

INVITED REVIEW

Frontal lobes and human memory Insights from functional neuroimaging

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Summary

The new functional neuroimaging techniques, PET and functional MRI (fMRI), offer sufficient experimental flexibility and spatial resolution to explore the functional neuroanatomical bases of different memory stages and processes. They have had a particular impact on our understanding of the role of the frontal cortex in memory processing. We review the insights that have been gained, and attempt a synthesis of the findings from functional imaging studies of working memory, encoding in episodic memory and retrieval from episodic memory. Though these different aspects of memory have usually been studied in isolation, we suggest that there is sufficient convergence with respect to frontal activations to make such a synthesis worthwhile. We concentrate in particular on three regions of the lateral frontal cortex—ventro-

lateral, dorsolateral and anterior—that are consistently activated in these studies, and attribute these activations to the *updating/maintenance* of information, the *selection/manipulation/monitoring* of that information, and the *selection of processes/subgoals*, respectively. We also acknowledge a number of empirical inconsistencies associated with this synthesis, and suggest possible reasons for these. More generally, we predict that the resolution of questions concerning the functional neuroanatomical subdivisions of the frontal cortex will ultimately depend on a fuller cognitive psychological fractionation of memory control processes, an enterprise that will be guided and tested by experimentation. We expect that the neuroimaging techniques will provide an important part of this enterprise.

Keywords: frontal; memory; functional MRI; PET

Abbreviations: AFC = anterior frontal cortex; DLFC = dorsolateral frontal cortex; ERP = event-related potential; FC = frontal cortex; fMRI = functional MRI; HERA = hemispheric encoding–retrieval asymmetry; LTM = long-term memory; VLFC = ventrolateral frontal cortex; WM = working memory

Introduction

PET and functional MRI (fMRI) have demonstrated consistent activations of the frontal cortex (FC) in a number of memory tasks. Interpretations of these activations vary widely, however, as do their precise locations within FC. In this article, we review these findings and offer a new interpretation that takes heed of the broad anatomical variation of activations within FC.

Our main hypothesis is that functional specialization, within the context of memory-related processes, exists across at least three anatomically distinct frontal regions. This principle of functional–anatomical specialization has proved remarkably successful in, for example, the study of the visual cortex, and we see no *a priori* reason why analogous

specialization might not exist within FC. We believe this approach will prove more fruitful than attempting to define a general and abstract function for FC as a whole. Ultimately however, the validity of this level of functional specialization is best judged by its success in explaining extant neuroimaging and neuropsychological data.

Neuroimaging offers a number of advantages over neuropsychology with regard to understanding the functional parcellation of FC. First, neuropsychological studies deal with lesions that often differ markedly in size and location across different patients. PET and in particular fMRI offer a more precise spatial characterization of functional differentiation across FC. Secondly, the memory deficits

produced by frontal lesions tend to be subtle, and it is likely that the sorts of memory processes subserved by FC are some distance 'upstream' of observed behaviours (Burgess, 1997). Patients may, for example, achieve comparable behavioural performance with varying degrees of frontal mediation and compensatory strategies. Functional neuroimaging offers the possibility of detecting differences in the strategies that subjects or patients employ. Thirdly, functional neuroimaging techniques can elucidate different stages of a memory process. For example, they can examine separately the encoding and retrieval of memories, a dissociation that cannot be made with confidence from anterograde memory deficits following frontal lobe lesions. Finally, FC is unlikely to function independently of other brain systems with which it interacts (Fuster, 1997). Neuropsychological study can show whether a region is necessary for a given task, but not usually the broader system of which that region forms a part. Acquisition of whole-brain images enables the characterization of spatially distributed functional networks of activity. Moreover, analytical techniques have been developed that allow the characterization of the effective connectivity between different brain regions during task performance (McIntosh and Gonzales-Lima, 1994; Büchel and Friston, 1997).

It has been suggested that a regional activation observed in functional imaging tells us little about the necessity of that region for task performance (Price and Friston, 1999; Fletcher, 2000). For example, a number of studies of healthy subjects show frontal activation in association with recognition memory (e.g. Tulving *et al.*, 1994b; Rugg *et al.*, 1996) while neuropsychological studies (e.g. Stuss *et al.*, 1994) have indicated that such tasks may be performed relatively normally even in the face of widespread frontal damage. One possibility is that such activations are epiphenomenal, in the sense that they are not directly task-related. A more interesting possibility, however, is that the functional imaging data contain important additional information about the way healthy subjects perform the task. If so, the failure of behavioural measures to distinguish between the performance of a task in patients and in controls may indicate a limitation or insensitivity in the behavioural measures. That is, discrepancies between functional imaging and neuropsychological data may point to flaws in our cognitive models of how tasks are performed and how performance is measured. In this sense, such discrepancies may represent a strength of the functional imaging techniques rather than, as has been suggested, a weakness.

The use of functional imaging to address functional specialization within FC is, however, problematic. The most fundamental problem lies in the rudimentary state of current understanding of the types of processes subserved by FC. In most functional neuroimaging experiments, changes in the haemodynamic response of a region are correlated with a manipulation of the subject's task. This change is attributed to a specific psychological process supposedly isolated by the task manipulation. The pattern of brain activity is therefore

only meaningful to the extent that the psychological theory of task performance is accurate. A specific example of this problem is the assumption that a task manipulation changes only a single cognitive process, leaving other processes unaffected. This assumption of 'pure insertion' (Friston *et al.*, 1996; Donders, 1969) is particularly relevant to simple subtractive methods of analysing imaging data, in which mean brain activity during the performance of one task (the control) is subtracted from that during the performance of another task that is assumed to differ only in the single psychological process of interest. The difference between the two tasks may in fact be accompanied by numerous cognitive changes (which may not be evident from behavioural measures alone). This is why the 'activations' reported by neuroimaging experiments cannot be evaluated without reference to the control task. This problem may be particularly relevant to the relatively high-level (non-automatic) and inter-related processes generally believed to be subserved by FC. Isolating such processes requires experimental manipulations that not only engage each of them to different degrees while holding the others constant, but do so without changing lower-level (e.g. perceptual) processes (e.g. changing the instructions rather than the stimuli).

It is important to raise this problem—that neuroimaging 'activations' are only interpretable in the context of a particular theory of task performance and often with respect to a specific control—at the outset of this review (other problems associated with current neuroimaging experiments are discussed in the Conclusions section). This is because we describe and organize recent neuroimaging findings initially in terms of one or more conventional labels and within the context of specific theories. In the final section, however, we offer a re-evaluation of the prominent findings within a modified theoretical framework. We note also that our approach differs from formal meta-analyses, such as that recently performed by Duncan and Owen (Duncan and Owen, 2000). When plotting the Talairach coordinates of activation maxima from a number of studies, these authors found a subset of lateral and dorsomedial FC regions that were commonly activated across a range of different cognitive tasks, but failed to find evidence for functional segregation of the maxima within these regions. Our approach begins with prior, anatomically defined regions and, while accepting some errors in the attribution of functional activations to these regions, examines whether a consistent theoretical account emerges from differential activations of these regions.

We propose to distinguish between activations occurring in the following FC regions: ventrolateral FC (VLFC), dorsolateral FC (DLFC) and anterior FC (AFC). We chose these regions, confined to the lateral aspect of FC, because they are the regions most commonly activated in memory-related tasks. DLFC consists of the area lying superior to the inferior frontal gyrus and VLFC to the area below it, i.e. the inferior frontal gyrus. AFC is defined more arbitrarily as the frontopolar area lying anterior to the anteriormost extent of the inferior frontal gyrus (Fig. 1). We make these

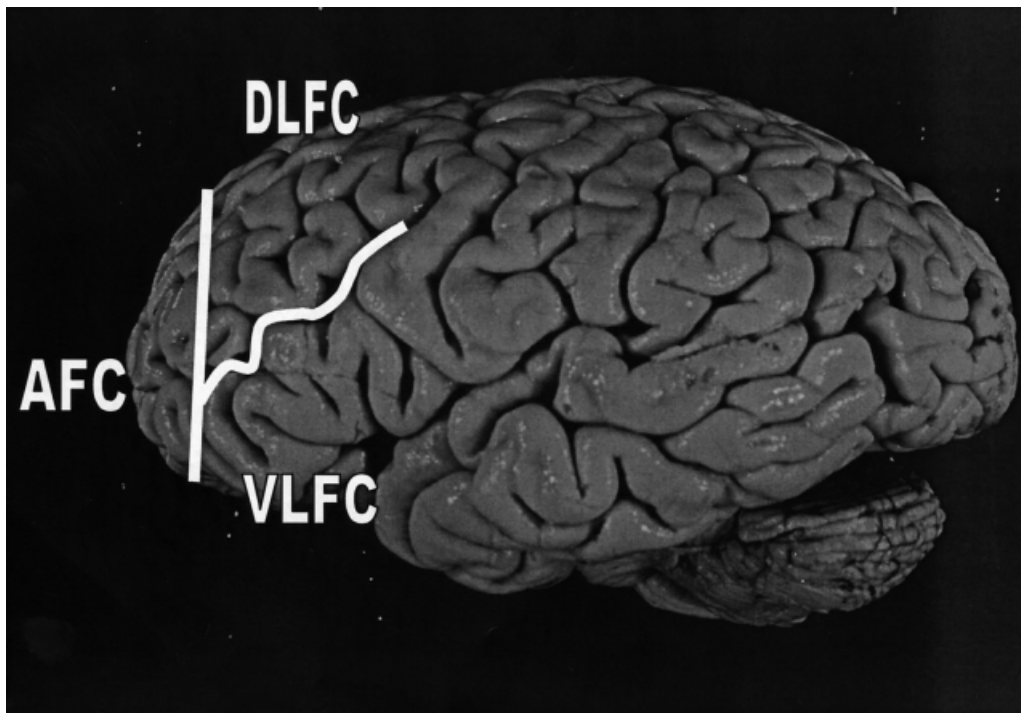


Fig. 1 Left-sided view of human brain showing our working subdivisions of lateral FC. The border between VLFC and DLFC is marked by the inferior frontal sulcus. The posterior border of AFC is marked by a line drawn vertically at the anterior edge of the inferior frontal gyrus.

distinctions (in addition to the left–right lateralization of the regions) with due consideration of the imperfect spatial resolution of the techniques, of the enormous anatomical variability among subjects, and of the likelihood that, ultimately, these broad areas will themselves be shown to be functionally subdivided. The rationale behind this division is, on the one hand, an attempt to acknowledge the limited spatial information provided by group studies (particularly with PET) and, on the other hand, to avoid treating clearly separate regional responses as undifferentiated ‘frontal’ activations. Our particular subdivisions are based on existing functional imaging data rather than microstructural findings, although they may be considered to provide some clues to the underlying anatomy. Thus, VLFC corresponds loosely to Brodmann areas 44, 45 and 47, DLFC to areas 9 and 46 and AFC to areas 8 and 10. It is our intention, however, to avoid relying upon the uncertain and inconsistent relationship between macroscopic sulcal/gyral features (onto which the PET and fMRI activations are mapped) and the boundaries of the Brodmann areas (Roland *et al.*, 1997; Zilles *et al.*, 1997). Amunts and colleagues, for example, noted a 10-fold difference in the size of Broca’s area across a group of 10 individuals, the microscopic boundaries bearing little consistent relationship to macroscopic landmarks (Amunts *et al.*, 1999). Caution must therefore be exercised in relating macro- to microanatomy, and we will avoid the use of Brodmann’s definitions. The chosen subdivisions are also likely to reflect differences in patterns of connectivity (Passingham, 1993; Fuster, 1997). Once more, however,

we cannot be certain of the precise relationship between connectivity and macroanatomical landmarks, and we refrain from further speculation. Finally, we confine our review to studies of groups of young, healthy individuals.

The nature of the contribution of the frontal lobe to memory is clouded by the division of the experimental literature into two broad fields: working memory (WM), the ability to maintain information temporarily over periods of seconds, and long-term memory (LTM), the ability to retain information for much longer periods. While there are good reasons for distinguishing between these two types of memory, it is also likely that considerable overlap exists between the frontally mediated processes involved in each. Many imaging studies of encoding and retrieval in LTM, for example, are likely to entail maintaining and manipulating information in WM. Conversely, information maintained in WM may be encoded into LTM. It is interesting, therefore, that similar FC dissociations of function have been proposed in both LTM and WM imaging studies, and yet these findings, with certain exceptions (Wagner, 1999), are not often considered together. Nonetheless, a convenient way to introduce the evidence is to consider each field separately, before subsequently discussing how they may converge. We therefore address the patterns of memory-related FC activation in two stages. First, we consider interpretations of FC activations offered by researchers within each domain (WM, LTM encoding, LTM retrieval). Secondly, in the concluding section, we attempt a more general interpretation that extends to FC activations across the different domains.

