

The neural basis of episodic memory: evidence from functional neuroimaging

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We review some of our recent research using functional neuroimaging to investigate neural activity supporting the encoding and retrieval of episodic memories, that is, memories for unique events. Findings from studies of encoding indicate that, at the cortical level, the regions responsible for the effective encoding of a stimulus event as an episodic memory include some of the regions that are also engaged to process the event 'online'. Thus, it appears that there is no single cortical site or circuit responsible for episodic encoding. The results of retrieval studies indicate that successful recollection of episodic information is associated with activation of lateral parietal cortex, along with more variable patterns of activity in dorsolateral and anterior prefrontal cortex. Whereas parietal regions may play a part in the representation of retrieved information, prefrontal areas appear to support processes that act on the products of retrieval to align behaviour with the demands of the retrieval task.

Keywords: encoding; event-related potential; familiarity; functional magnetic resonance imaging; recollection; retrieval

1. EPISODIC MEMORY

We use the term 'episodic memory' to refer to the set of cognitive processes that support the ability consciously to recollect unique events and the context in which they occurred (for a recent review, see Baddeley *et al.* (2001)). The processes include ones that are engaged when an event is experienced and that lead to the formation of a new memory representation (encoding processes), and others that support the recollection of the event at some later time (retrieval processes). In the experiments reported here, the events are discrete experimental stimuli, usually words. These items were presented to volunteers in a 'study phase', usually in the context of a specific task that constrains the nature of the processing engaged by each item. Memory for the items was tested in a subsequent 'test phase' with a 'direct' memory test, such as yes–no recognition.

In the following sections, we describe findings from some of our recent studies in which brain activity was non-invasively measured in healthy volunteers as they performed tasks that engage episodic encoding and retrieval. It is important to note that while such studies in principle permit a distinction to be made between neural systems supporting encoding and retrieval—a distinction that is hard to draw on the basis of lesion data alone (Fletcher *et al.* 1997)—this does not mean that these two 'stages' of memory should be regarded as being independent of one

another. As was pointed out by Tulving *et al.* (1994), among others, in as much as an event is interpreted in terms of its meaning, its encoding is intimately associated with retrieval of information, albeit from 'semantic' rather than episodic memory. The retrieval of episodic information or, indeed, the mere presentation of a stimulus that triggers a retrieval attempt (a 'retrieval cue'), are events that may themselves be subject to episodic encoding (cf. Moscovitch & Nadel 1998). It should also be kept in mind that episodic memories can be elicited by a variety of tests that employ a range of different kinds of retrieval cue (e.g. 'copy' cues in tests of recognition memory, 'partial' cues in cued recall). There are no grounds for assuming *a priori* that the neural correlates of either encoding or retrieval are independent of how memory is tested. Thus, it is an empirical question which of the findings obtained with one kind of memory test generalize to other kinds.

2. FUNCTIONAL NEUROIMAGING METHODS

A description and comparison of methods for the non-invasive measurement of human brain activity can be found in Rugg (1999). The methods can broadly be divided into those based on haemodynamic measures, notably PET and fMRI, and those that detect neural activity through the measurement of time-varying scalp electrical (EEG) or magnetic (MEG) fields. The signals detected by both classes of method appear predominantly to reflect—directly in the case of electrophysiological measures, indirectly in the case of haemodynamic methods—the aggregated post-synaptic activity of relatively large populations of neurons (Wood 1987; Logothetis *et al.* 2001;

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see also Logothetis 2002). Whereas the resulting measures of stimulus- and task-related neural activity are considerably coarser than those yielded by single-neuron studies, they can be obtained concurrently from the entire brain. Thus, neuroimaging methods can identify the set of functionally specialized neuronal populations that are active during a given cognitive task, allowing a 'systems-level' analysis of the neural correlates of task engagement. On the negative side, however, the methods provide little information about the precise form of the neural activity, and hence the local neural computations, that take place within these populations to give rise to the detected signal. Such information remains the province of invasive studies and can be obtained only very rarely in humans (see Heit *et al.* (1990) and Cameron *et al.* (2001) for examples relevant to memory).

In the studies described in §§ 3 and 4, neural correlates of memory processing were obtained using both electrophysiological (EEG) and haemodynamic measures (fMRI). In each case, activity was obtained using an 'event-related' approach, which permits characterization of the neural activity elicited in response to the presentation of individual experimental stimuli. Whereas event-related methods have been employed with EEG recordings for more than 30 years (Donchin & Lindsley (1969); so-called ERPs), only within the last five years have analogous methods been developed for fMRI (Dale & Buckner 1997; Josephs *et al.* 1997; Zarahn *et al.* 1997). Using the event-related approach, it is possible to measure and contrast the time-locked modulations of neural activity elicited by different classes of experimental items, even when these classes are defined *post hoc* on the basis of the subject's behavioural responses. This makes it possible to investigate, at the level of the single item, differences in brain activity associated with successful versus unsuccessful memory performance (e.g. 'hits' versus 'misses' in a recognition memory task). Whereas fMRI has far better spatial resolution than the ERP method, the sluggishness of the haemodynamic response means that the temporal resolution of event-related fMRI signals is typically of the order of hundreds of milliseconds. This compares unfavourably with the millisecond-level resolution that can be attained with ERPs. Thus, the two methods provide complementary perspectives on event-related brain activity.

3. STUDIES OF ENCODING

In a series of recent studies, we have investigated the neural correlates of episodic encoding by studying what have become known as 'subsequent memory effects' (see Rugg (1995) and Wagner *et al.* (1999) for reviews of early work). In the subsequent memory procedure (see figure 1), event-related activity elicited by a series of study items is contrasted according to whether the items were remembered or forgotten on a subsequent memory test, the assumption being that differences in activity that 'predict' successful versus unsuccessful memory reflect the differential engagement of processes supporting effective encoding. Clearly, there are circumstances when this assumption is likely to be invalid, or when any such differences would convey only trivial information about memory encoding. For example, if subjects attended to only

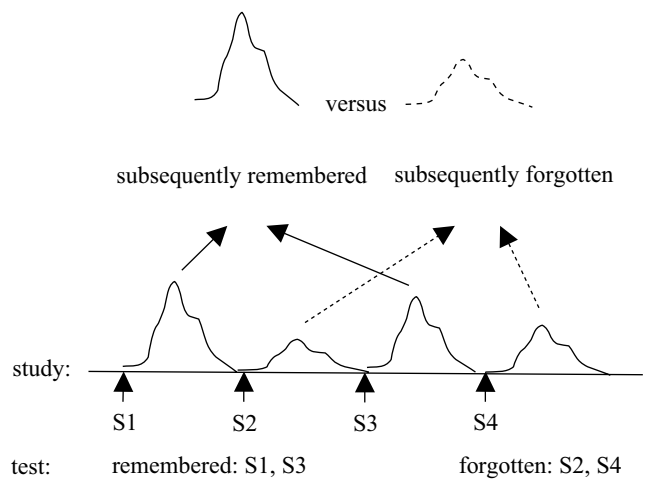


Figure 1. The subsequent memory paradigm. The experiment is split into a 'study' and a 'test' phase. During the study phase, neural activity is recorded while volunteers are presented with a series of items. Later, their memory for the items is tested. The neural activity elicited by each item at study is then sorted according to whether the item was remembered or forgotten on the subsequent memory test. The differences between the neural activity elicited by subsequently remembered and subsequently forgotten items are taken as putative neural correlates of memory encoding.

some study items while ignoring others, there would be a strong correlation between the engagement of attentional processes and subsequent memory performance. Thus, the resulting subsequent memory effects would largely reflect differences in neural activity related to differential allocation of attention rather than to differences connected more directly to memory encoding. To anticipate, such confounds are unlikely to exist in the experiments described in § 3a. In each case, 'online' measures of performance were obtained during the study tasks. Trials on which errors were committed were eliminated from the analysis and, across the experiments, we observed no consistent differences in reaction time for study items that were subsequently remembered as opposed to those that were forgotten. Thus, the subsequent memory effects that we observed in brain activity were unlikely to have been confounded by factors contributing to the general efficiency with which study items were processed.

