

Episodic memory retrieval: an (event-related) functional neuroimaging perspective

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1 Introduction

In this chapter we focus on recent studies employing functional imaging methods to investigate human episodic memory retrieval. Episodic retrieval was one of the first aspects of memory to receive systematic study using neuroimaging methods, and has continued to be intensively studied since. Many of these studies have been described in review articles published within the last few years (see Buckner & Koutstaal, 1998; Cabeza & Nyberg, 2000; Desgranges, Baron, & Eustache, 1998; Fletcher, Frith, & Rugg, 1997, for reviews of neuroimaging studies; and see Friedman & Johnson, in press; Rugg, 1995; Rugg & Allan, 1999, for reviews of related electrophysiological work), as have some of the theoretical notions inspired by this research (Rugg & Wilding, 2000; Tulving, Kapur, Craik, Moscovitch, & Houle, 1994a; Wheeler, Stuss, & Tulving, 1997). It is not the goal of the present chapter to re-visit the ground covered by these earlier reviews; instead, we concentrate on recent studies of retrieval that have employed ‘event-related’ neuroimaging methods. We address three principal questions: to what extent are the findings from event-related studies consistent with those obtained using older methodologies? What do the findings tell us about the functional and neural bases of episodic retrieval? What directions should be taken by future research employing these methods?

1.1 Episodic memory

For present purposes, episodic memory retrieval is defined as the cognitive operations necessary to support the explicit (conscious) retrieval of information about recently experienced events and the spatial and temporal contexts in which they occurred. The majority of neuroimaging studies of episodic memory retrieval have been conducted within the ‘verbal learning’ tradition, wherein to-be-remembered items (‘study’ items) are lists of pre-experimentally familiar words. Most studies have employed memory tests that involve the presentation of cues that are in some way related to the studied items. One of the simplest and most popular such tests is ‘yes/no’ recognition memory, when entire items (‘copy cues’) are presented, and the subjects’ task is to judge whether or not each item was presented at study. Other tests employ less informative cues. For example, in word stem cued recall the test items comprise the first three letters of a word (e.g. MOT___), and the task is to decide whether a word fitting the cue was presented at study.

Whatever the retrieval task that is employed, two important considerations arise. The first concerns the need to try to distinguish between ‘pre-‘ and ‘post-‘ retrieval processing (see Rugg & Wilding, 2000, for a detailed discussion of the different kinds of process that might be active during an episodic retrieval task; and see Burgess & Shallice, 1996, for a functional model of retrieval that embodies many of these processes). Pre-retrieval processing refers to those cognitive operations that support an attempt to use a cue to retrieve information from memory. Post-retrieval processing, by contrast, involves cognitive operations that operate on the products of a retrieval attempt; these operations might include, for example, the maintenance in working memory of retrieved information and its evaluation with respect to current behavioural goals. Importantly, the notion of post-retrieval processing is distinct from that of ‘retrieval success’. The latter term refers to the situation wherein a retrieval attempt leads to successful recovery of information about a relevant past episode. Whereas retrieval success may often be sufficient to engage post-retrieval processes, it is unlikely to be necessary. Post-retrieval processing will be engaged to some extent whenever the products of a retrieval attempt must be evaluated prior to a memory judgement, even if the judgement is ultimately negative (signalling a failure to retrieve). The distinction implied here between processes involved in monitoring the outcome of a retrieval attempt and those that operate on the products of successful retrieval appears to be important for the interpretation of some of the findings reviewed in Section 3.0 below.

A second consideration when interpreting findings from functional imaging studies of memory retrieval arises from the argument that few, if any, retrieval tasks are ‘process pure’ (Jacoby & Kelley, 1992). One well known example of process ‘impurity’ is the influence of explicit memory on indirect memory tests intended to assess implicit memory. But as pointed out by Jacoby and his associates (e.g. Jacoby & Kelley, 1992), performance on direct memory tests used to assess explicit memory might also be influenced by more than one kind of memory. For example, correct performance on word stem cued recall can reflect both episodic retrieval and implicit memory (i.e. the same processes that support priming effects on word stems; Jacoby, Toth, & Yonelinas, 1993). Clearly, if a retrieval task engages multiple kinds of memory, interpretation of the resulting imaging data will be far from straightforward. It is therefore unfortunate that the most common retrieval task in neuroimaging studies of episodic memory – recognition memory – is a task on which

performance is almost certainly determined by the contribution of multiple processes (e.g. Yonelinas, 1994). It is possible to design recognition-like retrieval tasks that allow the contributions of episodic and non-episodic memory to be fractionated. For example, memory judgements based on episodic retrieval can be identified by requiring judgements of source rather than simple recognition, or alternatively by requiring recognition judgements to be accompanied by introspective report. Such tasks have been employed in several electrophysiological studies of retrieval (e.g., Rugg, Schloerscheidt, & Mark, 1998b), but they have only recently seen use in studies employing functional neuroimaging methods.

1.2 Neuroimaging: methods and measures

A description of currently available methods for the non-invasive measurement of human brain activity can be found in Rugg (1999). Irrespective of the method employed, an important distinction is that between transient changes in neural activity that follow a specific event such as the presentation of a stimulus (*item-related* activity), and more sustained modulations of activity that accompany engagement in a specific task and are unaffected by the presentation of specific items (*state-related* activity). This distinction is important because it is likely that the two kinds of activity reflect different kinds of cognitive operation (Rugg & Wilding, 2000), and also because it is central to the current debate about the functional significance of many neuroimaging findings regarding episodic retrieval.

Until relatively recently, studies employing functional neuroimaging methods based on the detection of blood flow and oxygenation – the so-called ‘haemodynamic’ methods of positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) – were designed in such a way that item- and state-related brain activity were always confounded. Because of the constraints imposed by PET methodology, PET images of regional cerebral blood flow are integrated over an acquisition period (and a corresponding block of experimental trials) lasting some 40-60 sec., making it impossible to distinguish between item- and state-related activity. The same problem is encountered in so-called ‘blocked’ fMRI designs, when contrasts are performed on data from two or more blocks of trials, each representing an experimental condition. In both of these cases, any differences between experimental conditions in patterns of cerebral activity represent an unknown mixture of item- and state-related effects. Whereas it is possible in principle to design

blocked studies to fractionate these effects, in practice it is difficult if not impossible to demonstrate that the fractionation was successful. For example, in an effort to investigate the item-related neural correlates of successful retrieval of episodic information, researchers have compared mean brain activity during recognition memory judgements made on a blocks of predominantly old vs. predominantly new items (Kapur, Craik, Brown, Houle, & Tulving, 1995; Nyberg et al., 1995; Rugg et al., 1998a; Rugg, Fletcher, Frith, Frackowiak, & Dolan, 1996; Rugg, Fletcher, Frith, Frackowiak, & Dolan, 1997). Although attempts were made to disguise the manipulation of the ratio of old to new items, between-block differences in brain activity cannot be attributed unequivocally to item-related effects. Differences in state-related activity might still have occurred, for example, if subjects adopted different task strategies following a few consecutive presentations of items belonging to the same class.

Historically, methods capable of distinguishing item- and state-related effects unequivocally have been based on electrophysiological rather than haemodynamic measures, notably, scalp-recorded electrical activity (the electroencephalogram or EEG). Electrophysiological methods can be employed in cognitive studies to measure time-locked modulations of the EEG elicited by a particular class of experimental items (e.g. 'new' as opposed to 'old' items in a recognition memory task). The resulting waveforms, known as event-related potentials (ERPs), provide a measure of that component of item-related neural activity that can be detected at the scalp. Within the last three years or so advances in fMRI methodology have led to the development of 'event-related' methods which permit functional images to be obtained in a manner analogous to that employed to record ERPs (Dale & Buckner, 1997; Josephs, Turner, & Friston, 1997; Zarahn, Aguirre, & D' Esposito, 1997). As is the case with ERPs, event-related fMRI allows item-related effects to be identified unequivocally. Whereas fMRI has by far the better spatial resolution, the sluggishness of the haemodynamic response means that the temporal resolution of event-related fMRI signals is on the order of hundreds of milliseconds. This compares unfavourably with the millisecond-level resolution that can be attained with electrophysiological measures. Thus, the two methods provide complementary perspectives on event-related brain activity.