Frontal function in working memory tasks

The term ‘working memory’ is generally used to refer to the ability to maintain information on-line, often in the service of a particular task or goal. However, the term has different connotations in different fields. In the animal literature, it is often used to describe the ability of an animal to remember a stimulus for a short period after it is removed (in order to perform e.g. delayed matching-to-sample tasks). In the cognitive psychological literature, on the other hand, WM frequently refers to a mental workspace in which multiple sources of information are manipulated in order to perform complex problem-solving tasks. We begin by introducing the background to these two perspectives, before considering recent imaging studies that have attempted to synthesize ideas from these traditionally quite distinct fields of investigation.

Perspectives from animal studies: domain-versus process-specific theories

Two competing ideas concerning functional specialization of FC in WM are ‘domain-specific’ and ‘process-specific’ theories. These theories concentrate in particular on dissociations between ventral and dorsal regions of lateral FC.

According to the domain-specific theory, FC is the primary site of WM processes and different regions within FC process different types of information (Goldman-Rakic, 1987, 1998). Specifically, VLFC is believed to be responsible for the maintenance of stimulus form (object information), whereas DLFC is believed to be responsible for the maintenance of stimulus location (spatial information). This theory is based largely on electrophysiological recordings and is an extension of the object–spatial (‘what’ versus ‘where’) visual processing streams found in posterior regions (Mishkin *et al.*, 1983). More specifically, Wilson and colleagues found that FC cells ventral to the principal sulcus code for object information during a delay, whereas frontal cells within and dorsal to the principal sulcus code for spatial information during a delay (Wilson *et al.*, 1993). More generally, Goldman-Rakic and colleagues suggested that the object–spatial VLFC–DLFC distinction reflects all components of WM: the ‘attentional, memorial and response control mechanisms’ (Goldman-Rakic, 1998). That is, there is no suggestion of specialization for different WM processes across FC, only specialization for the domains over which these processes operate.

The alternative, process-specific theory proposes that the difference between VLFC and DLFC lies not in the type of material being maintained but in the type of processes operating on that material (Petrides, 1994, 1995). This theory derives mainly from animal lesion data (Petrides, 1994) and has been extended to human lesion data (Petrides and Milner, 1982; Owen *et al.*, 1990). According to this theory, VLFC supports processes that transfer, maintain and match information in WM. This information may have been perceived recently or retrieved from LTM. DLFC, however, supports

more complex processes operating on information that is currently maintained in WM. These include processes such as monitoring and higher-level planning.

The process-specific distinction can be illustrated by comparing two types of WM task. ‘Delayed matching tasks’ simply require that the subject decides whether a probe stimulus matches one of a set of stimuli held in WM. This task requires maintenance only. In ‘self-ordered tasks’, however, the subject must select one stimulus at a time from the set presented previously, such that, over trials, every stimulus has been selected once (without repetition). This requires that the subject not only selects stimuli from a set maintained in WM but also updates and monitors the set of previous responses. According to Petrides and colleagues, a delayed matching task would engage VLFC, whereas a self-ordering task would engage DLFC. Consistent with this view, DLFC lesions in primates produce deficits on self-ordering tasks but not typically on delayed-matching tasks (Petrides, 1995). Self-ordering deficits are also seen following frontal lesions in patients, which typically include DLFC (Petrides and Milner, 1982; Owen *et al.*, 1990). Furthermore, a review by D’Esposito and Postle found no evidence that patients with DLFC lesions were impaired on simple verbal or spatial span tasks that require only maintenance of a stimulus on-line (without any manipulation) (D’Esposito and Postle, 1999).

Though often placed in opposition, the domain-specific and process-specific theories are not necessarily incompatible. FC may be functionally dissociable according to both the type of material and the type of process. Moreover, the precise site of lesions in the primate DLFC (e.g. Brodmann areas 9 or 46) can affect whether impairments are seen in simple spatial delayed response tasks or only in more complex situations, such as self-ordering tasks. Nonetheless, we will compare these two general theories for their ability to account for the human imaging data. The data are introduced later, after considering an alternative perspective on WM deriving from the human psychological literature.

Perspectives from human cognitive psychology: multiple-component models

Baddeley and Hitch’s theoretical model of WM function (Baddeley and Hitch, 1974) has been highly influential in framing functional neuroimaging studies. This model was developed to account for a range of different WM functions, from temporary maintenance of a single stimulus to the manipulation of multiple types of information. It evolved from earlier conceptions of a single short-term buffer (Atkinson and Shiffrin, 1968), which acted simply as a gateway between perception and LTM, to a multicomponent system in which a number of subsidiary ‘slave’ systems are coordinated by a common ‘central executive’. The slave systems, the ‘phonological loop’ and ‘visuospatial scratch-pad’, are limited-capacity, material-specific stores, concerned with the maintenance of verbal and visuospatial material respectively.

An important distinction within the slave systems of the WM model is between passive storage and active rehearsal. In the case of the phonological loop, for example, Baddeley distinguished a 'phonological store' from an 'articulatory control process' (Baddeley, 1986). Verbal material is assumed to enter the phonological store, where it is vulnerable to interference and/or rapid decay over time. The rapid decay of material in the phonological store can be offset, however, by (subvocal) rehearsal via the articulatory control process. The proposal of a 'visual cache' and an 'inner scribe' (Logie, 1995) represents an analogous storage–rehearsal distinction within the visuospatial scratchpad.

For the purpose of this review, we make a coarse distinction between imaging studies of WM that employ maintenance tasks and those that employ manipulation tasks. Maintenance refers to the process of keeping information in mind in the absence of an external stimulus (and perhaps in the presence of distraction). This would correspond to use of the slave systems of the WM model. Manipulation refers to the reorganization of the information that is being maintained, and would correspond to the use of the central executive in the WM model. We begin by considering maintenance tasks. Early imaging studies of such tasks have tended to support the neuropsychological evidence for a role of posterior regions in the passive storage of material and of posterior FC in the rehearsal of material. Both have been lateralized to the left for verbal material and to the right for spatial material. We then consider manipulation tasks. These have been the subject of more recent imaging studies which have focused on dissociations between VLFC and DLFC and are thus relevant to the domain-specific versus process-specific debate outlined above.

Maintenance of verbal information

A common test of maintenance in WM is the Sternberg task (Fig. 2). Subjects are presented with a 'memory set' of typically three to nine stimuli, which are then removed for several seconds before the appearance of a single probe stimulus. The goal of the subject is to decide whether or not the probe stimulus was one of the stimuli in the memory set. To isolate brain areas involved in maintenance from those involved in perceptual or motor components of the task, functional images obtained during the Sternberg task can be contrasted against those obtained in a control task in which the memory set and probe item are presented simultaneously, alleviating any memory requirement. Using a verbal Sternberg task in which the stimuli were letters (Fig. 2A), Awh and colleagues reported significant activations in several left hemisphere regions, including parietal, dorsal premotor and ventral premotor/VLFC (Awh *et al.*, 1996). Similar regions were implicated by Paulesu and colleagues when they compared two Sternberg tasks, one using letters and one using non-verbalizable symbols (Fig. 2A and C) (Paulesu *et al.*, 1993). This left hemisphere network of the VLFC, parietal and motor areas (plus right cerebellum) is a consistent

finding in studies of maintenance in verbal WM (Smith and Jonides, 1997; Henson *et al.*, 2000b).

To distinguish the storage and rehearsal components of verbal WM, Paulesu and colleagues (Paulesu *et al.*, 1993) compared a verbal Sternberg task with a control task in which subjects judged whether letters rhymed with a target letter [a task that is believed to require the same articulatory processes as those used in rehearsal (Besner, 1987)]. This comparison revealed left inferior parietal activation but no FC activation. Awh and colleagues compared a 2-back task (in which a positive response is required whenever the current stimulus matches the stimulus presented two trials previously) (Fig. 2D) with a continuous subvocal repetition task with no storage requirement (Awh *et al.*, 1996). Again, activation of the inferior parietal cortex was observed, but no difference in FC activation was seen. Both studies therefore implicate the left inferior parietal cortex as the locus of a phonological store, which was engaged in the memory tasks, and the left VLFC in subvocal articulatory rehearsal, which was assumed to be engaged in both memory and control tasks and therefore not observed in the subtractions.

Maintenance of spatial and object information

Imaging studies of WM using non-verbal material have focused on differences between the maintenance of spatial and object information. In a study using a spatial Sternberg task (Fig. 2B), activations were seen in several right hemisphere regions, broadly homologous to those seen in verbal maintenance tasks (Jonides *et al.*, 1993). These included the right parietal cortex, right dorsal premotor cortex and right VLFC. (The FC activations resulting from comparison of the Sternberg task with its control are sometimes bilateral for both verbal and spatial material. However, the left–right verbal–spatial lateralization is normally clearer when direct comparisons of verbal and spatial material are made.) Smith and colleagues reported similar findings in a direct comparison of visuospatial and verbal Sternberg tasks, the networks of parietal, dorsal premotor and VLFC regions being left- and right-lateralized for verbal and spatial tasks, respectively (Smith *et al.*, 1996).

Smith and Jonides used an object version of the Sternberg task that tested memory for abstract shapes (for which spatial location was irrelevant) (Fig. 2C) (Smith and Jonides, 1995a). This task produced activations that were predominantly left-lateralized, including the inferior parietal cortex, inferior temporal cortex and left VLFC. In a direct comparison of object and spatial maintenance (Smith and Jonides, 1995b), participants were presented with two abstract shapes and, after a 3-s delay, a single probe shape prompting a yes–no response. In the test of object WM, the task was to decide whether the probe matched one of the memory set in shape (regardless of its location on the screen). In the test of spatial WM, the task was to decide whether the probe matched one of the memory set in its location (regardless of its shape). The regions more active in the object task than in the spatial

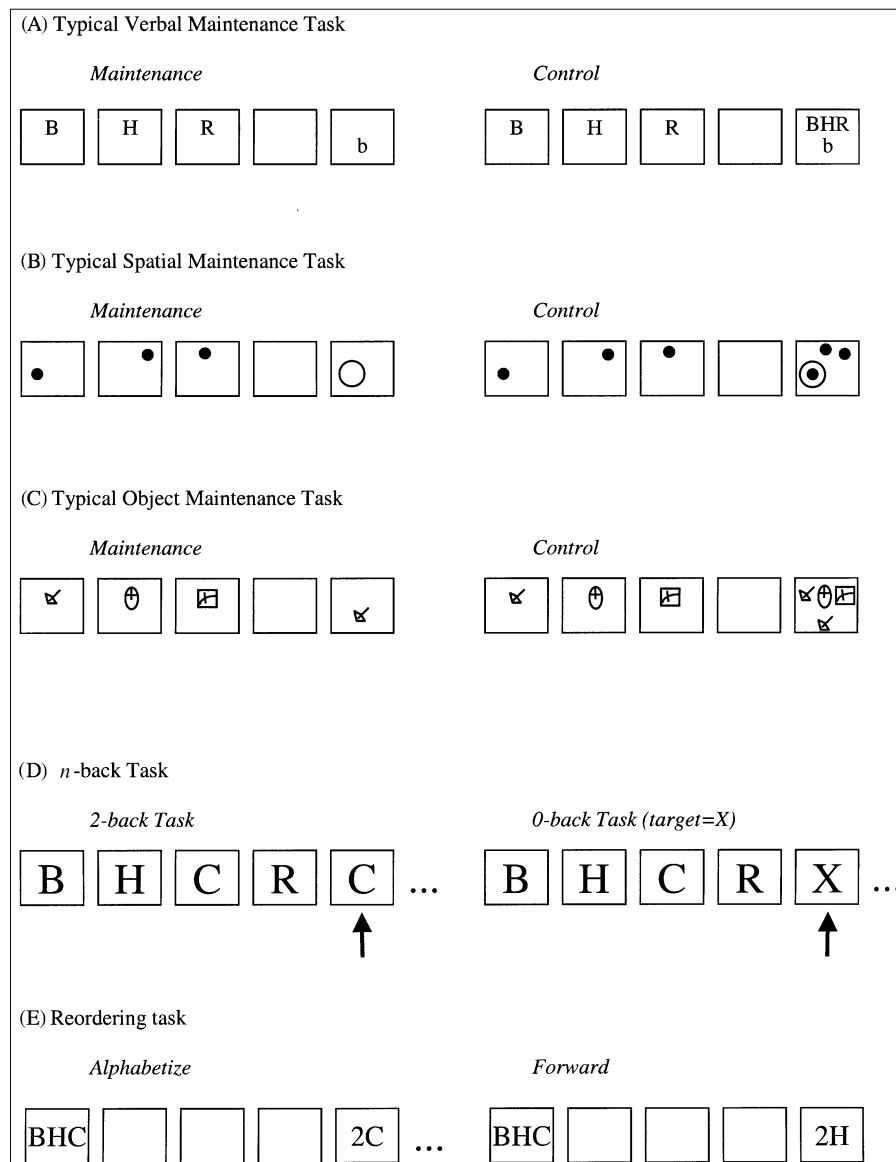


Fig. 2 Schematic representation of working memory tasks.

task were the left posterior parietal cortex and left inferior temporal cortex, a subset of the areas implicated in the study (Smith and Jonides, 1995a, b). The areas more active in the spatial task were the right VLFC and the right posterior parietal, right anterior occipital and right premotor cortices.