(a) *Semantic versus non-semantic encoding*

Our first fMRI study (Otten *et al.* 2001) took as its starting point previous findings indicating that the left inferior prefrontal cortex plays a key part in the episodic encoding of verbal material. These findings came from 'blocked' PET and fMRI studies in which activity was obtained while subjects engaged in tasks that were known *a priori* to produce differences in subsequent memory (e.g. semantic versus non-semantic processing (Kapur *et al.* 1994; Demb *et al.* 1995; Wagner *et al.* 1998); full versus divided attention (Shallice *et al.* 1994); intentional memorizing versus passive reading (Kapur *et al.* 1996; Kelley *et al.* 1998)), as well as from previous event-related fMRI studies using the subsequent memory procedure (Wagner *et al.* 1998). Together with other results pointing to a role for the left prefrontal cortex in semantic processing (Poldrack *et al.* 1999), these findings were taken as evidence that acti-

vation of the left prefrontal cortex during successful encoding reflects its role in meaning-based processing; the greater the engagement of this region, the greater the semantic processing accorded a study item and hence the greater the probability of successful subsequent retrieval (Tulving *et al.* 1994; Gabrieli *et al.* 1998; Wagner *et al.* 1998, 1999; Buckner *et al.* 1999).

The first aim of our experiment was to investigate the relationship between the regions exhibiting a subsequent memory effect for semantically studied words, and regions where activity was greater for study items subjected to semantic rather than non-semantic processing. If the subsequent memory effects exclusively reflect modulation of semantic processing, they should be found only in regions also sensitive to the semantic versus non-semantic contrast.

The second aim of the experiment was to investigate whether the pattern of subsequent memory effects found for semantically encoded items extends to effects elicited by items encoded non-semantically. For example, is the left prefrontal region generically involved in the episodic encoding of verbal material, as was suggested following early neuroimaging results (Tulving *et al.* 1994), or does the participation of this region in encoding depend upon the explicit engagement of semantic processing?

We addressed these issues by scanning volunteers while they performed two randomly interleaved study tasks, only one of which necessitated semantic processing. Items comprised visually presented words. These were preceded by one of two possible cues that signalled whether the upcoming word required an animacy (does the word refer to a living or nonliving entity?) or an alphabetical (are the first and last letters in alphabetical order?) judgement. About 15 min later, recognition memory for all of the study items, now intermixed with a set of unstudied words, was tested with a four-choice procedure (confident old, non-confident old, confident new, non-confident new). Study items were defined as 'remembered' if they were confidently judged to be old and forgotten if they were either incorrectly judged to be new or judged old with low confidence (nonconfident old judgements were about as likely for unstudied words as they were for studied words, indicating that these judgements mainly reflected guessing).

Figure 2a illustrates where subsequent memory effects were found for items subjected to animacy judgements. The regions include both ventral (BA 47) and dorsal (BA 9/44 and 45) regions of the inferior frontal gyrus bilaterally, albeit more strongly on the left, a medial superior prefrontal region (not illustrated) and left anterior and posterior hippocampal formation. Figure 2b shows which of these effects remained after 'masking' with the outcome of the between-task contrast so as to leave only those voxels in which task (animacy > alphabetic) and subsequent memory effects coexisted. It can be seen that only in the left ventral prefrontal cortex and left anterior hippocampal formation did task and subsequent memory effects overlap. Figure 2c shows that subsequent memory effects for the alphabetical task were found in two regions, left ventral prefrontal cortex and left anterior hippocampal formation, both of which also exhibited subsequent memory effects in the semantic task.

These findings have two principal implications. First, whereas some of the regions exhibiting subsequent mem-

Table 1. Proportions of trials given a 'sure old' judgement in the recognition memory tests of Otten *et al.* (2001) and Otten & Rugg (2001a).

(Values are across-volunteer means (s.d.). The semantic decision task consisted of animacy judgements in both experiments. The non-semantic decision task consisted of alphabetical judgements in Otten *et al.* (2001) and syllable judgements in Otten & Rugg (2001a).)

word type	experiment	
	Otten <i>et al.</i> (2001)	Otten & Rugg (2001a)
old		
semantic study task	0.58 (0.19)	0.59 (0.15)
non-semantic study task	0.29 (0.15)	0.37 (0.14)
new	0.10 (0.07)	0.07 (0.06)

ory effects in the animacy task overlapped with those sensitive to the semantic versus non-semantic contrast, several other regions did not. Activity in these latter regions may, therefore, support processes unrelated to semantic processing that nonetheless facilitate subsequent memory. Second, the findings offer no support for the idea that the neural circuitry supporting effective episodic encoding is task sensitive: subsequent memory effects in the alphabetical task were found exclusively in a subset of the regions exhibiting these effects in the animacy task (cf. Baker *et al.* 2001).

We discuss the functional significance of these findings in § 3d, after describing the results of three further experiments that took this initial study as their starting point. The first of these (Otten & Rugg 2001a) was motivated by concerns that the failure to find evidence of qualitatively different subsequent memory effects in the two study tasks might have been a consequence of the non-semantic task that we elected to employ. As would be expected for such a 'shallow' task (Craik & Lockhart 1972), relatively few items were subsequently recognized (see table 1). The low level of recognition performance for the alphabetical task ($p_{\text{Hit}} - p_{\text{FalseAlarm}}$ for confident recognition responses was 0.19, compared with 0.48 for the animacy task) raises the possibility that the subsequent memory contrast lacked power because of the relatively small number of items contributing to the 'Remembered' category. Another possibility is that the processing needed to perform the alphabetical task may have led to the formation of episodic memory representations that were so weak as to be unable to support subsequent recognition memory judgements. By this possibility, the only alphabetically encoded words to be given a correct recognition judgement were those that also received incidental semantic processing. As a consequence, the neural correlates of episodic encoding in the alphabetical task were a weak reflection of those seen for the animacy task.

In light of these possibilities, we repeated our original experiment (with some minor procedural modifications) using a different non-semantic task: syllable judgement. This task, which required subjects to judge whether the number of syllables in a word was odd or even, places heavy demands on phonological processing and yielded somewhat better subsequent memory performance than