Event-related methods have advantages that go beyond the capacity merely to detect item-related activity. First, the methods make it possible to employ randomised

experimental designs, whereby trials belonging to different experimental conditions are intermixed in an unpredictable sequence. With such designs, effects on item-related measures resulting from the adoption of condition-specific ‘sets’ are eliminated. Furthermore, by comparing the item-related activity elicited in randomised vs. blocked designs, set effects can be identified and characterised. For example, using ERPs, Johnson et al. (1997b) compared the item-related activity elicited by ‘true’ and ‘related lure’ items in a ‘false memory’ paradigm (see Section 3.2) when the two classes of item were randomly intermixed and when they were presented in separate test blocks. Differences in the ERPs elicited by the two kinds of item were found only for the blocked conditions, indicating that such differences were dependent on the adoption of different task sets (and, perhaps, on different patterns of state-related activity, although Johnson et al., 1997b, did not address this issue).

A second benefit of event-related methods, of particular importance for memory studies, is that they permit experimental trials to be allocated to different experimental conditions *post hoc*, on the basis of behavioural performance. Thus, it is possible to compare brain activity elicited by, say, ‘old’ items in a recognition memory test according to whether the items were correctly detected or misclassified as new. The comparison of the patterns of brain activity elicited by items attracting different responses has been a cornerstone of ERP studies of memory retrieval for a considerable time (Rugg, 1995) and, as will become apparent, has already proven to be important in the case of event-related fMRI.

Despite the advantages of event-related designs in studies of memory retrieval, there remain circumstances when such designs are difficult to employ, and blocked procedures are preferable. This will be the case for example when the retrieval task does not involve the presentation of discrete retrieval cues, such as in free recall. More generally, the advantages of event-related over blocked designs will decline as the time-locking between external events and the cognitive operations of interest becomes weaker, and the inter-trial variance in the timing of item-related activity correspondingly greater.

Finally, it is important to note that the employment of event-related designs does not by itself resolve the issue of how to identify and characterise state-related changes in brain activity. It is possible however to design both electrophysiological (Duzel et al., 1999) and fMRI studies (Chawla, Rees, & Friston, 1999; Donaldson, Petersen, Ollinger, &

Buckner, in press) in such a way that item- and state-related activity can be assessed concurrently; as will become clear, there are good reasons why such designs are preferable to those focusing exclusively on event-related activity.

1.3 Interpretation of event-related fMRI data

An important issue in the interpretation of event-related data relates to the nature of the contrasts employed to identify brain regions that are active in different experimental conditions. In our view, the claim that a given brain region is selectively activated by items belonging to a given experimental condition is justified only when the event-related responses elicited by those items differs significantly from the responses elicited by items from another experimental condition. In other words, the finding that items from one condition elicit responses which differ reliably from the inter-stimulus baseline, whereas items from another condition do not, provides insufficient grounds for concluding that the responses elicited by the two conditions are significantly different (requiring, as it does, an acceptance of the null hypothesis).

More generally, it is arguable that ‘raw’ event-related responses – item-related signal changes relative to a inter-stimulus baseline - are difficult, if not impossible, to interpret in the context of studies of higher cognitive processing. This is because the responses reflect a mixture of ‘low-level’ processes common to all tasks, task-specific processes common to all item-classes, and processes specific to the item-class eliciting the response. Unlike, say, the simple case of visual cortex responses to brief visual stimulation against a static background, we cannot be certain what cognitive processes are engaged during the baseline periods between events in typical memory tasks. In the period prior to the presentation of a new item for example, the subject might still be engaged in evaluating the episodic information retrieved in response to the previous old item. To separate these different kinds of item-related activity, it is necessary to contrast directly the responses elicited by the same types of item in different tasks, and by different item-types within the same task. Therefore it is important that event-related fMRI studies are designed so that differential item-related activity can be detected with adequate sensitivity. It turns out that for the kinds of randomised designs favoured in experimental psychology, sensitivity to differential activity is an inverse function of stimulus onset asynchrony (Josephs & Henson, 1999). For this reason, the more recent event-related fMRI studies of episodic retrieval have employed relatively short SOAs (ca. 2– 4 sec). With such short intervals it is not

possible to obtain the ‘raw’ response elicited by each type of item relative to the pre-stimulus baseline. Nonetheless, the form of these responses can be important in constraining the interpretation of differential effects (e.g. whether the effects reflect differences in the amplitude or the latency of the responses elicited by different item-classes; Henson, Price, Rugg, Turner, & Friston, submitted). It has therefore become common for event-related studies to include so-called ‘fixation’ or ‘null’ trials along with other trial types (Buckner et al., 1998a), effectively producing a stochastic distribution of SOAs (Friston, Zarahn, Josephs, Henson, & Dale, 1999), which allows item-related activity relative to baseline to be estimated.

2 Blocked studies of episodic retrieval

In this section, we briefly review what we see as the more important of the findings to have emerged from PET and blocked fMRI studies of episodic retrieval. In these studies, several regions have been consistently reported to be active when subjects engage in an episodic retrieval task relative to a non-episodic control task. Chief among these regions are dorsolateral and anterior prefrontal cortex, and medial and lateral parietal cortex. It is noteworthy that, on the basis of ‘classical’ findings from human and animal neuropsychology, most of these regions would not be regarded as playing a central role in episodic memory.

2.1 Prefrontal cortex

Activation of prefrontal cortex has been reported in the majority of functional neuroimaging studies of episodic retrieval (see Desgranges et al., 1998; Fletcher & Henson, submitted; Nolde, Johnson, & Raye, 1998b, for detailed reviews of these findings). In light of reports from the neuropsychological literature of relatively subtle memory impairments following frontal lesions (Incisa Della Rocchetta & Milner, 1993; Janowsky, Shimamura, Kritchevsky, & Squire, 1989; Stuss et al., 1994) such findings were, perhaps, to be expected. What was not expected however was the finding that retrieval-related frontal activations were often right-lateralised, even when the experimental material was verbal. Thus, right-lateralised prefrontal activation (relative to appropriate control tasks) has been reported for free recall (e.g. Fletcher, Shallice, Frith, Frackowiak, & Dolan, 1998), word-stem cued recall (e.g., Squire et al., 1992), recall of paired associates (e.g., Shallice et al., 1994), and recognition memory (e.g., Nyberg et al., 1995).

The consistency with which right prefrontal activation has been reported in studies of episodic retrieval contrasts with the diversity of views that have been put forward as to its functional significance. One issue that arose early on, and which stills remains to be settled fully, concerns whether retrieval-related activity in the right prefrontal cortex is state- or item-related (cf. Kapur et al., 1995; Nyberg et al., 1995 vs. Rugg et al., 1998a; Rugg et al., 1996). One reason why this debate has continued is that this is an issue which, for the reasons noted in Section 1.2 above, is not easy to resolve within the confines of blocked experimental designs. Thus, the findings from blocked studies leave it uncertain whether the right prefrontal activations reflect task-specific (state-related) effects, item-related effects, or some mixture thereof.

A second issue concerns the extent to which retrieval-related right prefrontal activity can be neuroanatomically and functionally dissociated. It has been suggested, for example, that a distinction should be drawn between the retrieval functions supported by dorsolateral (BA46/9), ventrolateral (BA 47) and anterior (BA10) regions (Fletcher & Henson, submitted; Henson, Shallice, Rugg, Fletcher, & Dolan, in press-a; see also Christoff & Gabrieli, in press). A further anatomical dissociation, in the form of differential lateralization, has been proposed in light of the fact that activation of right prefrontal cortex is accompanied in many studies by activity in one or more left prefrontal regions. Nolde and colleagues (Nolde et al., 1998b) suggested that left prefrontal activity reflects the engagement of what they termed ‘reflective’ retrieval processes, contrasting these with the ‘heuristic’ processes supported by right prefrontal cortex.

