs because such stimuli are encoded into memory less effectively. There is evidence that this happens at least with some kinds of priming [88]. It is known that encoding which leads to subsequent explicit memory produces more MTL activation than encoding which fails to do this (e.g. Refs. [8,89]). However, this effect could occur either because more information and, particularly more associations, are encoded or because encoded information is better consolidated. The MTLs might be more activated for unprimed versus primed stimuli either because more associative information is represented and/or because the strength of subsequent consolidation is greater when triggered by greater activation of the MTLs at initial encoding. These effects are most likely correlated with, but not *identical* with the enhanced fluency which is priming, although this still needs to be determined convincingly. To show that priming is the cause of activations or deactivations whether in the MTLs or elsewhere in the brain, effects of priming on subsequent memory need to be separated from those of priming itself through the use of appropriate analysis procedures.

There are also several psychological factors that need to be controlled in functional neuroimaging comparisons of recent and remote episodic memory retrieval. Unless these controls are applied, it is impossible to be sure that any differences or similarities relate directly to the question of whether time, repetition and/or rehearsal cause remote memories to cease to depend on the MTLs. There are several confounding factors that need to be controlled if studies are to be interpretable. There is one indirect way of determining whether such factors have confounded the results of a study comparing retrieval of episodic memories that were acquired either recently or remotely. It is universally agreed that successful retrieval of semantic memories that are old and overlearned no longer requires MTL activity. This agreement can be exploited to determine whether such confounds are operating in studies that fail to find that retrieving remote episodic memories activates the MTLs less. All studies should compare retrieval of recent and remote *semantic* as well as episodic memories under as similar conditions as possible (see Ref. [50]). If retrieval of remote semantic memories activates the MTLs as much as retrieval of recent semantic memories, confounds and/or insensitivity of the imaging procedures are concealing a reduction in MTL activity. By analogy, the same thing may be happening with episodic memory retrieval.

At least three factors need to be controlled if comparisons of recent and remote episodic memories are to be interpretable. First, if the detail and richness (perceptual, emotional

etc.) of what is retrieved differs between recent and remote memories, this could explain differences in MTL as well as neocortical activations. These differences would not be related to the age of the memories. This is because such differences should also be present when detailed and rich recent memories are compared with less detailed and rich *recent* memories. There may be a general tendency for memories to become less detailed and rich as they become older, but it is surely not the case that there are no older memories that can be matched to recent memories in these respects. Matching remote and recent memories for detail and richness will require very detailed post-scan debriefing. This will not be easy to do in a convincing fashion. It might be easier to ensure that the remote memories are, if anything, more detailed and richer, than recent memories.

Second, and relatedly, if the retrieval route to older memories is longer and more indirect than the one used for newer memories, this might have effects on which brain structures show activational changes. Most likely, such effects will be be most prominent in the PFC because they are likely to involve differences in the extent to which executive processes are called upon during retrieval. However, it would be more serious if en route to retrieving a target older episodic memory, younger memories of a similar kind were briefly activated. If the retrieval of older episodic memories really does cease to involve or involves less the mediation of the MTLs, then the inclusion of a mixed set of young and old memories when subjects should be retrieving remote memories could prevent this change from being identified. This possible confound can be controlled in several ways, which include recording how long it takes subjects to reactivate old memories and detailed debriefing of the kind necessary to control for the first confound. Selection of strong older episodic memories would also serve to ensure that such memories were rapidly, directly and richly retrieved.