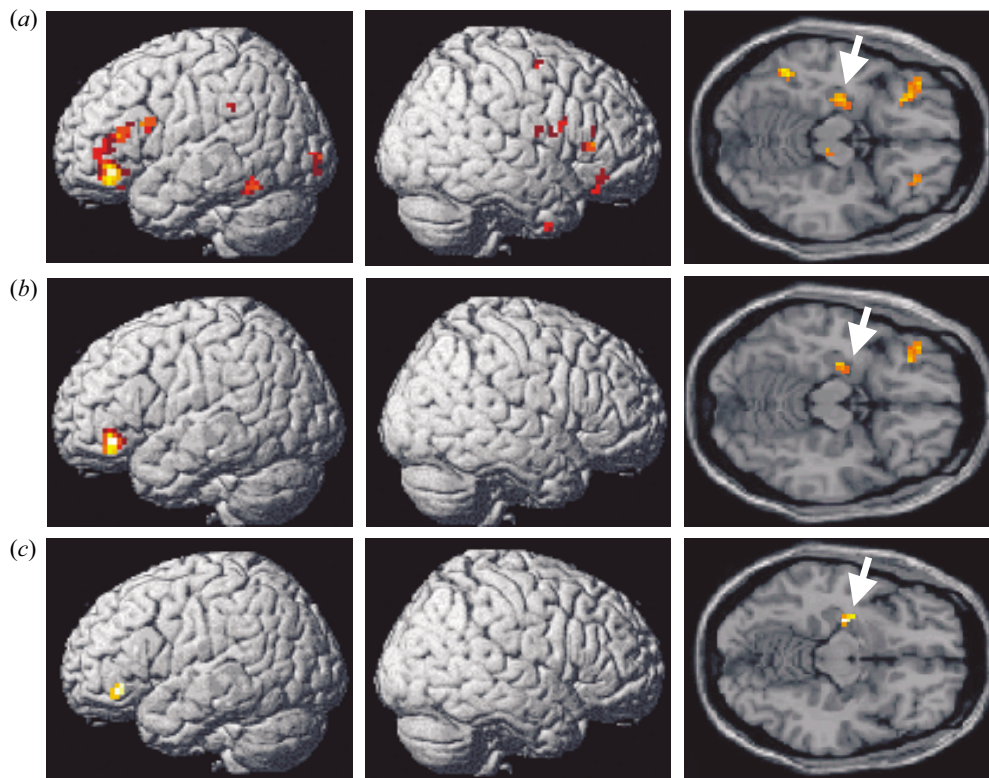


Figure 2. Data from Otten *et al.* (2001). (a) Regions showing significant ($p < 0.001$) fMRI signal increases for subsequently remembered versus subsequently forgotten words from the animacy task. Subsequent memory effects can be seen in the prefrontal cortex bilaterally and in two regions of the left hippocampal formation. (b) Subsequent memory effects in the animacy task, masked by the regions that showed significant signal increases for the animacy versus alphabetical contrast (both contrasts thresholded at $p < 0.001$). Overlap between subsequent memory and task effects was found in the left ventral prefrontal cortex and the left anterior hippocampus. (c) Regions showing subsequent memory effects for words studied in the alphabetical task. The effects are evident in the left ventral prefrontal cortex and the left anterior hippocampus. All results in this and subsequent figures are rendered onto the Montreal Neurological Institute reference brain. The arrows denote the left anterior hippocampus. The colour of activated voxels (red \rightarrow yellow) indicates the level of statistical significance beyond the threshold.

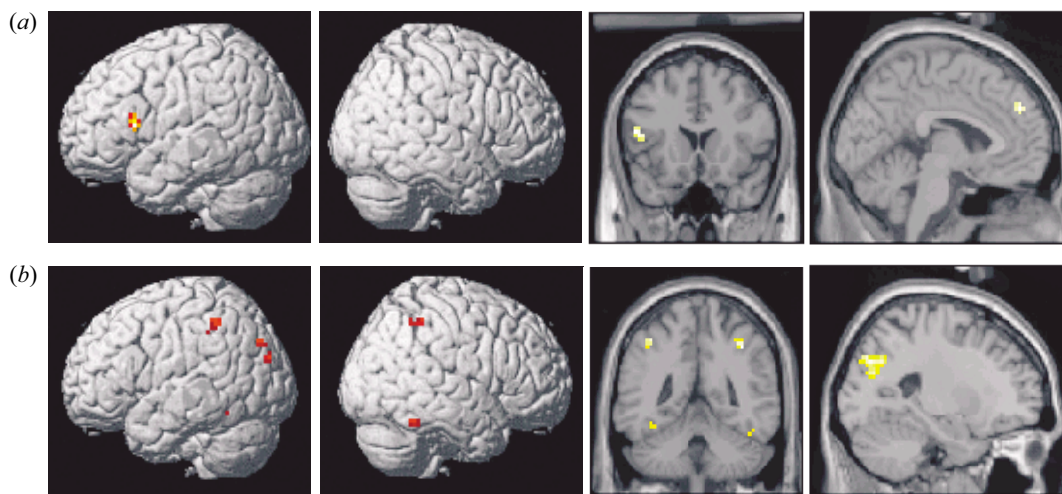


Figure 3. Regions showing significant ($p < 0.001$) subsequent memory effects in Otten & Rugg (2001a). (a) Subsequent memory effects in the animacy task were found in the left inferior and medial frontal regions. (b) Subsequent memory effects in the syllable task were found in the bilateral intraparietal sulcus, the bilateral fusiform gyrus and the left superior occipital gyrus.

did the alphabetical task employed previously (see table 1). $p_{\text{Hit}} - p_{\text{FalseAlarm}}$ for confident responses was 0.29 as opposed to 0.19 in the previous study. By contrast, scores for the animacy task were very similar across the two

experiments (0.51 versus 0.48 for the present and previous experiments, respectively).

The subsequent memory effects for the animacy judgement task are shown in figure 3a. At our standard statisti-

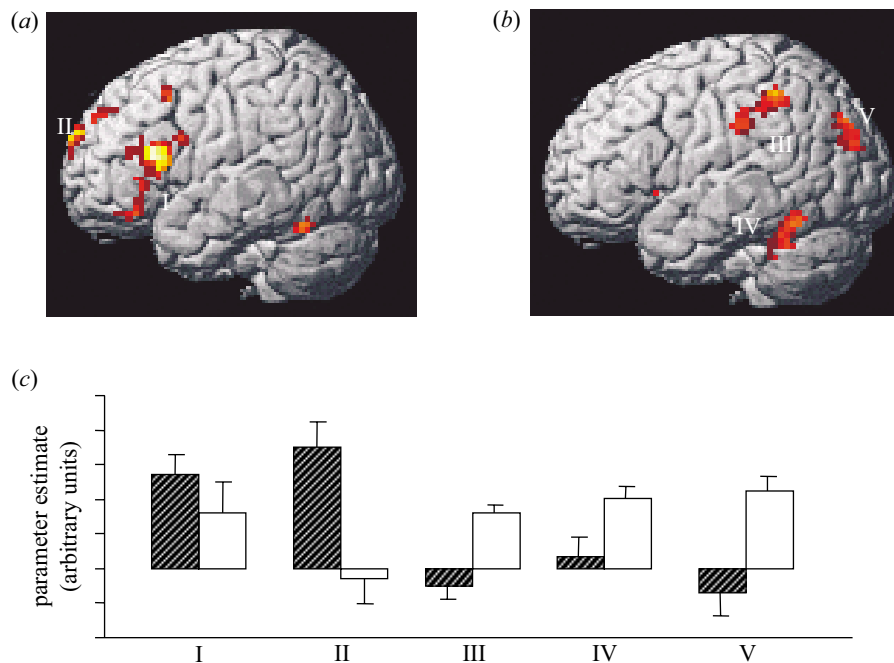


Figure 4. Comparison of the subsequent memory effects in the (a) animacy and (b) syllable study tasks of Otten & Rugg (2001a). The effects are illustrated at a significance threshold of $p < 0.01$. (c) The parameter estimates for subsequent memory effects in the animacy and alphabetical tasks are depicted for the voxels showing the peak effect in (I) the left inferior frontal gyrus, (II) the medial frontal gyrus, (III) the intraparietal sulcus, (IV) the fusiform gyrus, and (V) the left superior occipital gyrus. For regions III and IV, the parameter estimates were averaged across homotopic voxels in each hemisphere. The bars show the standard error of the mean. Significant region by task interactions were found for the subsequent memory effects in all but the left frontal region. Hatched bars, animacy task; open bars, syllable task.

cal threshold ($p < 0.001$), these effects were more limited in their spatial extent than was the case in our first experiment and were observed solely in the medial prefrontal cortex and in the dorsal part of the left inferior frontal gyrus. With the employment of a more liberal threshold (figure 4a), the effects more closely approximated those observed previously, although there remained no sign of any effects in the vicinity of the hippocampus. Figures 3b and 4b illustrate the findings for the syllable judgement task. In striking contrast to the animacy task, subsequent memory effects failed to achieve statistical significance in any part of the left prefrontal cortex, even at the relatively liberal threshold of $p < 0.01$. Robust effects were found, however, in bilateral parietal and fusiform regions and in the left occipital cortex. The same parietal regions were also revealed in an inter-task contrast that identified where activity was greater for items subjected to syllable rather than animacy judgements, indicating that these regions support processes engaged selectively by the syllable task. The most important implication of these findings, however, is that they indicate that subsequent memory effects can differ in their localization according to the nature of the processing engaged during study.