2.2 Parietal cortex

Two parietal regions – medial and lateral - have been consistently reported to be active during episodic retrieval. Activation of medial parietal cortex often includes the precuneus (medial BA 7), as reported during retrieval of paired associates (e.g., Shallice et al., 1994), cued recall (e.g., Fletcher et al., 1998) and auditory recognition memory (e.g., Tulving et al., 1994b). Posterior cingulate activations (BA 23/31) have also sometimes been observed (Fletcher et al., 1998; Rugg et al., 1997). The functional significance of these findings is uncertain. There is some evidence from blocked experiments manipulating the relative proportions of old and new items that activation of the precuneus is associated with successful as opposed to unsuccessful retrieval (Kapur et al., 1995; Rugg et al., 1996), and

it has been suggested that the region may support the use of visual imagery during retrieval (Fletcher et al., 1995; but see Buckner, Raichle, Miezin, & Petersen, 1996).

A second region consistently activated during episodic retrieval lies on the lateral surface of the parietal lobe, often more so on the left than the right. These activations include both inferior (and temporoparietal, BA 39/40) and superior (BA7) regions (e.g., Buckner et al., 1996; Cabeza et al., 1997; Tulving et al., 1994b). Like the medial parietal region noted above, there is evidence that lateral parietal activation is associated with successful retrieval (Schacter, Alpert, Savage, Rauch, & Albert, 1996). Unlike medial parietal cortex, however, activation of lateral parietal regions appears to exhibit an element of task specificity, in that it appears to be more prominent during recognition memory than cued recall (Rugg et al., 1998a).

2.3 Medial temporal lobe

The importance of the hippocampus and adjacent regions for episodic memory is demonstrated by the many reports of profound memory impairment in humans and experimental animals following damage to the medial temporal lobe (Squire & Cohen, 1984; Zola-Morgan & Squire, 1990). In a review of medial temporal activations detected by PET, LePage, Habib, & Tulving (1998) proposed that posterior regions of the medial temporal lobe are associated with episodic retrieval (whereas anterior regions were associated with episodic encoding). Comparatively few fMRI studies have activated medial temporal regions during episodic retrieval tasks, though a review of such studies (Schacter & Wagner, 1998; see also Stark and Squire 2000ab) failed to find an anterior-posterior distinction between encoding and retrieval. We return to this issue later.

2.4 Summary

The findings from blocked functional neuroimaging studies have revealed a wealth of data about brain regions active during episodic retrieval, only the most consistently observed of which were noted above. For reasons already discussed, the interpretation of many of these findings is hampered because of the constraints of blocked experimental designs. Thus, it is difficult on the basis of these findings to distinguish between regions activated by mere engagement in a retrieval task (thereby exhibiting state-related activity) from those activated more transiently in response to the presentation of test items (item-related activity), let alone to distinguish between activity associated with different

categories of item or item/response combinations (e.g. hits vs. correct rejections vs. false alarms). The findings do however provide both an indication as to the regions where retrieval-related activations might be expected in event-related studies, and a source of hypotheses about the functional significance of these activations.

3. Event-related studies of episodic retrieval

Most of the studies discussed below employed as a retrieval task a variant of 'yes/no' recognition memory, and were directed towards identification of the neural correlates of retrieval success – that is, patterns of brain activation associated with the retrieval of information from memory. Findings relevant to this issue thus form the bulk of the review. One study, however, may also permit conclusions to be drawn about aspects of 'pre-retrieval' processes – operations carried out on a retrieval cue in service of memory search.

3.1. Processing common to old and new items

According to Rugg & Wilding (2000), the neural correlates of pre-retrieval processes are best investigated by recording item-related activity elicited by retrieval cues corresponding to unstudied items (e.g. 'new' items in a recognition memory test). These authors argued that such cues should be associated with minimal retrieval of information from the study episode, and hence the neural activity they elicit should be correlated primarily with processes subserving retrieval 'attempt' rather than retrieval 'success'. This argument is not entirely convincing however; as noted in Section 1.1, even new items are likely to elicit post-retrieval processing to some extent. It is arguable, however, that effects common to both new and old items are more likely candidates of pre-retrieval processing than are effects that vary according to item type.

Of the three studies (McDermott et al., 1999; Nolde, Johnson, & D' Esposito, 1998a; Ranganath, Johnson, & D' Esposito, in press) that have contrasted responses elicited by items according to the nature of the task in which the items were presented, only one (Ranganath et al., in press) assessed activity separately for cues corresponding to unstudied items. In McDermott et al. (1999) activity elicited by old and new words in a recognition task was contrasted with the activity elicited by words in an intentional encoding task. They reported a number of regions in which activity was greater during retrieval, including lateral and medial parietal cortex, and right anterior and dorsolateral prefrontal cortex. No

reliable differences were found however for the direct contrast between old and new test items, calling into question the power of the study (compromised perhaps by the long SOA of 16.5 seconds; see Section 1.2), and making it difficult to dissociate the between-task findings into those associated with attempted vs. successful retrieval. Similar problems afflict the study by Nolde et al. (1998a), in which retrieval-related activity was contrasted according to whether test items were subjected to a yes/no recognition or a source memory judgement. Three out of the 4 subjects tested showed significantly enhanced activity during the source task in one or more regions of the left prefrontal cortex, leading Nolde et al. (1998a) to argue that the additional 'reflective' retrieval operations required by source judgements were supported by left prefrontal regions (see also Nolde et al., 1998b). Inter-task contrasts were however collapsed across old and new items.

Unlike the two studies just described, Ranganath et al. (in press) elicited event-related responses from test items presented at an SOA (4 sec) more suitable for detecting differences in responses to different item types. Employing a common study task (perceptual judgements about objects), and the same classes of test item (new objects, and old objects presented at a size either larger or smaller than the size at study), two test tasks were contrasted. In the 'general' task, yes/no judgements were required, whereas in the specific task, subjects were required to discriminate between the two classes of studied item (i.e., whether the items were larger or smaller than at study). The inter-task contrast showed a relative increase in signal from left anterior prefrontal cortex (BA 10) for the specific task, an effect that was apparent for both old and new test items. This finding replicates some of the results of a previous blocked study that contrasted source and recognition judgements (Rugg, Fletcher, Chua, & Dolan, 1999), and suggests that left anterior prefrontal cortex supports operations engaged preferentially when the retrieval task requires recovery of a high level of perceptual detail. Ranganath et al. (in press) conjectured that these operations involve some kind of monitoring or evaluative function carried out of the products of retrieval attempts. Equally likely possibilities are that the findings reflect either task-dependent differences in the manner in which the retrieval cues were processed (i.e. differences in retrieval 'orientation', Rugg & Wilding, 2000), or differences due to the relative difficulty levels of the two tasks (i.e. differences in retrieval 'effort', Schacter et al., 1996), consequential upon the fact that specific task was the more difficult of the two.

3.2 Retrieval success

As noted previously, potential neural correlates of retrieval success are isolated by contrasting responses elicited by retrieval cues corresponding to correctly classified studied and unstudied items. In the studies discussed below, the cues have taken the form of old and new items in recognition memory tasks. Key findings from the studies using verbal material reviewed below are summarised in Tables 1 and 2. Note that unless stated otherwise, when describing these findings the designations ‘old’ and ‘new’ refer to items correctly classified as such (i.e. ‘hits’ and ‘correct rejections’).

Whereas old minus new contrasts will reveal activity related to successful retrieval, it is important to note that this activity may be confounded with other effects (Rugg & Wilding, 2000). These potential confounds include differences in response latency or confidence for old vs. new decisions, and the fact that while some cognitive operations may be initiated when a retrieval attempt is successful, other operations, notably those related to memory search, will be terminated. Until all of the effects of these possible confounds have been investigated (for example, by comparing old – new effects as a function of RT, obtaining confidence judgements, and examining responses to recognition misses and false alarms), it should not be taken for granted that differences in the responses elicited by old and new items are necessarily a direct reflection of cognitive operations supporting, or contingent upon, successful episodic retrieval.