Third, probably the most serious confound that undermines studies comparing the activating effects of retrieving recent and remote episodic memories is that retrieval of factual or episodic memories is accompanied by re-encoding effects. Subjects can later recall what they remembered in the scanner. Indeed, Buckner et al. [10] have shown that the incidental encoding that accompanies retrieval not only leads to subsequent recognition of foil words shown in the recognition task, but that these recognized words produce more left PFC activation than foil words that were subsequently not recognized, just as Wagner et al. [89] found in a standard incidental encoding task. Although it remains to be shown that the incidental encoding which occurs in retrieval activates the MTL more when subsequent memory is better, there is no reason to suppose that this will not occur when the remembered information includes complex episodic associations. The sceptic's argument is that one cannot be sure whether the re-encoding effects for recent and remote memories will be the same. For example, if remote memories are seen as more novel, then perhaps they will be encoded more effectively into memory so that the possibly reduced role of the MTLs in retrieving older memories cannot be detected. Alternatively, remote memories are more rehearsed so they may be re-encoded less well into memory and, as a result, it may be concluded that the MTLs are less involved in retrieval of older memories even if this is not so.

There are two theoretical responses to the problem created by the re-encoding confound. One response implies that the problem does not exist (at least in the MTLs) and the other implies that it is easily soluble provided fMRI has very good spatial resolution. The first response is that, *in the MTLs*, encoding and retrieval are physiologically identical so that the greater the activation produced by retrieval, the better subsequent memory will be for the retrieved information. The second response, based on the views of Lepage et al. [37], is that the MTL regions involved in retrieval and encoding are distinct with encoding producing discernibly anterior activations. Nevertheless, neither of the above responses is appropriate because the information encoded during retrieval includes, but is not identical with, the information that is retrieved. What is encoded and subsequently remembered is a set of associations between some of what has been retrieved and the context of the scanner in which retrieval occurs. Given the good evidence that encoding produces more MTL activation when subsequent memory is better, there may well be a good way of controlling for the encoding confound. At a reasonable delay following the completion of scanning, subjects should be required to recall in detail precisely what they retrieved in the scanner in a way that makes reference to the spatiotemporal and perceptual context (i.e. the specific episode). If the measures are detailed enough, this procedure should provide a means of either matching recent and remote memories or adjusting for the effects of differences in later memory.

Functional neuroimaging of appropriate patients should advance understanding not only of the functions of MTL component structures, but also of the neural bases of priming and recent versus remote memory. Thus, event-related functional neuroimaging studies may clarify why some patients show apparently preserved priming. Amnesics may show apparently preserved priming for several reasons. They may do so simply because the regions damaged in amnesics are not critically involved in priming. They may do so because their brains have undergone re-organization, which enables them to show relatively preserved priming. Or, they may do so because normal people have two routes available to achieve priming only one of which is damaged in amnesics as Curran et al. [14]) have suggested for cross-modal priming. It should be possible to identify which of these possibilities applies with event-related fMRI.

In a similar way, it would be very interesting to use functional neuroimaging to identify the activations shown by amnesic patients with near total MTL lesions, who can still retrieve remote memories relatively normally (e.g. Ref. [81]). These patients cannot be activating residual MTL

tissue because there is effectively none left, but they are retrieving remote memories at close to normal levels. Their performance either proves that storage of these memories no longer depends on the MTLs and can be mediated via a parallel route, which is also available to normal people, or it proves that normal people can only use the MTL route for remote memory retrieval and patients with good retrieval of remote memories have re-organized their brain functions. Which of these possibilities should be resolvable through the use of the appropriate fMRI procedures.

Over the next few years, acquisition of structural and functional images will continue to improve as machines become more powerful and methods get better, different techniques (e.g. fMRI, ERPs and MEG, and TMS) will be used more effectively together, and image analysis procedures (e.g. structural equation modelling) will continue to become more sophisticated. In parallel with these advances in functional imaging, the psychological control procedures used in both lesion and functional imaging studies will become more effective so that theoretically driven questions about the neural bases of memory can be more confidently answered. At present, attempts to resolve theoretical disputes about the neural bases of memory push available technical and analysis capabilities to their limits and sometimes beyond them. There is a need for researchers to be more modest about what they claim to have discovered and to indicate explicitly the technical reasons underlying their modesty. At the same time, it is appropriate for workers to use the best acquisition and analysis techniques to which they have access so as to be able to answer theoretical questions optimally.

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