(b) *Electrophysiological subsequent memory effects*

A second follow-up to our original experiment employed ERPs rather than fMRI as a measure of item-related brain activity (Otten & Rugg 2001b). As in the original experiment, subsequent memory effects were contrasted according to whether study words had been subjected to animacy or alphabetical judgements. The study

was motivated by two considerations. First, whereas subsequent memory effects in ERPs have been described since the late 1970s (Chapman *et al.* 1978; Sanquist *et al.* 1980; see Rugg 1995 and Wagner *et al.* 1999 for reviews), little data existed regarding the sensitivity of these effects to the manipulations of the study task along the lines described above (e.g. Paller *et al.* 1987). Second, the fMRI findings give little insight into the time course of encoding-related brain activity, a question for which the ERP method is well suited.

Some of the findings from this experiment are shown in figure 5. As shown in figure 5a, the ERP subsequent memory effect for semantically studied items took the form of a sustained increase in positivity for remembered words, consistent with numerous previous findings (Rugg 1995; Wagner *et al.* 1999). The scalp distribution of this effect (figure 5b) showed a tendency to evolve with time, from an initial quite focal maximum over the left frontal scalp to a more posterior distribution later on. Figure 5c shows the subsequent memory effect for the alphabetical task. In marked contrast to that for animacy judgements, the effect takes the form of greater *negativity* for subsequently remembered items, the distribution of which remained fairly stable over time (figure 5d).

Two main conclusions emerge from these results. First, and most starkly, the conclusion drawn on the basis of our fMRI findings about the qualitative similarity of the subsequent memory effects obtained in the animacy and alphabetical encoding tasks is called into question. In the present case, the effects associated with the two tasks were qualitatively different. These findings indicate that encoding-related neural activity in the two tasks differed

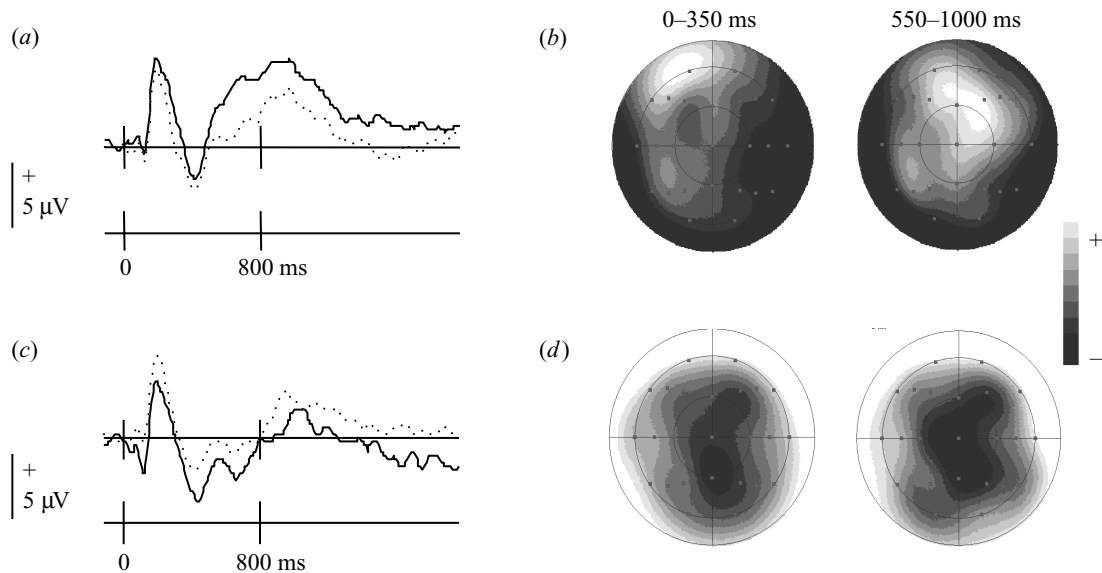


Figure 5. Data from Otten & Rugg (2001*b*). (a) Group-averaged ERP waveforms from a midfrontal electrode site demonstrating the subsequent memory effect for words studied in the animacy task. (b) Scalp distribution of the subsequent memory effect in the animacy task in the 0–350 and 550–1000 ms time ranges. (c,d) As for (a,b), but for the alphabetical study task. Note the differing polarity of the subsequent memory effects in each task and their early onset in both tasks. Solid lines, subsequently remembered; dotted lines, subsequently forgotten.

in location (such that the generators of the activity in the animacy and alphabetical tasks were orientated sufficiently differently to give rise respectively to scalp-positive and scalp-negative effects), in their neurophysiological characteristics, or both. Whatever the reason, the findings indicate that encoding-related neural activity is task-dependent, a conclusion more in line with the second of our fMRI studies than the original one. The reasons for the disparity between our fMRI and ERP results are unclear, although it is important to note that there are several reasons why data from the two methods may not always be convergent (Rugg 1999).

The second conclusion to emerge from the ERP results, equally evident for both tasks, is in respect of the timing of the subsequent memory effects. As is evident in figure 5*a,c*, the effects emerged extremely early, seemingly at the time of stimulus onset. Due to the fact that the waveforms were aligned on the pre-stimulus baseline, these observations indicate that the effects probably began before the onset of the stimulus, possibly in response to the task cue, which was presented some 2.7 s earlier. Thus, the effects observed here (and, possibly, in the two fMRI studies described in § 3*a*) seem likely to reflect a combination of stimulus-elicited and pre-stimulus activity.

(c) *Item- versus state-related activity*

The last of our fMRI encoding studies to be described here (Otten *et al.* 2002) was in part motivated by an important implication of the ERP findings. The finding that subsequent memory effects can be elicited by a pre-stimulus cue raises the possibility that encoding is affected not only by the processing received by a study item, but also by differences in general 'state', as reflected by neural activity unrelated to the processing of specific items (see figure 6). The distinction between item- and state-related processes has long been a subject of debate in the interpretation of findings from studies of episodic retrieval

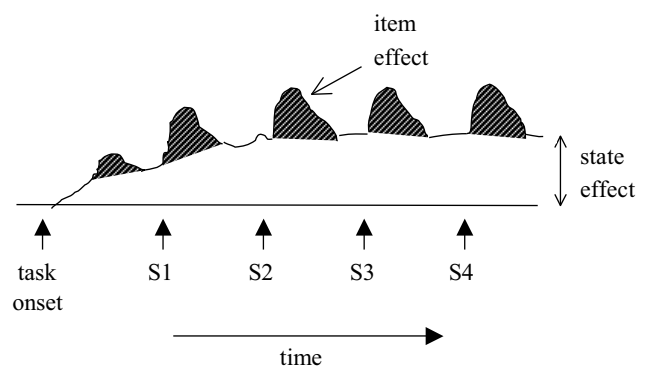


Figure 6. Schematic illustration of state- and item-related brain activity. State-related activity is elicited by engagement in the experimental task and is tonically maintained throughout the task epoch. Item-related activity (hatched areas) is elicited in response to the presentation of specific experimental stimuli.