The two earliest event-related fMRI studies of recognition memory (Buckner et al., 1998b; Schacter, Buckner, Koutstaal, Dale, & Rosen, 1997) to be described in any detail (see Friston et al., 1998, and Rugg, 1998, for brief descriptions of another early study) were unable to find any reliable differences between responses elicited by correctly classified old and new words. And as noted above, similarly negative findings were reported by McDermott et al. (1999). These null results were surprising given the ease with which robust ‘old/new’ effects can be obtained in recognition memory tasks with ERPs (Rugg, 1995), and almost certainly reflect no more than the lack of power of event-related fMRI studies to detect differential item-related activity when the SOA is long (16 or more seconds in the above cases; see Josephs & Henson, 1999).

In keeping with this conclusion, more recent studies that employed procedures better suited to the detection of inter-item differences have consistently reported differences

in the activity elicited by old and new items. In the study of Ranganath et al. (in press) already described, contrasts between old and new trials showed relatively greater activity for old items in a region of left dorsolateral prefrontal cortex (BA 9), along with a small region demonstrating the opposite effect in the right ventral prefrontal cortex (BA 47). Findings for regions outwith prefrontal cortex were not reported in that study.

In three studies employing simple yes/no recognition, reliable 'old/new' differences were reported in both prefrontal and posterior regions. In Konishi, Wheeler, Donaldson, & Buckner (2000) words were studied in an 'intentional' encoding task, and were subsequently presented at test intermixed with twice as many new items. Greater activity for old items was found in inferior (BA 39/40) and superior (BA 7) lateral parietal cortex bilaterally, in medial (BA 7/31) parietal cortex, in several regions of prefrontal cortex, including bilateral anterior (BA 10) and left ventral/dorsolateral (BA 45/47/46) areas, and in anterior cingulate cortex. A potential difficulty in the interpretation of these findings arises from the relative frequencies of new and old items in the test lists (2:1), which potentially could give the old items something of the quality of task-relevant 'oddball' stimuli. Because such stimuli elicit frontal and parietal activations even in simple tasks which place little or no demand on episodic memory (e.g. Stevens, Skudlarski, Gatenby, & Gore, 2000; Yoshiura et al., 1999) the findings of Konishi et al. (2000) might include effects that are only indirectly related to the memory demands of their task (see Rugg et al., 1996, for an example of a blocked design study of recognition memory that attempted to control for such oddball effects).

A similar problem pertains to the study of Saykin et al. (1999). Subjects were required to listen passively to a series of 48 words, 10 of which had been presented both visually and auditorily prior to scanning. Relative to the novel words, enhanced responses to old items were found in left posterior parahippocampal cortex, a swathe of right premotor and prefrontal regions including dorsolateral prefrontal cortex (BA 9), a large area of right temporal cortex, right anterior cingulate (BA 8/32), and left medial parietal cortex (BA 7). The reverse contrast revealed greater activity for novel words in left anterior hippocampus. As with Konishi et al. (2000) it is difficult to discern the extent to which these effects reflect cognitive operations linked to episodic memory, as opposed to the processing of two classes of item that differ markedly in their *a priori* probability of occurrence.

Donaldson et al. (in press) investigated both item- and state-related activity in a recognition memory task. Subjects studied a series of word pairs, and later performed a yes/no recognition task on single words drawn from the pairs, and an equal number of new items. To allow state-related effects to be identified, the test trials were interrupted approximately every 2 min by a 30 sec 'fixation only' rest period. State-related effects were defined as the difference between activity during the recognition task (after removal of item-related effects) and activity during the inter-block rest periods. Item-related activity was assessed relative to an interstimulus baseline, and in terms of direct contrasts between correctly classified old and new words. The analysis of state-related effects revealed signal changes in a number of regions, some of which overlapped those exhibiting item-related effects. Because Donaldson et al. (in press) did not include a control condition in which words were presented in the context of a task imposing no demands on memory, it is not possible to assess which, if any, of these regions exhibited activity tied specifically to the requirement to engage in recognition memory, rather than to more general aspects of word processing. Nor is it easy to make inferences about regions in which state-related effects were absent. For example, Donaldson et al. found no evidence of state-related activity in right anterior prefrontal cortex. While this could be taken as damaging for the 'retrieval mode' hypothesis of Tulving and colleagues (see section 2.1), it is possible that the absence of cognitive demands during the rest periods meant that subjects did not disengage fully from the task set engendered by the recognition test.

The same problems of interpretation do not exist for the contrast between responses elicited by old and new words. This contrast revealed enhanced activity for old items in several regions, including left anterior prefrontal cortex (BA 10), and medial (BA 18/31) and bilateral (BA 40) parietal cortex (more extensive on the left). These regions agree well with those identified as being sensitive to retrieval success by Konishi et al. (2000).

In two studies, Henson and colleagues (Henson, Rugg, Shallice, & Dolan, in press-b; Henson, Rugg, Shallice, Josephs, & Dolan, 1999b) investigated responses elicited during a recognition memory test when subjects were required not only to judge whether a word was old or new, but also to provide information about the subjective experience accompanying the judgement. In the first of these studies, 60 words were studied incidentally in the context of a lexical decision task. At test, subjects were presented with a list consisting of a mixture of these words and 30 unstudied items (note that this imbalance

between old and new words raises the same potential problem of interpretation as was noted previously for Konishi et al. 2000, albeit in this case with oddball effects working against, rather than with, a finding of greater activation for old than new items. This issue does not arise in the case of the contrasts that were performed between different classes of old item). The task requirement was to signal whether each word was new, whether it was judged old on the basis of recollection of some aspect of the study episode (a 'Remember' response; Gardiner, 1988; Tulving, 1985), or judged old solely on the basis of an acontextual sense of familiarity (a 'Know' response). Contrasts were performed between each class of old word and the new words, as well as between the two classes of old word.

Relative to new words, Remembered old words elicited enhanced activity in left ventral (BA 47) and dorsal (BA9/46) lateral prefrontal cortex, in left lateral inferior and superior parietal cortex (BA 7/40), medial parietal cortex (BA 7) and the posterior cingulate (BA 23/31), a network similar to that identified by Konishi et al. (2000) and Donaldson et al. (in press). (Henson et al. also described a small region of activation in the left posterior medial temporal region, the localization of which was indeterminate and which therefore is not further discussed here). Items assigned a Know judgement elicited greater activity relative to new items in similar left prefrontal regions to those activated by Remembered items, as well as in right ventral (BA 47) and dorsal (BA 46) prefrontal cortex, and anterior cingulate (BA 9/32). Direct contrasts between the two classes of old item revealed relatively greater activity for Remembered items in left dorsal anterior prefrontal (BA 8/9), inferior and superior lateral parietal cortex (BA 40/19) and the posterior cingulate (BA 24), whereas items assigned a Know judgement elicited relatively more activity in right dorsolateral prefrontal (BA 46), anterior cingulate (BA 9/32) and dorsal medial parietal (BA 7) regions (Table 2).

The second of Henson et al.'s studies (Henson et al., in press-b) was motivated by the finding from their first study that right dorsolateral prefrontal cortex was more active for old items accorded a Know judgement than it was for Remembered items. Henson et al. (1999b) proposed that this finding reflected the role of this region in monitoring the products of retrieval attempts. They argued that, if Know judgements are on average based on weaker evidence than are Remember judgements (that is, on evidence nearer to the decision criterion; Donaldson, 1996), relatively more processing would be required in order to assess whether the evidence provided a sufficient basis for an 'old' decision. Henson et

al. (in press-b) reasoned that if this proposal were correct, right dorsolateral activity should be greater when recognition decisions are based on evidence near to the 'old/new' response criterion than when the evidence is well above or below the criterion. They tested this prediction by requiring subjects to perform a recognition memory test in which decision confidence was signalled (sure new, unsure new, unsure old, sure old), predicting that nonconfident decisions would be associated with greater right dorsolateral activity than would confident decisions. This prediction was borne out; the same region responsive to Know judgements in Henson et al. (1999b) was more active when correctly classified items (whether old or new) were assigned a nonconfident than a confident decision.