In another study comparing spatial and object Sternberg tasks (Belger *et al.*, 1998), the spatial task activated the right DLFC, whereas the object task activated bilateral DLFC and left VLFC. A very similar pattern was reported by McCarthy and colleagues (though in this case the memory task required the participants to maintain more than 18 different locations/shapes, which is beyond the normal visuospatial memory span) (McCarthy *et al.*, 1996). Finally, in a study comparing a spatial delayed response task with an object delayed matching task (Baker *et al.*, 1996a), greater right DLFC activation was observed in the former and greater left DLFC in the latter. These studies suggest a role for the dorsal as

well as the ventral FC in the maintenance of information in WM. However, the difference between the maintenance of object and spatial information appears more likely to reflect a left–right lateralization than a ventral–dorsal one, spatial tasks activating the right FC and object tasks activating the left or bilateral FC. One exception to this pattern appears to arise when the objects are faces, for which object tasks tend to produce VLFC activation and spatial tasks DLFC activation (e.g. Courtney *et al.*, 1996). One possibility is that faces constitute a special class of visual objects [e.g. electrophysiological studies suggest that face-selective FC neurones are restricted to ventral FC regions (O’Scalaidhe *et al.*, 1997)].

It has proved difficult to isolate storage from rehearsal processes in spatial and object maintenance tasks. The hypothesis that visuospatial rehearsal corresponds to planned eye movements has little support, because activations of frontal

eye fields, the pulvinar nucleus or superior colliculus are not typically observed in neuroimaging studies of visuospatial WM. Another possibility, that rehearsal of visuospatial information involves an internal attentional mechanism, is consistent with neuroimaging studies of spatial attention, which activates similar areas of the right superior parietal cortex independently of eye movement (Corbetta *et al.*, 1993; Coull and Nobre, 1998). A tentative hypothesis is that visuospatial information is stored as abstract or object visual representations in the occipital cortex and inferior temporal cortex, respectively (perhaps corresponding to visual caches). The (egocentric) spatial organization of the stimuli may be represented by associations between these areas and the right parietal cortex, associations that may be refreshed by a process of sequential, selective attention (perhaps corresponding to an inner scribe) that engages the right superior parietal cortex, right premotor cortex and right FC.

In summary, imaging studies have produced good evidence for material-specific stores in posterior brain regions and some evidence for a left–right lateralization of FC regions for the rehearsal of verbal and spatial information, respectively. Contrary to suggestions from primate studies, however, there is little imaging evidence for ventral–dorsal object–spatial distinction in non-verbal maintenance tasks in humans. Rather, FC activation associated with the maintenance of object information appears to be more left-lateralized relative to that for the maintenance of spatial information. The FC region most consistently associated with the simple maintenance of verbal material is the left VLFC. The VLFC is often associated with the maintenance of spatial and object information (on the right for spatial information), though DLFC is also sometimes activated in these cases (e.g. Baker *et al.*, 1996a; Belger *et al.*, 1998).

Manipulation in working memory

Manipulation of the contents of WM involves an array of processes that may be loosely grouped under the heading of executive processes. Many different types of executive processes have been proposed and a huge range of different tasks have been examined. Without attempting a precise definition of different executive processes, we concentrate below on broad categories of manipulation task that have been used in neuroimaging: ‘*n*-back’, ‘reordering’, ‘generation’, ‘dual’ and ‘planning’ tasks. We emphasize that these terms are descriptive of the type of task employed and are not meant to imply different sets of executive processes.

N-back tasks

A task that combines maintenance and manipulation is the *N*-back task (Fig. 2D). This task requires the monitoring of a continuous sequence of stimuli; a positive response occurs whenever the current stimulus matches the stimulus *n* positions back in the sequence. For $n > 0$, this task requires both maintenance of the last *n* stimuli (in order) and updating of

these stimuli each time a new stimulus occurs (for $n = 0$ the task is simply to respond whenever a prespecified target occurs, thus no updating is required). The value of *n* is often viewed as proportional to the ‘working memory load’—the total demand placed on the maintenance and/or manipulation processes.

Braver and colleagues varied the verbal WM load by increasing *n* from 0 to 3 in a letter version of the *n*-back task (Braver *et al.*, 1997). Areas in which activity was a linearly increasing function of load included DLFC, VLFC and the parietal cortex, bilaterally in each case, as well as a number of left motor, premotor and supplementary motor areas. On the basis of the maintenance studies reviewed above, the VLFC, posterior parietal and motor activations are likely to reflect the network of areas involved in the maintenance of verbal information (e.g. the storage and rehearsal of the most recent *n* letters). If this is so, then these findings implicate the additional bilateral activation of DLFC in manipulation (e.g. updating of the particular letters being maintained).

In another study, Smith and colleagues (Smith *et al.*, 1996) reported bilateral DLFC/AFC activations in both a verbal and spatial 3-back task, though there is a tendency for greater left DLFC activation in the former and greater right DLFC activation in the latter (Smith and Jonides, 1997). In a similar study, Owen and colleagues compared spatial and object 2-back tasks (Owen *et al.*, 1998). Although differences between the spatial and object memory-related activations were observed in posterior regions, such as the posterior parietal cortex for the spatial task and the middle and anterior temporal cortex for the object task, the coordinates of the peaks of the bilateral DLFC/AFC activations for the two tasks were within 2 mm of each other. These data suggest that manipulation processes in DLFC are left–right lateralized for verbal versus spatial information, as for maintenance processes in VLFC, but that manipulation processes may be common to visual–spatial and visual–object WM. These two studies again question the specific dorsal–ventral spatial–object FC dissociation suggested by Goldman-Rakic, though support a material-specific left–right verbal–spatial FC lateralization.

Cohen and colleagues attempted to dissociate maintenance and manipulation in an *n*-back task by using event-related fMRI to measure activity at four intervals after each trial (Cohen *et al.*, 1997). Brain regions involved in transient processes, such as perceiving stimuli and producing responses, were predicted to show an effect of time but no effect of load (*n*). As expected, these regions included the visual and motor cortices. Regions involved in sustained processes, such as maintenance, were predicted to show an effect of load but not time. These regions included bilateral VLFC and right DLFC. Regions associated with transient manipulation processes, such as updating the *n* items to maintain, were predicted to show an interaction between load and time (i.e. greater transient effects at higher loads). The only lateral prefrontal region to show this pattern was left

VLFC. Though this was not the FC region that might have been expected on the basis of the above studies (i.e. the DLFC), this experiment illustrates the opportunity afforded by event-related studies to dissociate FC processes by time as well as condition.

Reordering tasks

The use of event-related fMRI to distinguish transient and sustained effects in WM tasks is clearly an important methodological advance, and one that is likely to prove valuable in teasing apart perception and maintenance, and maintenance and manipulation. D'Esposito and colleagues have used this technique to isolate brain regions responsive during the presentation, delay and probe phases of WM trials (see also Courtney *et al.*, 1997). D'Esposito and colleagues (D'Esposito *et al.*, 1999) and Postle and colleagues (Postle *et al.*, 1999), for example, presented subjects with a sequence of five letters, followed by either a 'forward' or an 'alphabetize' instruction. After a delay of 8 s, a probe was presented that consisted of a letter and a digit (Fig. 2E). The subject's task was to indicate whether the probe letter would appear in the position denoted by the probe digit if the sequence of five letters were maintained in the (original) forward order (in the 'forward' trials), or if the five letters were rearranged into alphabetical order (in the 'alphabetize' trials). The former trials require only the maintenance of five letters in order, whereas the latter trials require additional manipulation (i.e. reordering). Both VLFC and DLFC were responsive during the delay period, but DLFC showed a greater response during the alphabetize trials (bilaterally in all cases). Though broadly consistent with the process-specific FC model of Petrides and colleagues, these studies suggest a nested organization in which both VLFC and DLFC are involved in maintenance, but only DLFC is additionally involved in manipulation.

Generation tasks

In the self-ordering task mentioned earlier, stimuli must be generated without repetition, one at a time, from a finite set. This task has been explored in neuropsychological (Petrides and Milner, 1982) and neuroimaging studies. Petrides and colleagues (Petrides *et al.*, 1993a, b) compared brain activity during the performance of a self-ordering task with activity during a control task in which participants responded to externally produced stimuli, without the requirement to order their own responses. When abstract figures were used, the self-ordering task produced greater activation in right DLFC, as predicted (Petrides *et al.*, 1993a), supporting the right lateralization of manipulation processes in visuospatial WM. With verbal stimuli (digits), DLFC activation was bilateral (Petrides *et al.*, 1993b). This FC activation did not depend solely on the self-generated nature of the ordering task: when an externally ordered condition was tested in which participants listened to a random sequence of digits in order

to detect which digit was omitted, the same bilateral DLFC activation was observed (Petrides *et al.*, 1993b).

A related task is random number generation (Baddeley, 1966), in which numbers must be generated without conforming to any rule or pattern. Tasks like these involve not only internal monitoring of previous responses (as in self-ordering tasks), but also inhibition of prepotent responses and well-learned routines. Frith and colleagues reported bilateral DLFC activations when generative, random key pressing was compared with reactive, stimulus-driven key pressing (Frith *et al.*, 1991). Jahanshahi and colleagues observed left DLFC activation when random number generation was compared with counting, and this activity was negatively related to indices of randomness at higher generation rates (Jahanshahi *et al.*, 2000). Interestingly, VLFC activation was also seen when random number generation was compared with counting, but did not correlate with indices of randomness or the generation rate, supporting the proposal that this region is involved in maintenance processes that are required by, but not related to, random generation.

Other generation tasks, such as verbal fluency, a common clinical test of frontal lobe damage, involve the selection of stimuli from much larger sets. The verbal fluency task requires generation without repetition of, for example, as many animal names (category fluency) or words beginning with a specified letter (letter fluency) as possible in a short period of time. This task involves not only monitoring but also the development of new strategies to aid generation (e.g. when a subject is required to generate as many animals as they can, they may begin by thinking of pets, then safari animals, etc.). The PET study of Frith and colleagues found left DLFC activation when letter fluency was compared with word repetition (Frith *et al.*, 1991).

Considerable evidence thus exists for a role of DLFC, on the left for verbal and the right for visuospatial information, in the manipulation processes necessary for generation tasks.

Dual tasks

Performing two tasks simultaneously makes demands on WM (Baddeley, 1986), most probably reflecting the switching between information appropriate for one or other task. Patients with frontal lesions may be disproportionately impaired in dual-task versus single-task performance (McDowell *et al.*, 1997), again suggesting a frontal role in these aspects of WM. D'Esposito and colleagues compared brain activity when participants performed two tasks concurrently with the brain activity when each task was performed alone (D'Esposito *et al.*, 1995). Neither of the two tasks, a spatial rotation task and a semantic judgement task, produced significant activation of DLFC when performed alone; only when they were combined was significant bilateral activation of this area observed. This activation was unlikely to be due simply to the impaired performance of both tasks when combined, because a second experiment in which performance of the rotation task was impaired by decreasing the

interval between stimuli did not reveal any significant increase in DLFC activity. However, in another dual-task study, using a visual and an auditory task in which participants indicated when a stimulus was of lower luminance or pitch than the previous stimulus, Klingberg and colleagues found no cortical area that was activated specifically in the dual-task condition (Klingberg *et al.*, 1998). Moreover, Goldberg and Berman found that the DLFC activation associated with the Wisconsin Card-Sorting task was actually diminished when combined with an auditory verbal shadowing task (Goldberg and Berman, 1998), and Fletcher and colleagues found that the DLFC activation associated with elaborative verbal encoding was diminished when the task was combined with a visuo-motor secondary task (Fletcher *et al.*, 1998*b*). One possible explanation for these results is that one or both tasks, unlike the tasks used by D'Esposito and colleagues, included manipulation requirements even when performed alone, activating DLFC. This might leave less scope for additional DLFC activation when the tasks are combined, or even a decrease in DLFC activation when the performance of both tasks suffers under dual-task conditions (for arguments against the association of specific regions with the executive demands of dual-tasking, see Adcock *et al.*, 2000; Bunge *et al.*, 2000).

Planning tasks

Shallice introduced the Tower of London task in order to test planning deficits in patients with frontal lesions (Shallice, 1982). Participants in this task must rearrange a set of balls in order to match a specified goal state. Because of the constraints on legal movements of the balls, this task requires advance planning of a number of separate moves in order to attain the goal state, often via various subgoals, in the minimum number of moves. Owen and colleagues found activation of left DLFC associated with this task relative to a simple visual-motor control, as well as several regions in the right premotor and parietal cortices that may be associated with visuospatial maintenance (Owen *et al.*, 1996). Baker and colleagues used a version of the Tower of London task requiring no movement (participants were shown an initial state and a goal state and simply indicated the minimum number of moves from the initial to the goal state) (Baker *et al.*, 1996*b*). They found that subtraction of easy (two or three moves) from difficult (solutions involving four or five moves) conditions revealed activation in bilateral DLFC and right AFC. These studies are at least suggestive of a (perhaps bilateral) role of DLFC in manipulation, even if manipulation was not completely dissociated from maintenance in this task.