(Rugg & Wilding 2000), but has received less attention with respect to the neural correlates of encoding (although see Fernández *et al.* 1999). The experiment described here constitutes our first effort to determine whether the distinction is relevant to the understanding of the determinants of successful encoding.

To separate item- and state-related activity, it is necessary to use a design that ensures that the two classes of activity are as uncorrelated as possible (cf. Chawla *et al.* 1999; Donaldson *et al.* 2001). We achieved this by employing a series of task blocks, during each of which individual study items were presented at highly variable inter-stimulus intervals (figure 7). The blocks were separated by short rest periods, at the end of which a cue was presented to signal whether the items in the upcoming block required an animacy or a syllable judgement (these tasks were identical to those employed in the second of

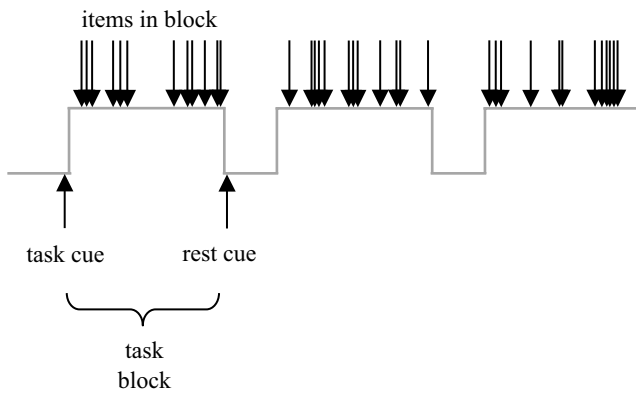


Figure 7. Design for investigation of state- and item-related effects using fMRI. Cues were continuously present during entire task and rest blocks. During the task blocks, items are presented at irregular intervals. By judicious selection of these intervals, the correlation between the regressors employed to model the state- and item-related signal changes can be kept acceptably low (Chawla *et al.* 1999).

the experiments described in § 3a). The principal question was whether state-related neural activity associated with engagement in the study tasks (i.e. task-related activity remaining after the removal of transient activity elicited by the study items) reflected efficacy of encoding. We addressed this question by performing, separately for each encoding task, a block-wise analysis that identified regions where state-related activity covaried with the number of items that were subsequently confidently recognized.

We focus here on the animacy task, as this yielded the clearest and most robust findings. Figure 8 illustrates the results of both the aforementioned state-related analysis and also our 'standard' analysis of item-related subsequent memory effects. Turning to these latter results first (figure 8a), the most notable finding was that subsequent memory effects were once again observed in the left inferior prefrontal cortex. It is also noteworthy that whereas effects were also observed in ventral anterior temporal cortex, there was no sign of an effect in the vicinity of the hippocampus. As shown in figure 8b, the analysis of state-related effects revealed two regions in which activity predicted the number of items from a block that would later be remembered: a medial parietal area in which greater activity was associated with better performance and a left inferior frontal region where the reverse relationship was obtained. The latter region was part of the same left frontal area that showed a subsequent memory effect at the item level.

Two main conclusions can be derived from these findings. First, subsequent memory performance is indeed associated with variations in state-related activity, indicating a role for factors such as 'set' in the modulation of efficacy of encoding (cf. the notion of 'retrieval mode'; Wheeler *et al.* 1997; Düzel *et al.* 1999; Rugg & Wilding 2000). Second, the same region can demonstrate both item- and state-related subsequent memory effects. Intriguingly, the relationship between these 'shared' effects in the present experiment was reciprocal, inviting speculation about a trade-off in this left frontal region between the resources allocated to item- and state-related processing. Further research is required both to replicate

these findings and to begin to elucidate their functional significance.

(d) Concluding comments

Before further discussion of the implications of these findings, mention should be made of an important caveat related to the use of recognition memory to assess subsequent memory performance. It has been proposed that recognition judgements are supported by two kinds of memory (Mandler 1980; Jacoby & Kelley 1992). Recognition can occur when a test item elicits retrieval of a specific past episode involving the item ('recollection')—the focus of interest in the current studies. It is argued, however, that a test item can also be recognized on the basis of its 'familiarity'—an acontextual form of memory held to be dissociable from recollection on phenomenal (Gardiner & Java 1993), functional (Yonelinas *et al.* 1998) and neurological (Aggleton & Brown 1999) grounds. The question thus arises whether the subsequent memory effects described in § 3a–c are associated with the encoding of 'true' episodic memories rather than memory representations supporting subsequent familiarity judgements.

A full answer to this question will have to await the more extensive use of retrieval tasks where familiarity plays less of a role than it appears to do in yes–no recognition. There are, however, grounds for thinking that at least some of the findings described here are relevant specifically to episodic memory. First, by focusing on confident recognition judgements, we biased our definition of 'remembered' items in favour of those recognized on the basis of recollection (Yonelinas *et al.* 1996). Second, findings similar to some of those described here have been reported in studies employing retrieval tasks designed explicitly to distinguish between recollection- and familiarity-based recognition. For example, Henson *et al.* (1999a) reported that left prefrontal (BAs 9 and 47) activity at study was greater for subsequently recognized words that were assigned 'Remember' rather than 'Know' judgements (introspective judgements held to distinguish between recognition based on recollection as opposed to familiarity (Tulving 1985; Gardiner & Java 1993)). Similar findings, albeit for the right prefrontal cortex, were reported by Brewer *et al.* (1998) in a study employing pictures. An alternative means of separating recognition based on episodic retrieval and familiarity is to employ a retrieval task that requires both a recognition judgement and a judgement as to the context in which the test item was originally encoded (a 'source' judgement). The assumption underlying this procedure is that recognition accompanied by successful contextual retrieval is more likely to have involved recollection than when contextual retrieval is unsuccessful. Using such a procedure with pictures of common objects, Cansino *et al.* (2002) observed subsequent memory effects in, among other regions, an area of the left inferior frontal gyrus (BA 44/6) that overlapped part of the left frontal region found by Otten *et al.* (2001) to exhibit subsequent memory effects for confidently recognized words.

On the assumption that our findings do indeed reflect the neural correlates of episodic encoding, the question arises as to the light they shed on the encoding process and its neural bases. As already mentioned, one key con-

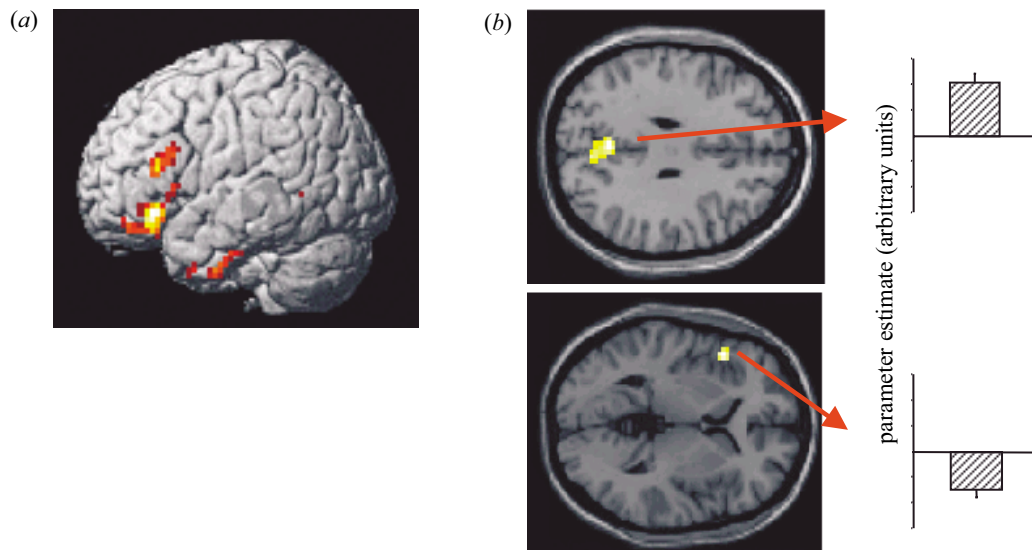


Figure 8. (a) Subsequent memory effects for items studied in the animacy task of Otten *et al.* (2002). Effects can be seen in the ventral and dorsal inferior frontal gyrus, and anterior ventral temporal cortex. Results are illustrated at a threshold of $p < 0.001$. (b) Regions where state-related activity during the animacy task blocks covaried ($p < 0.001$) with the number of subsequently recognized items. Greater activity was associated with better memory performance in the medial parietal cortex, and with worse performance in the left inferior prefrontal cortex. The bars show the mean parameter estimates and standard errors for the voxels showing the peak effect in each region.