The study of Henson et al. (in press-b) also provided an opportunity to investigate effects related to retrieval success, although there were insufficient trials available to allow contrasts to be separated according to response confidence. The old minus new contrast revealed greater activity for old items in left lateral (BA 40) and medial (BA 7) parietal regions and the posterior cingulate (BA 23), as well as in left anterior prefrontal cortex (BA 10). In addition, a late-onsetting effect (old > new) was found in right anterior prefrontal cortex (BA 10).

A further study using the Remember/Know procedure was reported by Eldridge, Knowlton, Furmanski, Bookheimer, & Engel (in press). Unlike Henson et al. (1999b), these authors employed a procedure whereby subjects first signalled their old/new decision and then, for old judgements only, made a subsequent Remember/Know decision. Eldridge et al. (in press) argued that in contrast to the procedure adopted by Henson et al. (1999b), when a single, three-choice response was made to each item, the double response method produces a cleaner separation between recognition based on episodic retrieval as opposed to an acontextual sense of familiarity (Hicks & Marsh, 1999). The adoption of the double response procedure carries with it however the disadvantage that while activity associated with Remember and Know judgements can be compared, contrasts between old and new items are confounded by the differential response requirements for the two classes of item. Among the areas reported by Eldridge et al. (in press) to be more active for Remember than Know judgements were left dorsolateral prefrontal cortex (BA 8/9), right inferior prefrontal cortex (BA 6/44), bilateral inferior parietal cortex (BA 40), posterior cingulate cortex (BA 23/31) and, importantly, left hippocampus. The reverse subtraction revealed greater activation in a region of right anterior prefrontal cortex (BA 9/10) and the anterior cingulate

(BA 32). Thus, the findings were in some respects similar to those reported by Henson et al. (1999). Among the more striking differences from the results from that study, however, were the greater hippocampal activation for Remember vs. Know judgements, and, for the reverse contrast, greater activity in a more anterior portion of right prefrontal cortex.

Maratos, Dolan, Morris, Henson, & Rugg (submitted) employed a recognition memory procedure to investigate the neural correlates of the incidental retrieval of emotional context. At study, subjects gave valence ratings to a series of sentences that described emotionally negative, positive, or neutral situations. Immediately after the rating, a word from the sentence was presented on its own with the instruction to remember it for a subsequent test. These words were later presented, along with new items (giving an old/new ratio of 3:1) in a recognition memory test, during which event-related fMRI data were obtained. Of primary interest were the outcomes of contrasts between the responses elicited by the three classes of old item (i.e. items from the three different kinds of study sentences). However, Maratos et al. (submitted) also reported those regions where each of the three possible old vs. new contrasts demonstrated an enhanced response for recognised words. With the exception of the hippocampus, these regions included all of those discussed above, notably, bilateral (but predominantly left-sided) anterior and ventral prefrontal cortex (BA 10 and BA 47), bilateral medial and lateral parietal cortex (BA 7 and BA 40), and posterior cingulate (BA 23).

The final two studies to be discussed also investigated retrieval success effects in recognition memory, but compared these with the effects elicited by 'lure' items likely to elicit 'false recollection' (see Roediger, 1996, and accompanying articles). In McDermott, Jones, Petersen, Lageman, & Roediger (in press), subjects studied compound words such as 'nosebleed' and 'skydive'. At test, yes/no recognition judgements were made on new words, studied words, and new words formed by recombining the component parts of some of the study words (e.g. 'nosedive'). Recombined items attract considerably more false alarms than do new items formed from unstudied words and, it has been proposed (Jones & Jacoby, in press), are rejected as old when they trigger recollection of one or both of the original study words, allowing the sense of familiarity engendered by the items to be successfully 'opposed'. On the basis of this proposal, McDermott et al. (in press) hypothesised that regions sensitive to retrieval success should be more active, relative to unrelated new items, for both recognised old items and correctly rejected recombined items.

Among the regions identified as showing greater activation for truly old items than for new items were bilateral parietal cortex (BA 7/40) and bilateral anterior prefrontal cortex (BA 10). The only region found to be more active for old words than correctly rejected recombined items was bilateral temporoparietal and inferior parietal cortex (BA 39/40). By contrast, regions more active for the correctly rejected recombined items (relative to both old and new items) included bilateral dorsolateral prefrontal cortex (BA 9/46) and medial frontal/anterior cingulate cortex (BA 8/32). These latter findings must be interpreted with caution given that response times were longer for the recombined items than they were for either truly old or new words, raising the possibility that the findings reflect ‘time on task’ effects (the same caution applies to the findings of Henson et al., in press-b, and Henson et al., 1999b, with respect to their Know vs. Remember, and Low vs. High confidence judgements respectively). This caution does not apply however for those regions in which activity was enhanced equally for old and correctly rejected recombined items relative to new items, and indicates that, for these regions at least, the enhanced activity cannot be attributed to such factors as the detection of relatively rare ‘target’ items, or differential processing associated with ‘yes’ vs. ‘no’ responding.

In Cabeza, Rao, Wagner, Mayer, & Schacter (submitted), a different method for eliciting false memories was employed (Deese, 1959; Roediger & McDermott, 1995) and the analyses focused not on the ‘lure’ items that were successfully rejected, but the items that were falsely accepted as old. At study, subjects watched videos that depicted two speakers taking turns to read a list of semantically related words. Test items were presented visually and consisted of new and old words, along with ‘related lure’ items – new words strongly related semantically to study items. Consistent with much previous research, subjects incorrectly classified the great majority of these items as old. Relative to the activity elicited by new items, Cabeza et al. (submitted) reported that a region of the anterior temporal lobe bilaterally, including the hippocampus, was more active for both old and related lure words (the activated region of left hippocampus was within a few millimetres of that reported by Eldridge et al., in press). By contrast, a left posterior parahippocampal region showed enhanced activity for old words relative to the other two item classes, which did not differ. Other areas showing differential item-related activity included bilateral dorsolateral prefrontal cortex (BA 46), where both old and related lure items elicited greater activity than did new words. A similar pattern was observed in

bilateral temporoparietal and inferior parietal cortex (BA 39/40) and precuneus (BA 7/19/31). The left temporoparietal region (BA 39/40) also showed greater activity for old words than related lure words, as did the anterior cingulate (BA 24). Among areas showing relatively greater activity for related lures was a region of orbitofrontal cortex on the right (BA 11).

Cabeza et al. (submitted) interpreted their findings for the medial temporal lobe as evidence for a dissociation between regions subserving the retrieval of ‘semantic’ vs. ‘sensory’ information. They argued that the more anterior, semantic, effects were responsible for the attribution of ‘oldness’ to both lure and truly old items, whereas the posterior effect reflected the recovery of sensory detail specific to the truly old words, which the encoding task had ensured were associated with rich sensory information. As was the case for McDermott et al. (in press), Cabeza et al. (submitted) interpreted their findings for the dorsolateral prefrontal cortex as evidence for the role of this region in the monitoring of retrieved information.

3.3 Summary

As already noted, with the exception of Ranganath et al. (in press), none of the reviewed studies specifically addressed item-related ‘pre-retrieval’ processing. The foregoing review does, however, provide a reasonably consistent picture of regions sensitive to retrieval success during tests of recognition memory and, on the basis of the manipulations employed in the different studies, some useful hints emerge as to the possible functional significance of these effects. Across studies, the regions most consistently reported (i.e. identified in more than half of the studies reviewed) were in left anterior prefrontal cortex, left inferior and superior parietal cortex and precuneus. Less consistently reported (but identified in more than one study) were differential activity in right anterior, left and right dorsolateral and left ventrolateral prefrontal cortex, right inferior and superior parietal cortex, and posterior cingulate. Differential activity in the medial temporal lobe was reported in three studies. Below, we discuss the possible functional significance of these findings.