The study by Baker and colleagues (1996*b*) is also one of the few WM studies we have considered thus far, apart from some *n*-back tasks with large *n* (Smith *et al.*, 1996; Owen *et al.*, 1998), in which AFC was activated. This activation is perhaps related to the complex planning required in the Tower of London task, which includes setting up and maintaining multiple subgoals at the same time as making (or imagining) movements between states. A more recent study showed an

association between bilateral AFC activation and a 'branching' task (Koechlin *et al.*, 1999). This task also required the participant to maintain an overall goal while concurrently setting and achieving subgoals. Importantly, the AFC activation was selective to the branching condition, and was not seen in comparable control conditions that required either switching attention between goals (dual-tasking, which activated right DLFC instead) or simply maintaining a single goal. In another WM study that activated AFC (MacLeod *et al.*, 1998), participants watched a sequence of words and kept a running count of the number of words that were names of dangerous animals. Relative to a passive word-viewing condition, activations were seen in both right DLFC and right AFC. Like the branching task, this task might also be viewed as entailing the maintenance and periodic updating of one type of goal information while a demanding task (semantic evaluation) is performed concurrently.

In a recent PET study, Burgess and colleagues observed bilateral AFC activation across a set of different prospective memory tasks (Burgess *et al.*, 2000*a*). These tasks again required delayed realization of an intention while performing a different task. Thus AFC activation may reflect a third level of executive control, beyond the manipulation in DLFC and maintenance in VLFC. Though this level of executive control is difficult to isolate and control in the laboratory setting, it is likely to be a vital component of everyday life (Burgess *et al.*, 2000*b*), such as when we are interrupted with a question while performing a complex task like reading.

Other working memory tasks

Yet more complex problem-solving tasks have been investigated with functional imaging, such as Wisconsin Card-Sorting, Raven's matrices, and inductive reasoning. These tasks have also tended to activate AFC as well as DLFC (for a review, see Christoff and Gabrieli, 2000). The component processes of such complex tasks remain even less well understood, however, and we do not discuss them further here.

Summary

Functional imaging of human WM has provided considerable evidence that broad anatomical divisions within the lateral FC subserve different processes. This evidence is summarized in Table 1. VLFC, for example, is more often activated during tasks requiring maintenance and DLFC is more often activated during tasks requiring manipulation. This is more consistent with the view of Petrides (Petrides, 1994) than with that of Goldman-Rakic (Goldman-Rakic, 1987). Nonetheless, there also appears to be a lateralization of FC processes according to the type of material. Though the FC activations are often bilateral (relative to baseline tasks), direct comparisons of verbal and spatial tasks suggest that left VLFC is primarily concerned with the maintenance of verbal information and right VLFC with the maintenance of spatial

Table 1 Working memory studies

	VLFC		DLFC		AFC	
	Left	Right	Left	Right	Left	Right
Awh <i>et al.</i> (1996)						
Verbal Sternberg	+	–	–	–	–	–
Paulesu <i>et al.</i> (1993)						
Verbal Sternberg	+	–	–	–	–	–
Jonides <i>et al.</i> (1993)						
Spatial Sternberg	–	+	–	–	–	–
Smith <i>et al.</i> (1996)						
Spatial–verbal Sternberg	–	+	–	–	–	–
Verbal–spatial Sternberg	+	–	–	–	–	–
Smith and Jonides (1994)						
Object Sternberg	+	–	–	–	–	–
Smith <i>et al.</i> (1995 <i>b</i>)						
Spatial–object Sternberg	–	+	–	–	–	–
Belger <i>et al.</i> (1998)						
Spatial–object Sternberg	–	–	–	+	–	–
Object–spatial Sternberg	+	–	+	+	–	–
McCarthy <i>et al.</i> (1996)						
Spatial–object running span	–	–	–	+	–	–
Object–spatial running span	+	–	+	+	–	–
Baker <i>et al.</i> (1996 <i>a</i>)						
Spatial–object delayed	–	–	–	+	–	–
Object–spatial delayed	–	–	+	–	–	–
Braver <i>et al.</i> (1997)						
Increasing <i>n</i> in verbal <i>n</i> -back	+	+	+	+	–	–
Smith <i>et al.</i> (1996)						
Verbal 3-back	+	–	+	+	+	+
Spatial 3-back	–	–	+	+	+	+
Owen <i>et al.</i> (1998)						
Spatial 2-back	–	–	+	+	+	+
Object 2-back	–	–	+	+	+	+
Cohen <i>et al.</i> (1997)						
Increasing <i>n</i> in verbal <i>n</i> -back	–	+	–	+	–	–
D'Esposito <i>et al.</i> (1999)						
Alphabetization	–	–	+	+	–	–
Petrides <i>et al.</i> (1993 <i>a</i>)						
Spatial reordering	–	–	–	+	–	–
Petrides <i>et al.</i> (1993 <i>b</i>)						
Verbal reordering	–	–	+	+	–	–
Frith <i>et al.</i> (1991)						
Random key-pressing	–	–	+	+	–	–
Letter fluency	–	–	+	–	–	–
Jahanshahi <i>et al.</i> (2000)						
Random key-pressing	–	–	+	–	–	–
D'Esposito <i>et al.</i> (1995)						
Dual- versus single-tasking	–	–	+	+	–	–
Owen <i>et al.</i> (1996)						
Planning versus difficult control	–	–	+	–	–	–
Baker <i>et al.</i> (1996 <i>a</i>)						
Planning versus control	–	–	+	+	–	+
Koechlin <i>et al.</i> (1999)						
Branching versus dual-tasking	–	–	–	–	+	+
Burgess <i>et al.</i> (2000 <i>a</i>)						
Prospective memory	–	–	–	+	+	+
MacLeod <i>et al.</i> (1998)						
Semantic monitoring	–	–	–	+	–	+

+ = Significant activation detected; – = no significant activation detected. Note that the label for each comparison is descriptive only; for more details see text. Studies are ordered according to their order of appearance in the text.

information. The maintenance of object information is sometimes left-lateralized, though the overall pattern is less clear. There is thus an apparent discrepancy between the findings from human and primate studies, because some of the latter have supported a ventral–dorsal object–spatial distinction. There may be several reasons for this. One possibility is a difference in the functional–anatomical mapping in the two species, contributed to by the effects of language evolution in humans. Indeed, one problem with human experiments is the potential for people to recode visuospatial stimuli verbally, effectively converting an object task, for example, into a verbal one (though this is difficult to imagine for very abstract visual stimuli). One solution may be to combine imaging of visuospatial tasks with concurrent articulatory suppression, to prevent verbal recoding of the stimuli. Another possibility is that both process-specific and domain-specific specializations exist within the human DLFC, but the current resolution of imaging techniques is unable to distinguish them.

Imaging studies have also supported the dissociations between storage and rehearsal of verbal and spatial information proposed by cognitive psychological models (e.g. Baddeley and Hitch, 1974). The demands of storage engage posterior brain regions, including the parietal, temporal and occipital lobes, whereas rehearsal engages a network of regions that include VLFC. As mentioned above, the cortical loci of both storage and rehearsal are left-lateralized for verbal information and right-lateralized for spatial information (consistent with different slave systems). Imaging studies have also highlighted the shortcomings of this model, particularly regarding the central executive. [This is a problem acknowledged by Baddeley (1996), who admitted that the central executive has been a rag-bag containing a potentially heterogeneous set of executive functions.] The evidence summarized above suggests that DLFC and AFC regions are associated with executive control of WM. Manipulation processes, operating on information already maintained in memory, engage DLFC, whereas more complex processes that entail maintaining the goals and products of one task while performing another, appear to engage AFC. These higher-level processes may also be lateralized; there is some evidence for left dominance for verbal material and right dominance for spatial material, though the evidence is less clear in this respect than for maintenance processes [perhaps because there have been fewer direct comparisons (see also Postle and D'Esposito, 2000)]. Nonetheless, while we regard the imaging data as good evidence for some functional specialization within FC, more precise definition of these functions remains constrained by our limited understanding of the commonalities and differences between the component cognitive processes involved in the range of different WM tasks that have been studied.

Frontal function in long-term memory tasks

Neuropsychological studies of patients with focal brain lesions have highlighted the importance of medial temporal

and diencephalic structures in human long-term declarative memory (Squire and Cohen, 1984). Functional neuroimaging studies of healthy subjects, however, have emphasized the engagement of FC structures during the performance of LTM tasks. FC lesions do not cause the same global amnesia that can result from medial temporal/diencephalic lesions, but they are associated with impairments in more complex memory tasks, such as memory for temporal order (Janowsky *et al.*, 1989) and tasks with high levels of interference (Incisa Della Rocchetta and Milner, 1993). FC activations during LTM tasks are, therefore, likely to reflect control processes that aid and optimize memory encoding and retrieval, rather than more automatic storage processes.

Most neuroimaging experiments on LTM consist of two phases: a study phase, in which multiple stimuli are presented (with or without explicit instruction to remember the stimuli), and a test phase, during which these stimuli must be recalled, or recognized from among other stimuli. The majority of these studies have used familiar words as stimuli. These studies allow a clear distinction between two types of LTM (Tulving, 1983): semantic memory, the knowledge of the words' meanings and associations, and episodic memory, the memory that a word was presented in a particular context in the past (i.e. the study phase). Thus, when a word such as DOG is presented during the study phase, information about its meaning and close associates (e.g. CAT) is likely to be retrieved from long-term semantic memory, and this information may be combined with contextual information in the encoding of a new episodic memory. If the word is presented again during a recognition test phase, information about its prior occurrence in the study phase may be retrieved from episodic memory. Given the long history of laboratory study of verbal learning and memory and the high level of experimental control afforded by such material (e.g. physical form, frequency, imageability and semantic associations), we focus here on neuroimaging studies of verbal episodic memory.

A clear methodological advantage of functional neuroimaging over neuropsychology is the possibility of dissociating the encoding and retrieval stages of episodic memory, given that it is difficult to attribute a patient's anterograde memory deficit specifically to either an encoding or a retrieval problem. Attempts to dissociate encoding and retrieval by neuroimaging are rarely straightforward, however, as they may share a number of subprocesses. For example, both are likely to involve searches of semantic memory, first to produce a rich memory trace of the encoding episode, and later to generate cues that aid access to that trace. Furthermore, an attempt to retrieve a word from episodic memory may result in a train of associative thought that will become the substrate of a further encoding episode. Thus the encoding–retrieval distinction is driven more by the format of the typical episodic memory task than by consideration of the executive processes involved. Nonetheless, one goal of functional imaging researchers over the last few years has been to isolate more specifically the cognitive processes that

differentiate encoding from retrieval. The encoding–retrieval distinction, therefore, provides a useful means of organizing our review of previous neuroimaging research.

Frontal function in long-term memory encoding

Many moment-to-moment experiences are forgotten; only some can later be remembered. For the purposes of this review, we define encoding as the process(es) that allow subsequent explicit (conscious) retrieval of memories. Early studies examining memory encoding showed evidence for the engagement of left FC. This functional lateralization formed part of the influential hemispheric encoding–retrieval asymmetry (HERA) generalization, which associates greater left than right FC activation with episodic encoding, and greater right than left FC activation with episodic retrieval (Tulving *et al.*, 1994a). Furthermore, the left lateralization during encoding is found whether or not subjects are aware that their recall will be tested later. That is, left FC activation is found in both incidental (Kapur *et al.*, 1994) and intentional (Shallice *et al.*, 1994) memory encoding.

The evidence for FC activation in incidental encoding comes from studies that manipulate the degree of semantic processing of verbal material. The relationship between semantic processing and memory encoding is referred to as the ‘depth of processing’ effect (Craik and Lockhart, 1972), whereby tasks producing better recall (‘deep encoding tasks’) are generally those that emphasize the meaning of items rather than their surface features (although recall performance can also depend on the nature of the subsequent retrieval task (Morris *et al.*, 1977)). Kapur *et al.*, for example, compared a deep encoding task (judging whether words referred to living or non-living entities) with a shallow encoding task (judging whether words contained the letter ‘a’) (Fig. 3A) (Kapur *et al.*, 1994). They found the anterior and posterior regions of VLFC to be associated with deep encoding, despite the fact that subjects were unaware that their memory would be tested subsequently.

In a study of intentional memory encoding, Shallice and colleagues used a paired associate task in which subjects were instructed to learn the pairings of a category (e.g. ‘poet’) with a specific exemplar (‘Owen’) (Fig. 3B) (Shallice *et al.*, 1994). When contrasted with a passive listening task, activation was seen in an anterior region of left VLFC. This activation was reduced when learning occurred in the presence of a distracting motor task. Moreover, this distraction produced an impairment in subsequent cued recall, suggesting that the processes associated with left VLFC activation are important for successful encoding.