clusion is that, at the cortical level, there does not seem to be a single region or circuit that supports episodic encoding regardless of the nature of the processing engaged at the time an event is experienced (Otten & Rugg 2001a; see also Davachi *et al.* 2001). Rather, it appears that effective encoding is associated with the enhancement of activity in regions supporting the ‘online’ processing of an event; regions that will differ depending on the specific cognitive operations that are engaged. Whether the different regions demonstrating such effects (e.g. figure 4) act cooperatively to form a durable memory representation, or whether instead they operate independently, is an important and unresolved question.

A related issue concerns the functional significance of the subsequent memory effects revealed in these and other studies. (Note that we are confining ourselves here to effects taking the form of greater activity for subsequently remembered relative to forgotten items, and do not consider the reverse pattern (Otten & Rugg 2001c; Wagner & Davachi 2001).) Why should enhanced activity in certain brain regions be associated with better subsequent memory? For the reasons outlined in § 1, it is unlikely that the effects merely reflect such factors as differential allocation of attention, or ‘time on task’. An alternative possibility is that the effects reflect the benefits to memory of processing an item beyond what is required for immediate purposes. This notion is a generalization of a proposal originally formulated to account for subsequent memory effects in the left inferior prefrontal cortex in relation to its role in semantic processing (Gabrieli *et al.* 1998). It raises the intriguing question of exactly what causes some items to receive ‘additional’ processing? Presumably this is determined by a combination of subject and item variables that are likely to prove difficult to disentangle.

The final issue to be mentioned relates to the role of the medial temporal lobe and, in particular, the hippocampus, in episodic encoding. Evidence from human and ani-

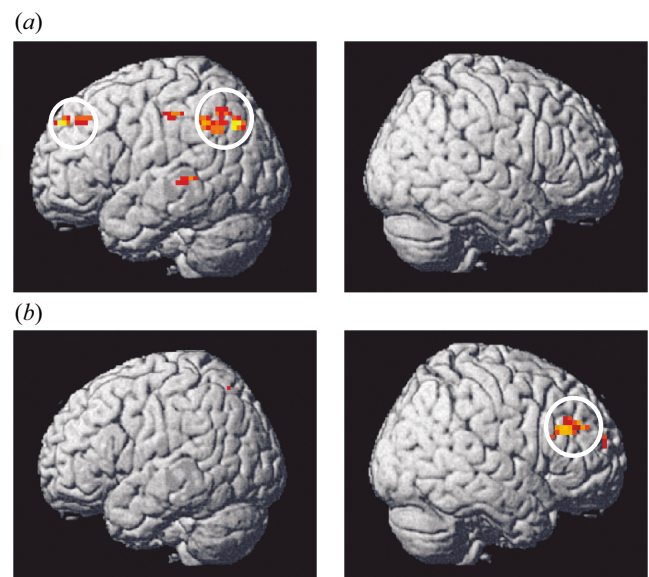


Figure 9. Data from Henson *et al.* (1999a). (a) Regions demonstrating greater activity for recognized items receiving Remember rather than Know judgements. These regions include the left anterior prefrontal and left lateral parietal cortex (indicated with white circles). (b) Right dorsolateral prefrontal region where the activity was greater for items receiving Know rather than Remember judgements. Images thresholded at $p < 0.01$.

mal lesion studies indicates that the hippocampal formation plays a fundamental role in episodic memory and several theoretical accounts propose that it is crucial for successful encoding (e.g. Alvarez & Squire 1994; O’Reilly & McClelland 1994). The finding of hippocampal subsequent memory effects in the study of Otten *et al.* (2001) is consistent with these accounts and, arguably, unsurprising. One might argue, for example, that the

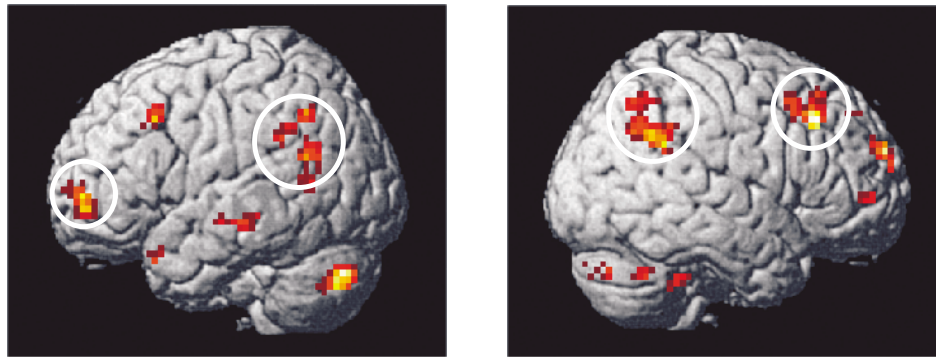


Figure 10. Data from Rugg *et al.* (2002) illustrating regions where activity was greater for correctly classified non-target items than for correctly classified new words in their recognition exclusion task. The regions include left anterior prefrontal, bilateral parietal and right dorsolateral prefrontal cortex (indicated by circles). Images thresholded at $p < 0.01$.

effects reflect the relatively greater hippocampal activity required to process the ‘additional’ information that helps make an item memorable (see above and Otten *et al.* 2001). More surprising, perhaps, is that most published studies employing the subsequent memory procedure have not reported hippocampal subsequent memory effects (for other exceptions see Kirchoff *et al.* 2000; Davachi *et al.* 2001), a pattern reflected on a smaller scale across the three fMRI studies described in § 3a–c. While we are confident that the finding of a hippocampal effect in our first study was not a false positive (the finding has been replicated both in currently unpublished studies in our own laboratory and elsewhere; Fletcher *et al.* 2002), we have no explanation for why subsequent memory effects in this structure are found so inconsistently.

4. EPISODIC RETRIEVAL

Episodic retrieval—recollection—occurs when an interaction between a ‘retrieval cue’ and a memory representation leads to the consciously accessible reconstruction of a past episode (Tulving 1983). The theoretical framework that we currently employ for the interpretation of ERP and haemodynamic studies of episodic retrieval is outlined in Rugg & Wilding (2000). There it was argued that it is useful to distinguish between processes that operate on a retrieval cue in the course of an attempt to retrieve information from memory (pre-retrieval processes) and processes that operate on the products of a retrieval attempt (post-retrieval processes).