4. Functional significance of activations

4.1 Prefrontal cortex

The prefrontal region most consistently associated with retrieval success in the foregoing event-related studies was anterior prefrontal cortex (mainly BA 10). In contrast with previous blocked designs, these anterior prefrontal effects were observed more often on the left than on the right. Dorsolateral prefrontal activations (BA 9/46) - both left- and right-sided - were also sometimes detected. Interestingly a recent meta-analysis of PET studies of recognition memory (Lepage, Ghaffar, Nyberg, & Tulving, 2000) identified both of these left prefrontal regions as being sensitive to the probability of successful retrieval.

The results reviewed here offer some clues as to nature of the processes supported by left prefrontal cortex during episodic retrieval. In the case of left anterior cortex, the finding of Henson et al. (1999b) that this region was more active for recognised items accorded Remember rather than Know judgements is consistent with a role in the processing of retrieved information with a relatively high level of episodic content. A similar conclusion can be drawn from the finding of McDermott et al. (in press) that left anterior prefrontal cortex was activated both by recognised old items, and by correctly rejected 'related lures' (items which, it is assumed, elicited recollection of the study episode). Just what the nature of this processing might be is unclear, although findings suggesting that left anterior prefrontal activity elicited by unstudied items is enhanced when the retrieval task requires a judgement of source, rather than mere recognition (Ranganath et al., in press; see also Nolde et al., 1998a; Rugg et al., 1999) may turn out to be an important clue.

As already noted, the question of whether activation of right anterior prefrontal cortex during episodic retrieval reflects state- or item-related processing has been debated for several years (Kapur et al., 1995; Nyberg et al., 1995 vs. Rugg et al., 1998a; Rugg et al., 1996 - see also Nyberg et al., 2000). According to Tulving and colleagues, the functional role of right prefrontal cortex is to support 'retrieval mode', a mental state in which environmental events are treated as retrieval cues, and retrieved episodic memories are experienced 'autonoetically' (Tulving, 1983; Wheeler et al., 1997). From this viewpoint, right prefrontal activity should be state- rather than item-related and, critically, should not vary according to whether a retrieval attempt is successful or unsuccessful. An alternative viewpoint, bolstered by evidence from both neuroimaging (e.g., Rugg et al., 1996) and electrophysiological studies (e.g. Wilding & Rugg, 1996), posits that right prefrontal activity is both item-related and associated specifically with retrieval success.

The findings from the event-related recognition studies reviewed above do not clearly distinguish these two positions; while the studies permit an assessment of whether right-prefrontal cortex exhibits item-related activity, to date no study has satisfactorily addressed the question of whether this region also demonstrates task-dependent state-related activity. Three of the studies (Henson et al., in press-b; Konishi et al., 2000; McDermott et al., in press) reported item-related right anterior prefrontal activation associated with retrieval success. The failure of other studies to observe this result could have arisen for a number of reasons. With regard to the conduct of future studies, arguably the most important of these reasons is the evidence suggesting that right anterior prefrontal cortex may exhibit atypical event-related responses, particularly with respect to onset latency. Buckner et al. (1998b) and Schacter et al. (1997) for example reported a relatively delayed response in this region, and Henson et al. (in press-b) were only able to detect differential right anterior responses to old and new words when the data were modelled with a response function that was delayed by 3s relative to a standard, or 'canonical', function. (Henson et al. proffered this result as an explanation for the failure to find right anterior prefrontal activation in their previous study, Henson et al., 1999b, when the data were modelled with a canonical response function only). It is unclear why this region should exhibit an atypical response function. The function could be a reflection of the dynamics of the underlying neural activity, consistent with the relatively late onset and prolonged time course of the 'right frontal' ERP old/new effect (Rugg & Allan, 1999). Alternatively, delayed right anterior frontal activity might merely reflect a peculiarity of vascular responses in this brain region, such that the interval between a change in neural activity and its reflection in the BOLD signal is delayed relative to other brain areas (Buckner et al., 1998b; Schacter et al., 1997). This latter explanation seems unlikely, however; it seems improbable that vascular properties of cortical regions would be laterally asymmetric, and yet the majority of the event-related studies reviewed here, regardless of the analysis method employed, were able to detect differential item-related activity in left anterior prefrontal cortex.

The other prefrontal region activated in some of the event-related studies reviewed above is dorsolateral prefrontal cortex. In most of these studies, dorsolateral prefrontal activation was detected during tasks with demands that exceeded those of simple recognition (Table 2) - whether by virtue of the requirement to make an introspective

judgement about the recognition decision (Eldridge et al., in press; Henson et al., in press-b; Henson et al., 1999b), or to discriminate between ‘true’ and ‘false’ recollections (McDermott et al., in press; Cabeza et al., sub). Thus, in keeping with the findings for the analogous right frontal ERP old/new effect (see for review Rugg and Allan 1999), it may be that differential activation of this region is more likely to be found when the retrieval task requires post-retrieval demands additional to those imposed by simple recognition judgements. As suggested previously (Fletcher et al., 1998; Henson, Shallice, & Dolan, 1999a), these demands may include the engagement of monitoring processes that operate on the products of retrieval. This suggestion perhaps receives its most direct support from the aforementioned studies of false recollection when, as with tasks involving source memory, the mere ‘success’ of a retrieval attempt does not in itself permit accurate responding.

In keeping with previous proposals (Fletcher & Henson, submitted; Henson et al., in press-a), the findings discussed above add weight to the view that dorsolateral and anterior prefrontal regions play different roles in the processing of retrieved information. Support for this proposal comes from the findings of Henson et al. (in press-a) and McDermott et al. (in press). As already noted, the former authors found greater dorsolateral activation for low versus high confidence judgements, whether the word was old or new. They found a different pattern of findings for anterior prefrontal cortex however, where activity was greater for old than new items. McDermott et al. (in press) found greater dorsolateral and anterior activation for old versus new items. They found in addition, however, that the dorsolateral, but not anterior, region was more active still for correctly rejected ‘recombined’ items versus truly old items. Taken together, these findings suggest two different kinds of post-retrieval processing. One kind of processing – supported by dorsolateral prefrontal cortex - operates on the products of a retrieval attempt regardless of the amount or the nature of the information retrieved. A second kind of processing – associated with anterior cortex – appears to be engaged only when a retrieval attempt culminates in the successful recovery of episodic information (i.e. recollection). It should be noted however that the data of Eldridge et al. (in press) complicate this picture somewhat. In contrast to Henson et al. (1999b), these authors reported greater activity in right anterior (rather than dorsolateral) prefrontal cortex for Know relative to Remember judgements, albeit in a region more superior than that identified by Henson et al. (in press-

b) and McDermott et al. (in press) as sensitive to retrieval success. As the precise functional boundary between dorsolateral and anterior prefrontal cortex is uncertain the extent to which the findings of Eldridge et al. (in press) conflict with previous results is not clear.

As already alluded to, the idea that right prefrontal cortex plays a role in post-retrieval processing receives support from findings from ERP studies, in which correctly classified old items have been found to elicit a late-onsetting, sustained positive wave focused over the right frontal scalp (Rugg & Allan, 1999). The ERP 'right frontal old/new effect' is often more prominent when elicited by items attracting high relative to low levels of recollection (as indexed, for example, by successful vs. unsuccessful retrieval of source information; Wilding & Rugg, 1996), and has been interpreted as reflecting the maintenance and further processing of retrieved episodic information. Such a proposal would be consistent with the role envisaged above for the right anterior prefrontal cortex based upon event-related fMRI findings. Recently, however, prominent right frontal ERP effects have been reported for old items associated with little or no recollection and likely recognised with low confidence (Rugg, Allan, & Birch, 2000). This result is more in keeping with the findings reported by Henson et al. (in press-b) for right dorsolateral cortex. Thus it is possible that the right frontal ERP effect may reflect activity in disparate, functionally heterogeneous regions of prefrontal cortex and, therefore, act as a rather 'impure' index of post-retrieval processing.