Early PET studies, therefore, established a link between left FC (predominantly VLFC) and successful word encoding. Converging evidence comes from studies that have explicitly correlated brain activity during a study task with subsequent retrieval performance. Using the event-related or trial-specific

analyses afforded by the faster acquisition times of fMRI, it is possible to scan people during the study phase of a memory task, measure their retrieval performance after scanning, and then use their memory performance to sort stimuli, *post hoc*, into those that were remembered and those that were forgotten. That is, each stimulus can be associated with either a ‘successful’ or an ‘unsuccessful’ encoding event. Using this approach, Wagner and colleagues showed that activity in left posterior VLFC was higher during the presentation of words that were subsequently remembered confidently than during presentation of those that were forgotten (Wagner *et al.*, 1998c). Given that the study task remained constant, this is more direct evidence that the left FC region is related specifically to successful encoding. In a similar event-related study using visuospatial rather than verbal material, Brewer and colleagues showed that *right* FC activity is associated with encoding success (Brewer *et al.*, 1998). This raises the question of whether the left lateralization of FC activations during encoding tasks is specific to the use of verbal material. We return to this question later.

Assuming, as the evidence strongly suggests, that successful encoding of verbal material engages left FC, the goal is to understand the component processes that contribute to this success. More generally, we know from behavioural studies that successful encoding depends not just on semantic processing, but also on, for example, the level of attention, the degree to which material is organized, and the extent to which visual imagery is used. Indeed, the depth of semantic processing and degree of divided attention can be shown to have separable effects (Craik *et al.*, 1996). The relationship between left FC activations and these different encoding-related processes therefore deserves closer consideration. The original suggestion of Tulving and colleagues that left FC activation is associated with the retrieval of semantic attributes of studied material (Tulving *et al.*, 1994a) has been both expanded (Gabrieli *et al.*, 1998) and re-evaluated (Thompson-Schill *et al.*, 1997). In brief, the main positions with regard to the role of left FC at encoding can be summarized as: (i) the generation/retrieval of semantic attributes and associates of a word (Tulving *et al.*, 1994a); (ii) the maintenance (in ‘semantic WM’) of these attributes and associates (Gabrieli *et al.*, 1998); (iii) the selection of task-appropriate attributes or associates from among those associated with the word (Thompson-Schill *et al.*, 1997); and (iv) the organization of multiple words or associates on the basis of those attributes (Fletcher *et al.*, 1998a). We shall refer to these positions as the ‘generation’, ‘maintenance’, ‘selection’ and ‘organization’ views of the contribution of the left FC to encoding.

Before evaluating these four processes, we observe that the picture is complicated by the fact that they seem to form a hierarchy: semantic information cannot be maintained on-line until it is first generated, and it cannot provide the basis for selection without on-line maintenance. Furthermore, effective organization of multiple items is unlikely to proceed unless appropriate attributes have been selected. Therefore,





(A) Single word encoding			
'Deep' encoding task <i>E.g. Living/non-living?</i>		'Shallow' encoding task <i>E.g. Contains letter 'a'?</i>	
<i>Chick...</i>	Y	N	
<i>Party...</i>	N	Y	
(B) Paired associate encoding			
Random	Related	Category-exemplar	
<i>Party...Tree</i> <i>Baby...Cloud</i>	<i>Chick...Bird</i> <i>Study...Notes</i>	<i>Poet...Owen</i> <i>Fish...Salmon</i>	
(C) Verb generation			
High Selection		Low Selection	
<i>Wheel-?</i>	TURN (ROLL, SKID...)	<i>Scissors-?</i>	CUT...
<i>Rope-?</i>	CLIMB (TIE, PULL...)	<i>Kite-?</i>	FLY...
(D) Classification			
High selection		Low selection	
 <i>Expensive?</i>	YES	 <i>Shark?</i>	YES
 <i>Heavy?</i>	NO	 <i>Banana?</i>	NO
(E) Comparison			
High selection <i>Most similar colour?</i>		Low selection <i>Most similar generally?</i>	
<i>Tooth...Tongue or Bone?</i> <i>Seagull...Crow or Dove?</i>		<i>Flea...Tick, Well, Shoe or School?</i> <i>Raisin...Ice, Suit, Tusk or Prune?</i>	
(F) Paired associate encoding with Proactive Interference			
Initial	Repeated....	Repairing	
<i>Chick...Bird</i> <i>Study...Notes</i> <i>Party...Ballroom</i> <i>Baby...Labour</i>	<i>Chick...Bird</i> <i>Study...Notes</i> <i>Party...Ballroom</i> <i>Baby...Labour</i>	<i>Chick...Baby</i> <i>Study...Ballroom</i> <i>Party...Labour</i> <i>Bird...Notes</i>	
(G) Organization			
	Low structure known; items organized	Medium structure known; items not organized	High structure unknown; items not organized
Breads	<i>Rye</i> <i>Naan</i>	<i>Beef</i> <i>Melon</i>	<i>Beef</i> <i>Melon</i>
Meat	<i>Ham</i> <i>Beef</i>	<i>Herring</i> <i>Orange</i>	<i>Herring</i> <i>Orange</i>
Fruit	<i>Orange</i> <i>Melon</i>	<i>Rye</i> <i>Naan</i>	<i>Rye</i> <i>Naan</i>
Fish	<i>Haddock</i> <i>Herring</i>	<i>Haddock</i> <i>Ham</i>	<i>Haddock</i> <i>Ham</i>

Fig. 3 Schematic representation of episodic memory encoding tasks. The stimuli shown in **D** are not the specific ones used by Thompson-Schill and colleagues (Thompson-Schill *et al.*, 1997).

the close relationship between these processes provides a challenge for experimenters attempting to dissociate them at the functional anatomical level.

Left frontal cortex and semantic generation

There is considerable evidence for the involvement of the left FC in the semantic processing of verbal material. The earliest functional neuroimaging evidence came from PET studies of language processing in which subjects were presented with nouns and required to generate semantically appropriate verbs (Petersen *et al.*, 1988; Raichle *et al.*, 1994). One study comparing semantically based decisions on words with pitch-based decisions on tones showed activations across widespread regions of left FC (Binder *et al.*, 1997). Likewise, Gabrieli and colleagues observed extensive left FC activation when subjects made semantic as opposed to phonological judgements (Gabrieli *et al.*, 1998). Other studies produced evidence that left VLFC is commonly activated when subjects make semantically based decisions on both words and pictures (Vandenberghe *et al.*, 1996) and when they name the colour of objects depicted by line drawings (Wiggs *et al.*, 1999). It might be argued that such semantic processing tasks are simply more difficult (e.g. more demanding of attentional resources) than their control tasks, this non-specific difficulty producing FC activation. Evidence against this alternative comes from an fMRI study showing that left posterior VLFC was more active during a deep than a shallow encoding task, but that this activation was insensitive to task difficulty (Demb *et al.*, 1995). Moreover, studies that compare deep and shallow encoding tasks typically ensure that the judgements required in the shallow tasks (e.g. deciding whether the first and last letter of a word are in alphabetical order) take longer and are subjectively more difficult than those required by the deep tasks (Otten *et al.*, 2001).

Because this type of semantic processing is normally associated with better subsequent memory, Tulving *et al.*, suggested that the left FC activation is related to successful encoding (Tulving *et al.*, 1994a). In particular, they drew attention to the observation that the left posterior VLFC and DLFC activation associated with verb generation (Fig. 3C) was stronger when subjects were performing the task initially (Raichle *et al.*, 1994). With practice, left FC activation disappeared. Similar decreases in response in left FC occur with repeated semantic decisions (Demb *et al.*, 1995). Even in intentional learning tasks, left FC activation decreases with repeated semantic processing of items. When Kopelman and colleagues, for example, correlated blood flow estimates with a measure of learning increments (which decreased with repetition), they found that the more learning that occurred the greater the level of activation in left DLFC (Kopelman *et al.*, 1998). Activation of left VLFC was associated with novel rather than repeated words. These findings are consistent with encoding into episodic memory occurring only for novel processing of the study material.

A common requirement in many of these tasks (e.g. verb

generation) is the production of a verbal response on the basis of its semantic relevance to a cue. This generally involves both the retrieval of relevant semantic features of the cue and the retrieval of the phonological/articulatory features of the response. Price and colleagues argued that the left FC activations in these tasks reflect general strategic processes to do with response production rather than semantic processes *per se* (Price *et al.*, 1997), in which case the practice-related left FC deactivations may relate to these general aspects of task performance. Poldrack and colleagues, however, explored functional divisions within left FC using simple semantic (abstract/concrete decisions), phonological (syllable counting) and low-level perceptual control (upper-case/lower-case) judgements that required minimal strategic processing (Poldrack *et al.*, 1999). Semantic judgements activated extensive left FC regions relative to the control, whereas phonological judgements activated a more focal, posterior left VLFC region. Direct comparison of the semantic and phonological conditions revealed a more anterior VLFC activation associated with semantic judgements. Poldrack and colleagues therefore proposed a broad division of VLFC into a posterior region concerned with phonological production (common to both semantic and phonological tasks) and a more anterior region concerned specifically with semantic processing. This would suggest that the semantic contribution to successful encoding may derive specifically from the anterior regions of VLFC. As described below, however, the posterior regions of VLFC have also been associated with selection from among semantic attributes, a process that may be important for encoding.

Left frontal cortex and semantic maintenance

Further consideration of the left FC contribution to language and memory has led to the suggestion that it has a role in 'domain-specific semantic WM' (Gabrieli *et al.*, 1998). Gabrieli and colleagues acknowledge the relationship of this suggestion to the broader view (Goldman-Rakic, 1998) that FC may be parcellated on the basis of the domains over which WM processes operate (see above, under Frontal function in working memory tasks). A number of observations are cited to support their claim. First, of course, it is consistent with the observations made in the studies of semantic generation cited above. Furthermore, Gabrieli and colleagues produced evidence that the left FC activation reflects maintenance processes rather than the processes required to generate a response *per se* (Gabrieli *et al.*, 1998). They compared brain responses with two types of word-stem completion. In the first type, the word stem could be completed in many ways (e.g. STA). In the second, they used word stems that could form the beginning of only a limited number of words (e.g. PSA). Subjects were instructed to complete each stem with the first word that came to mind. In this way, it was argued, they could dissociate the effort or search required in generating a response (maximized when word stems allowed few possible completions) from the amount of material that

subjects produce in making their response (maximal when the stems had many completions). They found greater left DLFC activation in association with word stems offering many rather than few possibilities, and concluded that this activation reflected the increased amount of material that was maintained in semantic WM.

One important issue raised by these results, however, is whether FC is associated with holding a set of possible responses on-line or whether it reflects the selection of one response from this set. Gabrieli and colleagues acknowledge this and ponder whether 'the amount and selection of information are inevitably intertwined or whether those two processing dimensions can be dissociated'. The possibility that the core function of left FC lies in selection is addressed in the next section.

Left frontal cortex and selection

Thompson-Schill and colleagues have suggested that left VLFC activation reflects the selection of semantic attributes from competing alternatives. They provided two strands of evidence to support this assertion. The first comes from a study (Thompson-Schill *et al.*, 1997) in which three types of task were compared: the generation of an appropriate response (Fig. 3C), the classification of a stimulus (Fig. 3D) and comparison of two or more stimuli (Fig. 3E). Crucially, each of these tasks was performed at two levels of selection. Their prediction of increased left FC activation in the high-selection condition compared with the low-selection condition was borne out in each of the three tasks. Interestingly, the focus of common activation appeared to be in more posterior and dorsal regions of VLFC and, indeed, for two of the tasks, classification and comparison, it localized to DLFC in our classification. Their interpretation that this broad region supports the selection of a response, of course, hinges upon the degree to which they successfully dissociated the level of selection from the amount of material generated: a difficult problem, as Gabrieli and colleagues observed (Gabrieli *et al.*, 1998). In the case of the generation and classification tasks, the high-selection condition was likely to involve the retrieval of a greater number of stimulus features than the low-selection condition, so it is unclear whether the dissociation was made successfully. Thompson-Schill and colleagues were most confident of their dissociation in the comparison task because, in the high-selection condition, subjects made a decision on the basis of a prespecified dimension (colour, function or shape), whereas in the low-selection condition a comparison judgement was based upon global features. If anything, they argued, more semantic features were likely to be produced in the latter task than the former task. This argument presupposes that the comparison condition is not treated as a simple classification task. That is, if subjects are given a target word (e.g. 'raisin') and required to select from among four alternatives in order to make a similarity judgement (e.g. 'ice', 'suit', 'tusk', 'prune') they may learn rapidly that the most efficient way of doing this is not to

retrieve a series of features of the target word until they find one that matches one of a series of features retrieved for the alternatives. Rather, the simplest approach would seem to be to classify the target (e.g. 'fruit') and identify the alternative that also falls into this classification. If this strategy were adopted for the low-selection condition, one could argue that the additional requirement to retrieve semantic information about a prespecified dimension in the high-selection condition would impose greater demands on generation and maintenance rather than selection. A further subtlety of the experimental design, however, was the introduction of two levels of the low-selection condition, involving different numbers of alternatives (two or four). No increase in the left FC response was observed when comparing two-choice with four-choice comparison conditions. This is less consistent with the generation or maintenance accounts, although, of course, caution should be exercised in drawing firm conclusions from a negative result.