We confine ourselves here to a discussion of these latter processes, focusing on the neural correlates of the retrieval and subsequent processing of recently acquired episodic information (so-called ‘retrieval success’ effects). To identify these correlates, certain methodological requirements must be met. First, it is necessary to characterize separately the activity elicited by test cues giving rise to successful versus unsuccessful retrieval. Early PET and fMRI studies of episodic retrieval, in which ‘blocked’ designs were employed, do not meet this requirement (for reviews, see Fletcher *et al.* 1997; Desgranges *et al.* 1998). The confounding of state- and item-related effects (figure 6) that occurs with such designs makes it difficult to distinguish between the phasic activity elicited by specific cues (e.g. recognition memory test items) and tonic

activity associated with mere engagement in the retrieval task. Furthermore, blocked designs do not permit separate assessment of activity associated with different classes of response (e.g. recognition hits versus misses). For these reasons, the neural correlates of successful retrieval are better studied with event-related methods.

A second desirable feature of studies of episodic retrieval is the use of retrieval tests that allow the neural correlates of recollection to be separated from those associated with other forms of memory. As was discussed in § 3d, simple ‘yes–no’ recognition does not suffice in this respect because recognition judgements can be based not only on episodic retrieval, but also a seemingly qualitatively different form of memory—familiarity (see also Brown & Bashir 2002). Again, as already noted, this difficulty can be overcome by the employment of procedures—such as ‘Remember–Know’ and source memory tasks—that allow identification of items whose recognition was accompanied by recollection of details of the study episode.

Most studies in which the above two methodological requirements were met have employed the ERP method and have led to the identification of what appears to constitute an electrophysiological ‘signature’ of recollection-based recognition memory (§ 4b). By contrast, most event-related fMRI studies of successful retrieval have employed yes–no recognition memory (for a review, see Rugg & Henson 2002). In these studies, the regions reported most consistently as showing greater activity for old than for new items are the left anterior prefrontal cortex (BA 9/10) and the lateral and medial parietal cortex (BA 7/39/40).

Findings from two event-related fMRI experiments (Henson *et al.* 1999a; Eldridge *et al.* 2000) that employed the Remember–Know procedure indicate that activity in some of these regions may be selectively associated with recollection. As illustrated in figure 9, Henson *et al.* (1999a) observed greater activity in the left anterior prefrontal and lateral parietal regions (as well as in the posterior cingulate) for recognized items judged as ‘Remembered’ rather than ‘Known’. Similar findings were described by Eldridge *et al.* (2000). Unlike Henson *et al.* (1999a), these authors also found that items judged as remembered elicited greater activity in the hippocampal formation.

(a) Event-related fMRI study of the exclusion task

We investigated the neural correlates of recognition memory using a procedure—based on the ‘exclusion’ task devised by Jacoby (1991)—more closely related to source memory than to introspective report. Study items were words presented in one of two contexts, defined by the combination of font colour and spatial position (e.g. green–left versus red–right). At test, the studied words, intermixed with unstudied ones, were presented in central vision in a white font. Words that had been studied in one of the contexts were designated as ‘targets’ and required a ‘yes’ response. Words studied in the other context—‘non-targets’—had to be classified along with the unstudied words as ‘new’. Following Jacoby (1991), we assume that whereas target items can be classified correctly on the basis of either recollection or familiarity, this is not so for non-targets. For these items, a correct response requires that familiarity be ‘opposed’ by the recollection that the item belongs to the non-target context. Thus, only recollection can serve as the basis for the correct classification of non-target items.

We looked for regions associated with the retrieval and subsequent processing of episodic information by contrasting the activity elicited by correctly classified non-targets and unstudied words. Unlike the contrasts employed in most previous studies of recognition memory, this comparison permits the neural correlates of successful retrieval to be assessed while holding constant factors linked to response choice—the same ‘no’ response is given to both classes of item. At issue is whether any of the regions identified by this contrast correspond to those identified as associated with recollection in the aforementioned Remember–Know experiments. As can be seen in figure 10, two regions—the left anterior prefrontal (BA 10) and the lateral parietal cortex (BA 7/39/40)—are in the general vicinity of regions revealed in Henson *et al.* (1999a; see figure 9) (although it should be noted that the anterior prefrontal area identified in that study is dorsal to the one illustrated in figure 10). Enhanced activity for non-targets was also found in regions not identified in the Remember minus Know subtraction; these regions included the right anterior and dorsolateral prefrontal cortex.

The results for the lateral parietal and left anterior prefrontal regions converge with previous findings to indicate that their engagement is a neural correlate of recollection and can be found across a range of different task and response requirements. This conclusion contrasts with that for the right prefrontal cortex and, in particular, for the right dorsolateral region illustrated in figure 10. As shown in figure 9, in the experiment of Henson *et al.* (1999a) the same region exhibited greater activity for items attracting Know than Remember judgements, that is, for items judged old in the *absence* of recollection. Henson *et al.* (1999a) found that, even when compared with the activity elicited by unstudied items, words attracting Remember judgements failed to activate the right dorsolateral region.

How can these seemingly disparate results be reconciled? An important clue comes from an experiment where recognition memory judgements were accompanied by confidence ratings rather than Remember–Know judgements (Henson *et al.* 2000). Henson *et al.* (2000)

found that right dorsolateral activity was greater for items attracting low rather than high confidence judgements, regardless of the items’ study history. They proposed that this region supports processes contributing to the ‘monitoring’ or ‘evaluation’ of the products of a retrieval attempt. They argued that when information supporting a recognition judgement was relatively impoverished, monitoring operations would be engaged to a greater extent than when the information was less ambiguous. This account sits well with the findings from the experiment described here: a correct response to a non-target item required not merely information that an item was ‘old’, but identification of the source of that information. Presumably, it was the ‘post-retrieval’ monitoring and evaluation operations necessitated by this latter requirement that engaged the right dorsolateral prefrontal region (see also Henson *et al.* 1999b). By contrast, a correct ‘new’ judgement could be based on the mere detection of novelty, without the need for further evaluation. The latencies of the responses to the two classes of word support this account, in that it took, on average, more than 200 ms longer to respond to non-targets (1392 ms) than to unstudied words (1165 ms).

The general picture to emerge from the foregoing discussion is one in which recognition accompanied by episodic retrieval is associated with engagement of both lateral parietal cortex and a variety of prefrontal areas. Whereas parietal and left anterior prefrontal activity seem to be relatively invariant across variations in task requirements, other prefrontal activity, especially in the right dorsolateral region, appears to be task sensitive. Right dorsolateral activity showed up as ‘recollection related’ in one study (figure 10) and ‘familiarity related’ in another (figure 9; Henson *et al.* 1999a), depending apparently upon which experimental conditions make the greater demands on post-retrieval monitoring operations.

(b) Relationship between fMRI and ERP correlates of recollection

The picture detailed in § 4a is broadly in line with that emerging from studies using ERPs to investigate episodic retrieval (see Rugg & Allan (2000) and Friedman & Johnson (2000) for reviews). Many of these studies have described the so-called ‘left parietal old–new effect’. This is a positive shift in ERPs elicited by correctly classified old items relative to waveforms elicited by new items. The effect (see figure 11) begins *ca.* 400–500 ms post-stimulus, is maximal over the left parietal scalp and, on the basis of its sensitivity to a variety of experimental variables, has been interpreted as a neural correlate of recollection (Rugg & Allan 2000). Notably, as is the case for the lateral parietal activity reported in fMRI studies, the left parietal ERP effect is larger for items accorded as Remember rather than Know judgements (Smith 1993; Düzel *et al.* 1997) and can be elicited in exclusion tasks by correctly classified non-targets (Wilding & Rugg 1997; Cycowicz *et al.* 2001). It has been proposed that the left parietal 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 the parietal cortex in attention (Kastner & Ungerleider 2000), is that the effect reflects an attentional shift or orientating