Some of the left prefrontal regions identified in the foregoing review as being sensitive to retrieval success have been associated previously with encoding rather than retrieval (Tulving et al., 1994a). The ventrolateral region in particular has been linked with semantic and phonological processing (see Poldrack et al., 1998, for a review), and has received considerable attention as a region supporting effective episodic encoding of verbal material (e.g., Kapur et al., 1994; Shallice et al., 1994). One speculative possibility is that activation of left ventrolateral and adjacent prefrontal regions during retrieval reflects the consequences of successful cue processing. By this argument, only test items that receive a sufficiently full semantic analysis can act as effective retrieval cues. Thus, left frontal activation reflects a form of 'pre-retrieval' processing that is 'predictive' of subsequent retrieval success in a manner analogous to that reported for these regions in event-related studies of encoding (Henson et al., 1999b; Wagner et al., 1998, see Wagner, Koutstaal, & Schacter, 1999, for a review). Another possibility is that successful episodic retrieval

reflects recapitulation of semantic processing performed at the time of study (Blaxton et al., 1996; Rugg et al., 1997).

The finding of increased left ventrolateral prefrontal activity for old versus new items during recognition memory stands in contrast to findings from studies employing indirect memory tasks such as semantic decision, when left ventrolateral activity is *lower* for old items (Demb et al., 1995; Wagner, Desmond, Demb, Glover, & Gabrieli, 1997; Wagner, Maril, & Schacter, submitted). This effect has been linked to ‘conceptual priming’, and held to reflect reduced demands placed on semantic processing by repeated items. Thus, to the extent that the left prefrontal effects identified in studies using direct (recognition) and indirect (priming) memory tasks occur in the same regions, it follows that the relative activity levels for old and new words must vary according to task. One possibility is that the adoption of ‘retrieval mode’ during direct memory tests (Tulving, 1983) alters the pattern of left prefrontal activity associated with processing old and new words, causing the former rather than the latter class of items to elicit the greater activity. Alternatively, it may be that the nature of the processing accorded words during recognition tasks differs sufficiently from that during study to eliminate any benefit (and any concomitant reduction in associated neural activity) arising from the words’ repetition (c.f. Demb et al., 1995). By this account, under conditions of high inter-task transfer, recognition-related increases in left ventrolateral activity may be offset by the neural correlates of the ensuing conceptual priming effects.

With regard to the foregoing issue it is noteworthy that it has been reported that left ventrolateral prefrontal activity elicited by new words ‘studied’ in the context of a recognition memory test is predictive of subsequent memory on a second, surprise recognition test (Buckner, Wheeler, & Sheridan, in press). It would be of considerable interest to know whether the left ventrolateral activity elicited during the surprise test by these items, when they were successfully recognised, was higher or lower than the activity elicited by the new words in the test.

4.2 Parietal cortex

In the majority of studies reviewed, lateral and medial parietal cortex were found to exhibit greater activity for items eliciting successful relative to unsuccessful retrieval, regardless of the exact form of the retrieval task. In most of the studies, the lateral parietal

activations were lateralised to, or more extensive, on the left, and more likely to be in inferior (BA 40) than superior (BA 7) parietal gyri. The findings are consistent with a number of previous studies in which retrieval success was investigated with blocked designs and, broadly speaking, with two meta-analyses of studies employing such designs (Habib & LePage, 1999; Lepage et al., 2000). There seems little reason therefore to doubt that activity in these regions is a correlate of successful recognition. The findings of Henson et al. (1999b) and Eldridge et al. (in press) that left lateral parietal activity was greater for items accorded Remember rather than Know responses suggest that activity in this region may be a function of the amount of episodic information retrieved in response to the test item.

The findings for these parietal regions are reminiscent of a memory-related ERP effect – the so-called ‘left parietal’ old/new effect. This effect takes the form of a positive shift in ERPs elicited by correctly classified old items relative to waveforms elicited by new items. The effect onsets around 400-500 msec post-stimulus, is maximal over the left parietal scalp and, on the basis of its sensitivity to a wide variety of experimental variables, has been interpreted as a neural correlate of episodic retrieval or ‘recollection’ (Rugg & Allan, 1999). Notably, as is the case for the parietal activations described in the foregoing event-related fMRI studies, the left parietal ERP effect is larger for items accorded Remember rather than Know judgements (Duzel, Yonelinas, Mangun, Heinze, & Tulving, 1997; Smith, 1993) and, in false memory paradigms, is elicited both by truly old items and semantically related ‘lures’ (Duzel et al., 1997; Johnson, Kounios, & Nolde, 1997a). It has been proposed that the left parietal ERP effect reflects cortical activity supporting the hippocampally mediated ‘reactivation’ or ‘reinstatement’ of retrieved information (Rugg et al., 1998b). An alternative possibility, arguably more compatible with the role posited for parietal cortex in attention (Kastner & Ungerleider, 2000), is that the effect reflects some kind of attentional shift or orienting triggered by successful episodic retrieval. It is perhaps relevant in this context that attentional orienting in time has also been reported to be associated with predominantly left-lateralised parietal activation (Coull, Frith, Buchel, & Nobre, 2000).

On the basis of the studies reviewed here, the functional role of medial parietal cortex in memory would appear to be similar to that proposed for lateral parietal cortex. In the reviewed studies, posterior medial activations related to retrieval success were found in

both the precuneus (BA 7/19) and the posterior cingulate (BA 23/31). There was little evidence however to suggest that activity in these two medial regions could be dissociated from one another, or from activity in lateral cortex, although other studies have demonstrated task-based dissociations between these regions (Rugg et al., 1998a; Shallice et al., 1994). Shallice et al. (1994), for example, found posterior cingulate activations associated with episodic encoding, whereas activation of the precuneus was observed at retrieval. The only hint of a dissociation in the crop of event-related studies reviewed here came from Henson et al. (1999b), who identified a region in the precuneus where activity was greater for Know than Remember judgements, in contrast to posterior cingulate and lateral parietal regions where Remember judgements were associated with the greater levels of activity.

As already noted, a frequently cited role for the medial parietal cortex is in the support of visual imagery (Fletcher et al., 1995; but see Buckner et al., 1996). According to this argument, activation of this region during successful retrieval reflects the strong demands placed on visual imagery by the representation of episodic information. While plausible, there is currently little direct evidence to support this proposal (though see Wheeler, Petersen, & Buckner, in press). Finally, it should be noted that there is currently no reason why medial parietal cortex is any less likely to contribute to ERP old/new effects than are lateral and inferior parietal regions.

4.3 Medial temporal lobe

In contrast to the findings for frontal and parietal regions, only three of the studies reviewed here reported retrieval-related activation in the hippocampus or adjacent medial temporal cortex. Indeed, if the findings of Saykin et al. (1999) are discounted on the grounds that the study confounded memory retrieval and oddball effects, the only studies to find hippocampal activation were those of Cabeza et al. (submitted) and Eldridge et al. (in press). These findings were obtained for test items likely to have elicited strong episodic recollection. Thus, they are consistent with the proposal that retrieval-related hippocampal activity is associated specifically with this form of memory (Rugg et al., 1997; Schacter et al., 1996) and, more generally, with the view that the hippocampus proper forms part of a circuit specialised for episodic memory rather than memory based on non-episodic information such as item familiarity (e.g., Aggleton & Brown, 1998). These findings lend weight to the possibility that the failure to find hippocampal activation in other studies of

yes/no recognition reflects the fact that, as noted in Section 1.1, this task is ‘process impure’; specifically, old/new decisions can be made on the basis of an acontextual sense of familiarity in the absence of the (putatively hippocampally mediated) retrieval of a study episode (Aggleton & Brown, 1998; Yonelinas, 1994). This possibility seems unlikely however to account fully for the inconsistent findings noted above for the medial temporal lobe. First, two other studies (Henson et al., 1999b; McDermott et al., in press) also employed procedures that permitted responses to items eliciting episodic recollection to be contrasted with responses to new items, but in neither case was differential hippocampal activity reported. Second, it has been suggested that item familiarity, the ‘non-recollective’ basis for recognition, depends upon perirhinal cortex, a medial temporal region which lies ventral and anterior to the hippocampus (Aggleton & Brown, 1998). Thus, to the extent that recognition judgements are based upon familiarity rather than episodic recollection (as is thought to be the case for items accorded ‘Know’ judgements, for example), one might expect to see retrieval related activation in anterior medial temporal cortex. We are however unaware of any report of such a finding.