Their second line of evidence comes from the idea that production of semantically relevant responses will require a greater level of selection when competing responses are introduced. In another study, subjects were scanned while generating colours or actions appropriate to cue words (Thompson-Schill *et al.*, 1999). Scanning occurred on the second presentation of these cues, and two conditions were compared. In the high-competition condition, an action had to be generated to a cue word previously generating a colour (or vice versa). In the low-competition condition, the same task (action or colour generation) was performed on a cue word during its first and second presentations. The high-competition condition produced greater left posterior VLFC activation, as predicted; this is consistent with increased selection demands (by assuming that the semantic attributions produced by the first presentation compete with those produced during the second presentation).

The selection hypothesis receives some support from studies that have manipulated the degree of 'proactive interference' during incremental learning tasks. Proactive interference refers to the reduced facility with which the encoding of a new association to a given stimulus occurs when a different association has already been learned. Activity in left DLFC during the encoding of word-paired associates was found to be greater when they had already been presented in different pairings than when they were novel (Dolan and Fletcher, 1997). That is, if subjects studied the pair DOG-BOXER during scanning, when they had previously studied DOG-LABRADOR, this region was more active than if an entirely new pair was presented during scanning. In an fMRI follow-up to this PET experiment (Fletcher *et al.*, 2000), subjects were presented repeatedly with a set of semantically related word pairs, after which they were presented with the same words again but in different pairings. Scanning occurred throughout this cycle, so that changes in FC could be observed as pairs became increasingly familiar and then when they were rearranged. The new pairings emphasized a different semantic relationship (Fig. 3F). Left posterior VLFC was

activated when initial learning was compared with the baseline task. Moreover, in keeping with previous observations (Raichle *et al.*, 1994; Demb *et al.*, 1995), repeated learning of the same pairs was associated with reduced levels of activity in this region. When the words were re-paired, however, this activation increased again. Furthermore, this activation was significantly greater than when a completely novel set of words was presented. The latter suggests that it is not word novelty *per se* that is important here, but novelty of the semantic processes performed on those words. This observation is consistent with an association between left posterior VLFC and the requirement to select from among semantic attributes.

With regard to the question of whether these experiments have been truly successful in dissociating selection from the generation and maintenance processes, one cannot be entirely confident. It might be argued that the re-pairing condition would be associated with two sets of semantic information: that pertaining to the previous pairing of the words and that pertaining to the new pairing. The net result would be a greater level of semantic generation (and maintenance) in this condition. This argument is difficult to answer, although Fletcher and colleagues suggested that it is not a satisfactory explanation for the left FC activation in the re-pairing condition because the previously learned pairing had ceased to engender activation in this region (i.e. by the fourth presentation of the original pairings, activity had fallen to a baseline level) (Fletcher *et al.*, 2000).

Thus, this set of highly comparable experiments (Dolan and Fletcher, 1997; Thompson-Schill *et al.*, 1997, 1999; Fletcher *et al.*, 2000) suggests that selection from among semantic attributes of studied verbal material is associated with activation of DLFC and posterior regions of VLFC. It is possible that minor differences in experimental design explain these subtle differences in localization. It is also possible, however, that limitations in spatial resolution make it difficult to differentiate fully between DLFC and VLFC regions on the basis of PET and fMRI localizations, particularly in group studies.

Left frontal cortex and organization

We know from behavioural experiments that divided attention while the subject is at study impairs subsequent memory (Baddeley *et al.*, 1984), and organization of study material aids subsequent memory (Segal and Mandler, 1967). In a PET study, Fletcher and colleagues manipulated both the level of attention to and the degree of organization of study material (Fletcher *et al.*, 1998a). Subjects were presented with word lists and were required to engage in one of three levels of organization (Fig. 3G). Left DLFC activity was maximal when organizational demands were greatest. Furthermore, when attention was divided between encoding and a concurrent motor distraction task, the DLFC activation related to the most organizationally demanding task was attenuated. Subsequent retrieval was also correspondingly

impaired. It was concluded that the left DLFC activation reflected the organization of study material, and that the distractor task disrupted this process.

Wagner and colleagues performed a similar study using fMRI in an attempt to relate LTM encoding to WM processes (Wagner *et al.*, 1999). Subjects were presented with three words that they had either to maintain in the same order for a short period (using subvocal rehearsal) or to reorder along some abstract semantic dimension (e.g. pleasantness). Both tasks activated left VLFC, but the reordering task produced greater additional activation of left DLFC (consistent with the ventral–dorsal maintenance–manipulation distinction described in the section headed Frontal function in working memory tasks). The reordering task led to better subsequent memory, also implicating this region in encoding. This result is consistent with an association between organization, encoding and DLFC (Fletcher *et al.*, 1998a).

The idea that left DLFC somehow mediates the organization of appropriate stimulus attributes is consistent with more general proposals that FC supports a supervisory system that controls processing in novel situations (Norman and Shallice, 1986). More specifically, FC enables non-routine responses when the context demands that routine responses are no longer appropriate. Frith has extended this proposal in reviewing a number of functional imaging studies that are not explicitly concerned with memory encoding (Frith, 2000). The selection of a non-routine response, he suggests, requires the creation of an arbitrary category of appropriate responses and the suppression of responses that lie outside this *ad hoc* and temporary category. He refers to this as ‘sculpting of the response space’. This sculpting, a combination of identifying the appropriate and inhibiting the inappropriate semantic features, may be crucial to the selection and organization processes referred to in the last two sections. It may be that this sculpting is closely bound with episodic memory encoding, particularly in view of suggestions (Sussman, 1973; Shallice, 1988) that encoding occurs specifically in non-routine situations. With regard to the anatomical instantiation of such sculpting processes, Frith postulated DLFC to be crucial. However, as described above, the other studies of selection have emphasized the role of VLFC, and we should be cautious with our localizations, given that the border between the ventralmost DLFC and the dorsalmost ventral FC is not always clear.

Concluding section on encoding

In brief, there has been consistent activation of left FC in association with incidental and intentional verbal encoding tasks. However, this lateralization is not always clear-cut (it is sometimes bilateral, depending on the control task), and the few studies that directly compared the encoding of verbal with the encoding of non-verbal material have suggested that the lateralization reflects the type of material rather than the nature of the processing (Kelley *et al.*, 1998; Wagner *et al.*, 1998b). Left FC activations have been observed mainly in

DLFC and VLFC regions (few activations of AFC have been observed during the encoding tasks used typically) (Table 2). These activations tend to occur in association with tasks requiring the semantic processing of verbal material, and correlate with subsequent 'successful' retrieval. It is not yet possible to distinguish fully between theories that associate the activations with the generation, maintenance, selection or organization of semantic information. This is probably related to the fact that these processes are difficult to dissociate, and to the possibility that the anatomical regions subserving them may lie in close proximity.

Nevertheless, we can make informed guesses as to how these processes might be functionally segregated within left FC. The most common activation associated with tasks requiring simple retrieval of information from semantic memory (such as animacy judgements) appears to be in an anterior part of left VLFC. When this information must be held on-line in verbal WM, for more complex tasks activation may extend into more posterior VLFC regions (perhaps corresponding to phonological rehearsal; see section headed Frontal function in working memory tasks). When task conditions explicitly require selection among multiple possible responses or semantic features in WM, activation may further extend into DLFC. Such conditions include high levels of competition (e.g. from proactive interference) and those requiring reorganization of information (e.g. into some meaningful hierarchy that can guide subsequent retrieval). All these types of processing—the generation of semantic information, the maintenance of that information in WM, and the selection/organization of that information—will tend to lead to successful memory encoding.

Frontal function in long-term memory retrieval

A broad fractionation of memory retrieval should comprise a number of component processes. These include the cueing and interrogation of an episodic memory 'store', the reinstatement of episodic information in WM ('ecphory'; Tulving, 1983) and the evaluation or monitoring of this information. Even higher-level functions, such as the development of retrieval strategies and metamemory reasoning, should also be considered. Unfortunately, few detailed psychological models of these retrieval processes have been developed, and extant imaging studies have concentrated on more basic, operational distinctions between, for example, retrieval attempt and retrieval success (Tulving *et al.*, 1994b; Kapur *et al.*, 1995; Nyberg *et al.*, 1995; Rugg *et al.*, 1996). Nevertheless, it is possible to gain some insight into the brain regions mediating the component processes from an exploration of these studies.

For the purposes of this review, we categorize retrieval studies into those exploring the effects of the retrieval task itself (effects dependent upon e.g. task instructions or the nature of retrieval cues) and those manipulating the amount

of information retrieved (such as the ratio of old to new items and the depth to which the items were originally studied). These manipulations do not necessarily isolate distinct retrieval processes, and we will discuss interactions between these two factors subsequently. Ultimately, we attempt to formulate the results in terms of a specific retrieval model, based on that of Burgess and Shallice (Burgess and Shallice, 1996). It is important to note that there are other ways in which these studies may be organized. Thus, Rugg and Wilding, in a review of functional imaging studies of memory, discussed the literature in terms of retrieval mode, effort, success and orientation (Rugg and Wilding, 2000).

As in the section headed Frontal function in long-term memory encoding, we focus primarily on the majority of imaging studies that have used verbal material. In contrast to encoding studies, the early studies of verbal episodic retrieval reported activations in right rather than left FC (consistent with the HERA generalization). However, more recent studies, particularly those using event-related designs, have identified retrieval-related activation of both left and right FC.

Task effects: intentional versus incidental retrieval

Environmental cues exert a great influence upon retrieval. Compared with free recall, in which no cues are provided, the provision of external cues dramatically improves the amount of information retrieved. The strength of these cues, i.e. the degree to which they specify the nature of material to be retrieved, can vary from a 'copy' cue of the target item itself, as in recognition memory tasks, to an associate that was previously paired with the target, as in paired associate-cued recall. Other types of cues include a word-stem (e.g. ST_) or a word-fragment (e.g. S_E_). The stronger the retrieval cue, the more likely it is that information will be retrieved and the less important are specific retrieval strategies. Different types of retrieval task are summarized in Fig. 4.

External cues may evoke episodic retrieval whether or not subjects have been instructed to use these cues as the basis for a memory search, i.e. whether retrieval is incidental or intentional. The earliest imaging study to examine this distinction (Squire *et al.*, 1992) used a word-stem completion paradigm in which subjects were presented with three-letter stems during PET scanning. In the intentional retrieval condition, they were required to complete these stems with words they had seen during a prescan study phase (word-stem-cued recall). This condition was compared with an incidental condition in which stems were completed simply with the first word that came to mind. This comparison revealed right AFC activation associated with intentional retrieval. This anterior activation could reflect the engagement of effortful memory search, or it could reflect the amount of

Table 2 Encoding studies

	VLFC		DLFC		AFC	
	Left	Right	Left	Right	Left	Right
Kapur <i>et al.</i> (1994)						
Semantic decision	+	-	-	-	-	-
Shallice <i>et al.</i> (1994)						
Paired associate encoding	+	-	-	-	-	-
Wagner <i>et al.</i> (1998c)						
Subsequent memory effect	+	-	-	-	-	-
Brewer <i>et al.</i> (1998)						
Subsequent memory effect	Not scanned		-	+	Not scanned	
Petersen <i>et al.</i> (1988)						
Single-word processing	+	-	+	-	-	-
Raichle <i>et al.</i> (1994)						
Noun-verb generation	+	-	-	-	-	-
Binder <i>et al.</i> (1997)						
Semantic versus auditory decision	+	-	+	-	+	-
Gabrieli <i>et al.</i> (1998)						
Semantic versus phonological	+	-	-	-	-	-
Many versus few possible completions	+	-	+	-	-	-
Vandenberghe <i>et al.</i> (1996)						
Semantic decision (words and pictures)	+	-	-	-	-	-
Wiggs <i>et al.</i> (1999)						
Semantic retrieval	+	-	-	-	-	-
Demb <i>et al.</i> (1995)						
Semantic task	+	-	-	-	-	-
Otten <i>et al.</i> (2001)						
Semantic decision and subsequent memory	+	+	-	-	-	-
Kopelman <i>et al.</i> (1998)						
Learning words	-	-	+	-	-	-
Novel versus repeated words	+	-	-	-	-	-
Poldrack <i>et al.</i> (1999)						
Semantic versus phonological/case	+	+	-	-	-	+
Case/phonological versus semantic	-	-	+	+	-	-
Thompson-Schill <i>et al.</i> (1997)						
High versus low selection	+	+	+	-	-	-
Thompson-Schill <i>et al.</i> (1999)						
Competition	+	-	+	-	-	-
Dolan and Fletcher (1997)						
Proactive interference	+	-	+	-	-	-
Fletcher <i>et al.</i> (2000)						
Proactive interference	+	-	-	-	-	-
Fletcher <i>et al.</i> (1998a)						
Organization of single words	-	-	+	-	-	-
Wagner <i>et al.</i> (1999)						
Semantic decision	+	-	-	-	-	-
Reordering	+	-	+	-	-	-
Kelley <i>et al.</i> (1998)						
Words	-	-	+	-	-	-
Objects	-	-	+	+	-	-
Faces	-	-	-	+	-	-
Wagner <i>et al.</i> (1998b)						
Verbal encoding	+	-	-	-	-	-
Non-verbal encoding	-	+	-	-	-	-
Grady <i>et al.</i> (1998)						
Intentional learning of word > pictures	+	-	-	-	-	-

+ = Significant activation detected; - = no significant activation detected. The label for each comparison is descriptive only; for more details see text.