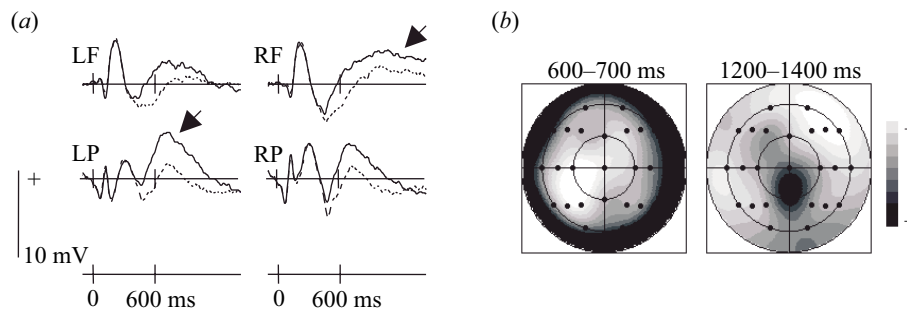


Figure 11. An example of left parietal and right frontal ERP effects, taken from Mark & Rugg (1998). (a) Group-averaged waveforms elicited by recognized items receiving correct source judgements ('recollected') and correctly classified new items ('correct rejections') from left and right frontal and parietal electrode sites. Left parietal and right frontal old–new effects are indicated by the arrows. Solid line, recollection; dotted line, correct rejection. (b) Scalp distributions of the two effects, obtained by subtracting waveforms elicited by correct rejections from those elicited by recollected items. The distributions show the characteristic scalp maxima of the two effects and their differing time courses.

triggered by successful episodic retrieval. On the basis of current evidence, it seems reasonable to suppose that the parietal activity identified in event-related fMRI studies of recognition memory, which is frequently more prominent on the left (Rugg & Henson 2002), is the haemodynamic correlate of the left parietal ERP effect.

A second ERP effect to have been associated with recollection-based recognition is the 'right frontal old–new effect'. This effect begins later than the left parietal effect and takes the form of a sustained positive shift with an amplitude maximum over the right frontal scalp (see figure 11). The effect is most evident in tasks, such as source memory, where recollected information must be evaluated before an appropriate response can be selected. It has been interpreted as a correlate of 'post-retrieval' operations engaged when retrieved information must be represented, maintained and monitored with respect to its relevance to current behavioural goals (Rugg & Allan 2000; Rugg & Wilding 2000). It is possible that the right frontal ERP effect reflects, at least in part, the right dorsolateral activity illustrated in figures 9 and 10 and reported in other fMRI experiments. In support of this idea is the finding that, as is the case for right dorsolateral activity, the right frontal ERP effect is not associated invariably with successful episodic retrieval. In one study of old–new recognition memory, the effect was elicited by items that, by virtue of their impoverished encoding, could be judged old only on the basis of weak familiarity information (Rugg *et al.* 2000). Such judgements would presumably place heavy demands on the monitoring operations held to be supported by the right dorsolateral prefrontal cortex (Henson *et al.* 1999a,b; 2000).

Whereas left parietal and right frontal ERP effects appear to map quite well onto analogous fMRI effects, it should be borne in mind that there is currently no direct evidence to support the proposed mapping. Moreover, it is difficult to find ERP parallels for other fMRI findings. In particular, we noted that the left anterior prefrontal cortex was among the regions identified in fMRI studies as likely to be associated with recognition based upon recollection. It has been suggested that activity in this region supports the switching between cognitive operations (Fletcher & Henson 2001), perhaps as a result of the need to engage post-retrieval processing. We are unaware, however, of an ERP effect that might be an analogue of this

fMRI finding. Whereas frontally distributed ERP effects additional to (and earlier than) the right frontal effect have been reported in several studies of recognition memory, these have been interpreted as correlates of priming or familiarity rather than recollection (e.g. Rugg *et al.* 1998a; Curran 2000; Tsivilis *et al.* 2001). The development of formal methods for the integration of ERP and fMRI data is likely to make a major contribution to the resolution of this and other apparent anomalies. It is important to bear in mind, however, that the correspondence between the neural correlates of memory processing revealed by electrophysiological and haemodynamic data is likely to be less than perfect (Rugg 1999).

(c) Role of the hippocampus in retrieval

Whereas Eldridge *et al.* (2000) reported greater activity in the hippocampal formation for 'recollected' than 'non-recollected' items, we failed to find evidence of such an effect in either our earlier study (Henson *et al.* 1999a) or in the one described here. These negative results are typical of event-related fMRI studies of recognition memory (Rugg & Henson 2002). The finding of Eldridge *et al.* (2000) seems unlikely to represent an anomaly, however, as elevated hippocampal activity for items likely to have elicited strong recollection has also been reported in other studies (Cabeza *et al.* 2001; Cansino *et al.* 2002). In the study of source memory by Cansino *et al.* (2002), for example, greater activity was elicited in the hippocampal formation by recognized items given correctly rather than incorrect source judgements. These positive findings are consistent with the proposal that retrieval-related hippocampal activity is associated specifically with recollection (Schacter *et al.* 1996; Rugg *et al.* 1997) and, more generally, with the view that the hippocampal formation forms part of a circuit serving episodic retrieval rather than the recovery of non-episodic information such as item familiarity (e.g. Aggleton & Brown 1999). The exact circumstances that lead to a detectable increase in hippocampal activity during episodic retrieval nonetheless remain unclear (for further discussion, see Schacter & Wagner (1999) and Rugg & Henson (2002)). One possibility, consistent with the findings from our first encoding experiment (Otten *et al.* 2001), is that contrasts between studied and unstudied items often fail to reveal retrieval-related effects because they are 'cancelled' by the encoding-

related activity elicited by unstudied items (Fletcher *et al.* 1995; Rugg *et al.* 1997). We know of no direct evidence in support of this possibility, however. In short, as is also true for encoding (§ 3d), positive findings obtained for the hippocampal formation are consistent with evidence from other methodologies, but shed little new light on the role of this structure in episodic retrieval.

5. OUTSTANDING ISSUES

We have focused on the loci and temporal properties of neural activity engaged during the encoding and retrieval of episodic memories. In addition, we have tried to describe our experiments in a way that allows the reader to appreciate some of the methodological issues involved in using non-invasive, event-related measures of brain activity to address such questions. Among the numerous issues raised by our and others' results, two stand out. First, the importance of developing methods for the integration of electrophysiological and haemodynamic data, permitting the derivation of a measure of neural activity with good spatial *and* good temporal resolution. Second, the need to use such a measure to investigate how the different brain regions identified in the above experiments interact during memory tasks. It will then be possible to gain an understanding of how these regions interact to form the functional networks that support the formation and retrieval of episodic memories.

The approach outlined in the present paper has identified several brain regions that had not previously been linked strongly with episodic memory (e.g. parietal and anterior prefrontal cortex). As such, it has brought a fresh perspective to the question of the neural bases of this fundamental cognitive function. It is important to acknowledge, however, that by themselves functional imaging data do not permit strong conclusions as to the regions that are *necessary* for the formation and retrieval of episodic memories (this is a specific case of the more general problem of drawing causal inferences from 'correlational' data, a problem that extends beyond functional neuroimaging to include other methodologies, such as single-neuron recordings). To draw such conclusions, convergent evidence is required from studies investigating memory performance after different brain regions have been rendered dysfunctional, as a result of either a lesion or, perhaps, the use of a reversible method such as transcranial magnetic stimulation (Rossi *et al.* 2001). The present findings identify some of the regions that should be targeted in such studies, and provide clues to their possible functional roles.

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GLOSSARY

- BA: Brodmann area
 EEG: electroencephalogram
 ERP: event-related potential
 fMRI: functional magnetic resonance imaging
 MEG: magnetoencephalogram
 PET: positron emission tomography