The reasons why event-related medial temporal activations cannot be consistently detected during episodic retrieval therefore remain unclear. One possibility is that this inconsistency reflects a limitation of the fMRI method, the sensitivity for which is compromised in regions, such as the anterior medial temporal lobe, which are prone to susceptibility artefact (though see Constable et al., 2000). Another possibility is that the null findings are a consequence of the neural dynamics of the hippocampus (such that retrieval-related neural activity does not generally give rise to changes in metabolic demand on a spatial scale large enough to be detected by current methods). Finally, the lack of positive findings may be a sign that the contribution of the medial temporal lobe to retrieval is often overshadowed by encoding-related activity. By this argument (Rugg et al. 1997; but see Gabrieli, Brewer, Desmond, & Glover, 1997), the failure to find differential activity for contrasts between responses to old and new items reflects the fact that medial temporal structures are active both in support of retrieval of old information, and encoding of the new information carried by contextually novel items (but see Stark and Squire, 2000ab).

5 Future research

It is clear that event-related fMRI has made important contributions to the study of the neural correlates of memory retrieval within a remarkably short time. It is equally clear

however that much remains to be done. Most pressing of all perhaps is the need to extend the event-related method to tasks other than those based around recognition memory. There are good grounds for thinking that some of the neural correlates of episodic memory retrieval are task-dependent (Allan, Dolan, Fletcher, & Rugg, 2000; Rugg & Allan, 1999; Rugg et al., 1998a), and it is important that hypotheses formulated on the basis of the existing, rather narrow data set are challenged by findings from a much wider range of tasks. It is also likely that tasks other than recognition memory may reveal functional dissociations additional to those reported to date (a good candidate for such a dissociation being medial vs. lateral/inferior parietal cortex).

A second issue that needs to be addressed concerns the relationship between item- and state-related activity. A promising start has been made in this regard (Donaldson et al., in press), and there is no reason why it should not be possible to identify regions exhibiting one or the other form of activity in the same study. It will then be possible to address such important questions as whether the prefrontal regions held to support tonically maintained states such as retrieval mode are dissociable from regions that exhibit item-related activity, questions that cannot be addressed on the basis of present findings.

A third point concerns the relationship between 'pre-' and 'post-' retrieval processes. The majority of current event-related fMRI studies have been concerned with retrieval success (comparing responses elicited by correctly classified old and new words), revealing prefrontal activations most likely associated with post-retrieval processing. It will be interesting to dissociate these activations from those produced by differences in task- or item-related effects associated with new items alone, for which episodic retrieval is minimal. This will allow investigation of so-called 'retrieval orientation' effects (Rugg & Wilding, 2000).

A final issue concerns the need to clarify the findings relating to retrieval success, for example by controlling more carefully for potential confounds, such as those associated with oddball effects and differences in the effort or difficulty of responding to old versus new words. It will also prove informative to investigate the patterns of neural activity associated with retrieval of different types of material (e.g. words vs. pictures), and different kinds of study processing (e.g. 'deep' versus 'shallow' study). Such studies will permit a delineation of the network of brain regions associated with episodic retrieval in

general, as opposed to other regions in which retrieval-related activity is dependent on the nature of the stored information.

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Table 1. Activation peaks by gross anatomical region and X,Y,Z Talairach coordinates (Talairach & Tournoux, 1988) for verbal retrieval success effects (old Vs new) in Section 3.2. Prefrontal regions: Anterior = anterior to definition of inferior frontal sulcus ($Y > +40$); Dorsal (lateral) = within and above inferior frontal sulcus; Ventral (lateral) = below inferior frontal sulcus. Parietal: Inferior = Lateral inferior parietal / superior temporal; Superior = superior parietal. Post Cing = Posterior Cingulate. For Henson et al. (1999b), old words confined to correct R judgements; for McDermott et al. (in press), hits and correct rejections of 'recombined' lures contrasted against correct rejections of new words; for Cabeza et al. (submitted), hits and false alarms to lures contrasted against correct rejections. L = left; R = right. BA = approximate Brodmann Area.

<i>Prefrontal</i>	L Anterior (BA 9/10)	L Dorsal (BA 9/46)	L Ventral (BA 45/47)	R Anterior (BA 9/10)	R Dorsal (BA 9/46)	R Ventral (BA 45/47)
Konishi et al.	-31 +51 +8	-41 +13 +26	-45 +27 +16	+33 +51 +12		
Donaldson et al.	-40 +51 +6					
Saykin et al.					+54 +14 +32	
Henson et al. (b)	-12 +63 +18	-54 +24 +33	-48 +39 -12			
Henson et al. (a)	-21 +63 +21			+48 +48 -12		
Maratos et al.	-20 +60 +12		-52 +30 -10			+38 +34 -10
McDermott et al.	-37 +53 +10			+35 +51 +4	+45 +23 +30	
Cabeza et al.	-39 +49 +8				+38 +38 +6	
<i>Parietal</i>	L Inferior (BA 39/40)	L Superior (BA 7)	Precuneus (BA 7/19)	Post Cing (BA 23/31)	R Inferior (BA 39/40)	R Superior (BA 7)
Konishi et al.	-39 -55 +36	-29 -69 +44	-7 -73 +34	-5 -39 +34	+33 -53 +44	
Donaldson et al.	-40 -51 +39	-34 -66 +42	-1 -63 +27		+49 -45 +48	+34 -63 +45
Saykin et al.			-14 -76 +44			
Henson et al. (b)	-51 -45 +39	-33 -60 +45	-6 -75 +42	-6 -24 +27		
Henson et al. (a)		-48 -57 +48	0 -69 +33	+3 -42 +21		
Maratos et al.	-42 -58 +26	-36 -62 +56	-6 -58 +36	+4 -54 +18		+34 -68 +40
McDermott et al.	-37 -51 +36				+35 -55 +42	+41 -57 +48
Cabeza et al.	-47 -50 +38		+12 -48 +37		+40 -51 +22	

Table 2. Activation peaks by gross anatomical region and X,Y,Z Talairach coordinates (Talairach & Tournoux, 1988) for other effects in Section 3.2. For Henson et al. (1999b) and Eldridge et al. (in press): Rem = correct Remember responses; Kno = correct Know responses. For Henson et al. (1999a): Low = low confidence responses; Hig = High confidence responses. For McDermott et al. (in press): Rec = recombined lures, correctly rejected; Hit = old words correctly recognised. For Cabeza et al. (submitted): Fal = False alarms to semantic lures; Tru = old words correctly recognised. See Table 2 legend for more details.

<i>Prefrontal</i>	L Anterior (BA 9/10)	L Dorsal (BA 9/46)	L Ventral (BA45/47)	R Anterior (BA 10/11)	R Dorsal (BA 9/46)	R Ventral (BA 45/47)
Henson (b) (Rem – Kno)	-21 +54 +39					
Henson (b) (Kno – Rem)					+51 +30 +27	
Henson (a) (Low – Hig)		-39 +21 +24			+54 +30 +24	
Eldridge (Rem – Kno)		-30 +32 +45				+55 +7 +25
Eldridge (Kno – Rem)				+23 +52 +25		
McDermott (Rec – Hit)		-49 +31 +24	-45 +37 +8		+45 +23 +30	
Cabeza (Fal – Tru)				+16 +53 -19		
<i>Parietal</i>	L Inferior (BA 39/40)	L Superior (BA 7)	Precuneus (BA 7/19)	Post Cing (BA 23/31)	R Inferior (BA 39/40)	R Superior (BA 7)
Henson (b) (Rem – Kno)	-57 -51 +39	-42 -72 +39		0 -30 +36		
Henson (b) (Kno – Rem)			-12 -60 +57			
Eldridge (Rem – Kno)	-43 -56 +40			+13 -23 +45	+53 -58 +35	
McDermott (Hits – Rec)	-59 -61 +24				+47 -49 +30	
Cabeza (Tru – Fal)	-53 -55 +32					