(A) Recognition		
Study	Test	
	Did you see...	
<i>Chick</i>	<i>Study?</i>	
<i>Study</i>	<i>Motor?</i>	
<i>Party</i>	<i>Stream?</i>	
(B) Word-stem		
Study	Cued recall	Completion
	Complete with study item...	Complete with first word that comes to mind...
<i>Chick</i>	<i>Chi--?</i>	<i>Chi--?</i>
<i>Study</i>	<i>Par--?</i>	<i>Mot--?</i>
<i>Party</i>	<i>Stu--?</i>	<i>Par--?</i>
(C) Word-fragment		
<i>Chick</i>	<i>C-i-k?</i>	<i>C-i-k?</i>
<i>Study</i>	<i>P-rt--?</i>	<i>M-to-?</i>
<i>Party</i>	<i>St-d-?</i>	<i>St-e--?</i>
(D) Paired associates		
<i>Chick...Baby</i>	<i>Study...?</i>	<i>Party...?</i>
<i>Study...Notes</i>	<i>Party...?</i>	<i>House...?</i>
<i>Party...Ballroom</i>	<i>Chick...?</i>	<i>Study...?</i>
(E) Free recall		
Study	Test	
	List all the words you can remember...	
<i>Chick</i>	?	
<i>Study</i>	?	
<i>Party</i>	?	

Fig. 4 Schematic representation of episodic memory retrieval tasks.

successful episodic retrieval, given that subjects were more likely to retrieve episodic information in the intentional than in the incidental condition. The authors preferred the former search account, because the same anterior FC region did not appear sensitive to two different incidental conditions in which the word-stems did or did not happen to match studied words. A similar pattern of right AFC activation with word-stem cues was reported by Buckner and colleagues (Buckner *et al.*, 1995).

Another PET study compared intentional with incidental retrieval in a recognition memory task (Rugg *et al.*, 1997). In the intentional condition, subjects indicated whether or not they had seen each word in the previous study phase. In the incidental condition, subjects were aware that some of the words had been seen previously, but simply had to decide whether each word was animate or inanimate (i.e. this task required semantic but not episodic retrieval). Right DLFC was active in intentional versus incidental recognition (as well as left VLFC and DLFC), and this activation occurred whether the words had been studied previously in a deep or a shallow encoding task (see section headed Frontal function in long-term memory encoding). Right AFC, however, was

more active during intentional than during incidental recognition only when the words were studied shallowly, i.e. when the words were less likely to evoke a strong episodic memory. Both this study and the study of Squire and colleagues (Squire *et al.*, 1992) suggest that retrieval-related right FC activations occur primarily during intentional memory search (or when the subject adopts a 'retrieval mode'), and right AFC activation in particular may only occur when these memories are weak or difficult to retrieve (but see later).

Task effects: paired associate-cued recall and free recall

Another early PET study used paired associate-cued recall (Shallice *et al.*, 1994). Before scanning, subjects studied category-exemplar pairs. During scanning, they were cued with the category names and required to recall the corresponding exemplar. This form of cueing, in comparison with a control task in which subjects were required merely to repeat stimuli aloud, was associated with activation in

right DLFC and a posterior region of right VLFC. A condition in which free associates were generated in response to a new set of categories did not produce any right FC activation when compared with the same control task, suggesting that right FC activation reflected episodic rather than semantic retrieval. No AFC activation was associated with episodic retrieval in this study, unlike the intentional stem-cued and recognition tasks of the studies of Squire and colleagues (Squire *et al.*, 1992) and Rugg and colleagues (Rugg *et al.*, 1997). The lack of AFC activation in the study of Shallice and colleagues (Shallice *et al.*, 1994) may reflect stronger memories (which come to mind more easily) in the paired associate task, particularly given the strong and unique semantic relationship between the category–exemplar pairs.

In a follow-on cued recall study, Fletcher explored the effects of parametric variation in the strength of semantic relatedness between word pairs (Fletcher *et al.*, 1996). Semantic relatedness in these lists of word-pairs varied from 5 (close semantic association) to 0 (no clear semantic relationship, i.e. randomly paired words). To control for the ease with which the cue prompted the appropriate response during retrieval, randomly and weakly related pairs received more study trials, so that overall performance at test was approximately balanced across the six levels of relatedness. PET scanning during retrieval revealed bilateral DLFC and AFC activations that decreased as the semantic relatedness between cue and response decreased (from 5 to 1). However, for a right AFC region at least, this trend reversed, and activation increased from weakly related to random pairs (i.e. as relatedness decreased from 1 to 0). The authors speculated that this U-shaped pattern of right AFC activation reflected different amounts of postretrieval ‘monitoring’. When word pairs are strongly related semantically, the response elicited by the cue during retrieval may require further processing to establish that it was not simply an automatically generated associate (i.e. to check that it came from episodic rather than semantic memory). When word pairs are completely unrelated, however, there is increased vulnerability to a different type of error: the production of an associate that was previously presented but paired with a different cue in the study list. Thus, for the two extremes (strongly related and unrelated), post-retrieval monitoring would be maximized, with resulting activation of right AFC. This monitoring hypothesis is also consistent with greater anterior right FC activation during intentional than incidental retrieval tasks (Squire *et al.*, 1992) and when memories are weaker (Rugg *et al.*, 1997), both situations in which close monitoring of retrieved information is required.

A further investigation of different retrieval tasks compared paired associate-cued recall with free recall (Fletcher *et al.*, 1998b). Subjects studied category–exemplar pairs and were then scanned while cued either with the category of previously studied pair (cued recall) or with only the word ‘next’ (free recall, i.e. effectively uncued). A double dissociation was seen between activation of right DLFC and posterior VLFC as a function of retrieval task. Right DLFC activity was

greater during free recall, whereas right VLFC activity was greater during cued recall. DLFC activation was attributed to the additional monitoring processes that are required during free recall in order, for example, to ensure that no items are repeated during recall. This concept of monitoring is related, but possibly distinct from, the use of monitoring in checking response appropriateness in the previous study, in which semantic relatedness was varied (Fletcher *et al.*, 1996). The greater VLFC activation during cued recall was attributed to the fact that each response was retrieved on the basis of a different, external semantic cue. In other words, each cue defined a new search space within which to select a candidate response, and more such search spaces would be defined, on average, in the cued than free recall condition. [Note that a similar study comparing paired associate-cued recall and free recall found the opposite pattern of greater left VLFC activation in free than in cued recall (Petrides *et al.*, 1995). The reason for this discrepancy between the two studies is unclear, but may be related to differences in procedural details and performance levels. For example, the study of Petrides and colleagues compared free recall of 20 words with cued recall of only five well-learned paired associates, in which case more internally generated cues may have been employed in the free than cued recall conditions.] This is consistent with the right posterior VLFC activation relative to simple repetition in the study of Shallice and colleagues (Shallice *et al.*, 1994) (see also Fletcher *et al.*, 1996).

In a study comparing paired associate-cued recall with recognition, Cabeza and colleagues (Cabeza *et al.*, 1997b) showed that, although both retrieval tasks activated right VLFC relative to a reading control task, no difference was detected between the two types of retrieval. This pattern may reflect similar cueing effects in paired associate-cued recall and recognition, and perhaps little difference in the monitoring requirements of the two tasks, given the careful precautions taken to match performance on the two tasks. Another PET study by Cabeza and colleagues (Cabeza *et al.*, 1997a) presented two words to subjects at test, and required either a two-alternative forced-choice recognition between a studied and a non-studied word in one condition, or a judgement of recency between two old words in another condition. The only FC difference between these two conditions was a right DLFC region that was more active during recency judgements than during forced-choice recognition. This pattern is consistent with a role for DLFC in ‘source monitoring’ (see next section), in which temporal or spatial context information is retrieved from the study episode in order to make the appropriate response.

Task effect: recognition and source memory

Other retrieval studies have kept cues constant, but varied the retrieval instructions. In one study, for example, Henson and colleagues presented study words either high or low on the screen and in one of two temporally grouped lists (Henson *et al.*, 1999b). In the standard recognition task (the ‘inclusion’

condition), subjects had to respond 'yes' to studied words, which were randomly intermixed with a set of new, unstudied words. In a second recognition condition (the 'exclusion' condition, based on Jacoby, 1996), subjects responded 'yes' only to words that were studied in a specific spatial or temporal context, i.e. either high or low on the screen or in one of the two study lists. Direct comparison of the exclusion and inclusion tasks revealed bilateral DLFC activation. The authors attributed this activation to source monitoring, during which the feeling of familiarity associated with studied words had to be checked against explicit retrieval of the study context. Furthermore, though bilateral VLFC regions were more active in the inclusion condition than in a simple perceptual control condition, the activity of these regions did not appear to differ between the inclusion and exclusion tasks. The latter is consistent with the proposal of Fletcher and colleagues that VLFC is involved in retrieval cueing, given that the externally provided 'copy' cues differed between the inclusion and control conditions but not between the inclusion and exclusion conditions (Fletcher *et al.*, 1998b).

A similar study by Nyberg, however, found only right VLFC activation during a standard recognition task compared with a spatial or temporal source discrimination task (Nyberg *et al.*, 1996). Yet another blocked fMRI study found greater activation of left AFC and left posterior VLFC associated with a source discrimination task compared with a standard recognition task (Rugg *et al.*, 1999). In this study, the source discrimination concerned whether the words had appeared to the left or right of fixation, a manipulation that also cued a different encoding task (animacy or pleasantness judgements). The reason for the lack of DLFC activation in the studies of Nyberg and colleagues and Rugg and colleagues is unclear, but may reflect the fact that subjects were aware in both cases that the majority (if not all) of the words were old. The reason for the opposite pattern and lateralization of VLFC activation between the studies of Nyberg and colleagues and Rugg and colleagues is even more puzzling. It may reflect the type of source information, from a conceptual or 'internal' source in the study of Rugg and colleagues, given the different semantic decisions at encoding, to a perceptual or 'external' source, which may have dominated in the study of Nyberg and colleagues.

Amount of information retrieved

In this section, we consider studies that have attempted to explore the FC response to the amount of information successfully retrieved from episodic memory. A specific interest is the extent to which FC is sensitive, for a given type of cue, to whether or not that cue prompts successful episodic retrieval. This question has been formulated in terms of 'retrieval attempt' versus 'retrieval success' (Kapur *et al.*, 1995; Nyberg *et al.*, 1995, 1996). One method of varying the probability of retrieval success in PET designs is to manipulate the ratio of studied to unstudied words during the critical scanning period. To disguise this old : new ratio

manipulation from subjects, the scanning period can be sandwiched between a lead-in and a lead-out period in which the old : new ratio is more balanced. A more recent method is to use event-related fMRI. In this case, old and new words in a recognition task can be intermixed randomly, and the amount of successful retrieval can be tested further by contrasting, for example, correct old versus correct new decisions, correct versus incorrect decisions to old words, or correct old decisions as a function of the subject's confidence or recollective experience.

Recognition

One of the first PET studies of episodic retrieval compared scans in which subjects listened to sentences that they had or had not heard before in a previous study phase (Tulving *et al.*, 1994b). The task was to maintain a running total of the number of 'oddball' sentences that deviated in episodic memory content from the majority. Thus, in a block consisting mainly of new sentences, the task was to count the number of studied sentences and vice versa. Comparison of the old and new sentence conditions revealed extensive right AFC and VLFC activation together with left AFC activation (according to our definition of these regions). In subsequent PET recognition studies by the same group, however, no differential right FC activation was found as a function of the old : new ratio, from 15 to 85% old words (Kapur *et al.*, 1995) or from 0 to 100% old words (Nyberg *et al.*, 1995). Nonetheless, right VLFC and DLFC activation was found when both high and low old : new ratios were contrasted against a control task (of animacy judgements and reading, respectively), suggesting that these regions are engaged in retrieval attempt (or the adoption of a 'retrieval mode') rather than retrieval success.

Subsequent studies, however, have found right FC activation correlating with retrieval success (Rugg *et al.*, 1996, 1998). In these studies, right DLFC and bilateral AFC activations increased across old : new ratios of 0, 20 and 80%. However, pairwise tests of these activations revealed a significant difference in the comparison of the 20% with the 0% condition but not in the comparison of the 80% with the 20% condition. Rugg and colleagues suggested that the FC activity that is associated with retrieval success (at least as measured in these blocked PET designs) quickly asymptotes as the old : new ratio increases (Rugg *et al.*, 1996). This might explain the presence of right FC activation in a 100 versus 0% comparison (Tulving *et al.*, 1994b) and the failure to find right FC activation in a comparison of 85 with 15% targets (Kapur *et al.*, 1995). [More recent blocked fMRI studies, which have greater sensitivity than PET, have found bilateral anterior FC activations when comparing an 80% old : new ratio with 20% (Rugg *et al.*, 1999)]. This proposal does not, however, explain the absence of right FC activation in a comparison of the 100 and 0% target conditions in the study of Nyberg and colleagues (Nyberg, 1995). This may arise from the high false-positive rate in this study (almost

one in five items were incorrectly identified as old in the 0% condition). This raises the interesting possibility that right AFC activation also occurs following 'false memories', i.e. incorrect recognition decisions. This possibility is consistent with two studies that have found right AFC activation when comparing recognition against a fixation baseline, but failed to find any differential FC activation for true recognition of old words relative to false recognition of semantic lures (Schacter *et al.*, 1996b, 1997). Alternatively, the extent of right FC activation as a function of old : new ratio may depend on the specific task instructions. For example, right AFC and DLFC activation were found during fMRI scanning of blocks of 91 versus 9% old words only when subjects were oriented towards the rarer words, i.e. new words in the 91% block or old words in the 9% block (Wagner *et al.*, 1998a). This would suggest that much of the confusion between studies using blocked manipulations of the old : new ratio may reflect small differences in the task instructions that could, for example, affect the way that subjects deal with differing frequencies of old–new responses (see below).

A number of theoretical problems remain in attempting to manipulate retrieval success within a blocked design. First, subjects may explicitly detect the manipulation of the ratio of old to new words. Even if they do not detect this manipulation (as determined by post-experimental debriefing), they may still realize that, in a run of predominantly new items, they are not recognizing many of the words. They might then question the reliability of their memory, and adjust their criterion for judging whether an item is old. Conversely, in a run of predominantly old items, they may realize that they have been endorsing nearly all items as old, and may wonder whether they are being too lenient in their response criterion. In other words, any differences in brain activity between two blocks may reflect different response criteria (or different expectancies, strategies or mental sets) rather than retrieval success *per se*. These confounds are less likely in event-related designs, however, wherein new and old items can be intermixed randomly [and such 'state' effects manipulated separately from 'item-specific' effects (Donaldson *et al.*, 2000)]. Indeed, direct evidence for these concerns come from an event-related potential (ERP) study by Johnson *et al.* (1997), which found that the differential ERP between old target items and semantic lures itself depended on whether the targets and lures were blocked or intermixed.

Some of the first applications of event-related designs to memory retrieval (Schacter *et al.*, 1997; Buckner *et al.*, 1998a) found activation of VLFC and AFC in response to words versus fixation, but failed to find any measurable difference as a function of whether the words were old or new (unlike the blocked designs reviewed above). This might suggest that the FC activations seen in blocked designs do reflect state effects rather than item effects. However, no differential responses to correct old and new decisions were found anywhere in the brain in these early event-related studies, suggesting a lack of statistical power [given that

event-related studies are typically less sensitive than blocked designs (Friston *et al.*, 1999) and that old–new differences are seen in analogous ERP studies (Rugg, 1995)].

Subsequent event-related fMRI studies, however, have found differences in FC activity between old and new words. Saykin and colleagues found greater right DLFC activation for old than new auditorily presented words in a recognition task (Saykin *et al.*, 1999). Furthermore, Henson and colleagues found that right and left FC activity for old words in a recognition task varied as a function of the conscious experience accompanying retrieval (Henson *et al.*, 1999a). This study used a method introduced by Tulving in which subjects indicated not only whether a word was old or new but also whether the word was accompanied by recollection of the specific episode in which it was studied, or simply a feeling of familiarity in the absence of recollection (Tulving, 1985). The former was indicated by a 'remember' (R) judgement, the latter by a 'know' (K) judgement, and unrecognized words by a 'new' (N) judgement. Both R and K judgements activated VLFC and DLFC relative to N judgements, but this FC activity was left-lateralized for R judgements. These results suggest that FC is generally sensitive to retrieval success. Moreover, a direct comparison of correct R and K judgements revealed greater left AFC for R judgements, and greater right DLFC activation for K judgements. Thus FC is sensitive not only to retrieval success but also to the type of information retrieved (as operationalized by the subjective experience accompanying retrieval). Left AFC activity was attributed to the retrieval of source information (forming the basis of an R judgement) and right DLFC activity to monitoring processes that are particularly important for K judgements, when an item seems familiar in the absence of any recollection of its prior occurrence (akin to the notion of retrieval monitoring discussed earlier).

A follow-on event-related fMRI recognition study used confidence judgements rather than R–K judgements (Henson *et al.*, 2000a). Subjects in this study indicated whether each old–new decision was made with high or low confidence. Greater monitoring for low- than for high-confidence decisions was predicted, regardless of whether the word was old or new. This prediction was based on a signal-detection model of recognition in which old and new words have overlapping distributions of 'memory strength' (or familiarity), and confidence is lowest when an item has a familiarity level close to the old–new response criterion. As expected on the basis of previous findings, greater right DLFC activation was found for low- than for high-confidence decisions, consistent with their monitoring prediction. The orthogonal comparison of old versus new words, regardless of confidence, activated left and right anterior FC, consistent with the blocked studies of retrieval success reviewed above. One important implication of this study is that, in the absence of confidence ratings, whether an old versus new recognition comparison activates DLFC may depend on whether the subject's response criterion is closer to the distribution of

memory strengths for the old items, or to that for the new items [a situation that may itself be sensitive to instructions (Wagner *et al.*, 1998a)].

Amount of information retrieved: depth of encoding during prior study

Another method of changing the probability with which a cue reinstates an episodic memory is by varying the depth with which words are studied (see section headed Frontal function in long-term memory encoding). Schacter and colleagues compared word-stem-cued recall of words previously studied deeply (and presented four times during study) with word-stem-cued recall of words previously studied shallowly (and presented only once during study) (Schacter *et al.*, 1996a). Bilateral AFC activations were found when the shallow recall condition was contrasted with a control condition in which stems of unstudied words were completed with the first word that came to mind. No FC regions were identified when the deep recall condition was contrasted against either the shallow condition or the control condition, leading Schacter and colleagues to suggest that the anterior FC activations reflected 'retrieval effort' rather than retrieval success. This interpretation is consistent with the finding (discussed above) of greater right anterior activation during intentional than incidental recognition following shallow rather than deep encoding of words (Rugg *et al.*, 1997).

A subsequent fMRI study, however, using a similar design in a recognition task, found the opposite pattern: greater right AFC activation during recognition of words previously studied deeply than of words previously studied shallowly (Buckner *et al.*, 1998b). Conversely, left DLFC and bilateral VLFC regions showed greater activation during recognition of shallowly than deeply studied words. Manipulations of study depth, like those of the old : new ratio, have therefore produced mixed results concerning the involvement of FC in retrieval attempt and retrieval success. One reason may be that the manipulation of study task may not be a good way to tease apart retrieval attempt and retrieval success, in that the cue for a deeply studied word may affect not only the ease of retrieval but also the type of information retrieved (e.g. conceptual versus perceptual). Indeed, the attempt–success dichotomy may not be such a useful distinction. Rather, the specific pattern of FC activation may depend on the particular type of retrieval task (see below) and perhaps on the overlap between the processes performed at encoding and the processes performed at retrieval (Morris *et al.*, 1977).

Interactions between retrieval task and amount of information retrieved

Some resolution of the above findings is suggested by a PET study exploring interactions between the retrieval task and retrieval success (Rugg *et al.*, 1998). Rugg and colleagues

compared old : new ratios of 0 and 80% for two types of task: recognition and word-stem-cued recall. A direct comparison between the two tasks in the 0% condition (compared with appropriate baseline conditions) showed greater left DLFC and bilateral AFC activation in cued recall than in recognition. These task engagement effects, in the absence of successful retrieval, suggest that these regions are concerned with generating possible completions to word-stem cues rather than simply probing with a copy cue, as in recognition. This proposal is consistent with the second finding of an interaction between the old : new ratio and the retrieval task in bilateral anterior FC regions. These regions showed greater activity in 80 than in 0% recognition (consistent with the studies of Rugg *et al.*, 1996), but greater activity in 0 than in 80% cued recall. This target sensitivity effect, which dissociates across task type, may be explicable in terms of processes occurring after candidate responses have been generated.

With old words in a recognition test, for example, memory processes that are incidental to task demands, such as conscious recollection of source information, may follow automatically. These additional processes become redundant as soon as the next copy cue is presented and subjects must switch back to the task at hand (to evaluate the next word). If this switching is minimal when a new (non-target) word is presented, AFC activity will be higher, on average, for high than for low old : new ratios. However, this may only be the case for recognition memory, as the non-targets in stem-cued recall are likely to demand further switching processes. When such stems are presented, a subject's inability to generate a completion that they recognize as old will result in attempts (ultimately unsuccessful) to generate other completions. This requires more frequent switching between search and monitoring processes. Thus, the interaction of task with target density may be carried by an AFC difference between 0% conditions. Rugg and colleagues' direct comparison of the 0% conditions for recognition and cued recall supports this view (Rugg *et al.*, 1998). This hypothesis is also consistent with the previous studies that found greater AFC activation during recognition following deep versus shallow encoding (Buckner *et al.*, 1998b) but greater AFC during cued recall following shallow versus deep encoding (Schacter *et al.*, 1996a).

A further test of this postretrieval monitoring hypothesis is provided by a PET study comparing old : new ratios of 0 and 80% for two types of cued recall task: recall cued by word stem (e.g. ST_) and word fragment (e.g. S_E_) (Allan *et al.*, 2000). The cues were chosen so that fewer completions were possible for fragments than for stems. Though right AFC was activated in the 0% condition of both types of task versus their respective controls, this region was significantly more active during stem-cued than during fragment-cued recall. This pattern is exactly that predicted by the above switching hypothesis, given that more completions could be generated from the stems than from the fragments. Left AFC showed greater activation associated with the 80% than with

the 0% condition for the stem-cued than for the fragment-cued condition, whereas right DLFC showed greater activation associated with the 80% than with the 0% condition for the fragment-cued than for the stem-cued condition. Interpretation of the last two results is not so clear [especially the former, as it is the opposite of that seen in a previous study by the same group (Rugg *et al.*, 1998)]. At a minimum however, they do suggest that more than one type of monitoring process operates during retrieval.

Concluding section on retrieval

Summarizing the patterns of FC activation across the above retrieval studies (Table 3) is not easy. Notwithstanding a number of inconsistencies, we attempt to do so with reference to a broad model of retrieval analogous to that put forward by Burgess and Shallice (Burgess and Shallice, 1996). The model includes two main stages of processing: the specification of search parameters and the verification/monitoring of the products of memory searches. The evidence is suggestive, though by no means overwhelming, that these processes map to VLFC and DLFC, respectively. Although there is some sequential dependence between these processes, retrieval is likely to involve frequent switching between them (e.g. monitoring may reveal inadequacies that prompt further searches). We also suggest a third stage, which loosely reflects additional control processes that supervise the switching between specification and monitoring, and also includes other retrieval-related strategies (such as metamemory inferences). These processes we tentatively map to AFC. (Although it has been argued that retrieval-related FC activations are right-lateralized, the above review illustrates that this lateralization is not clear-cut, and we make no left–right distinction in regard to the present retrieval model.)

The initial stage of the specification of search parameters and cues is akin to the semantic generation processes referred to above in the section headed Frontal function in long-term memory encoding, insofar as they retrieve information from long-term semantic memory. The results of such a search also need to be maintained in WM for the purposes of further monitoring and manipulation. In analogy with studies of WM and encoding, these processes seem to reflect activation of VLFC. The processes are likely to be sensitive to the nature of the retrieval task. Thus, in the paired associate-cued recall tasks described above (Shallice *et al.*, 1994; Fletcher *et al.*, 1998b), each successive category cue changes the semantic memory ‘space’ from which the correct response is likely to come, producing activation in VLFC relative to the control condition. In recognition memory tasks, on the other hand, in which the dominant cue is a copy cue of the target itself, little difference in search processes and VLFC activation would be expected (Henson *et al.*, 1999a). The lack of activation in VLFC when comparing intentional with incidental retrieval (Squire *et al.*, 1992; Rugg *et al.*, 1997) using word-stem completion suggests that this region is

insensitive to whether or not cue specification processes are occurring as part of an explicit memory task.

The second stage of retrieval involves the monitoring and manipulation of the products of this initial search process. When the demands of the retrieval task are more complex and involve the maintenance of the search products while further decisions or assessments are made, DLFC would be engaged. Such processes may be related to, but not directly contingent upon, the level of cueing. The requirement to determine the relative recency of two studied items (Cabeza *et al.*, 1997a), for example, would involve comparing the information retrieved in response to two cues. In the recognition experiments requiring remember/know (Henson *et al.*, 1999a) or confidence (Henson *et al.*, 2000b) judgements, the sensitivity of DLFC to weaker recognition (e.g. familiarity in the absence of recollection) is consistent with a greater level of monitoring before responses are produced. Sensitivity of this region to source judgement (Henson *et al.*, 1999a) and to internally structured free recall (Fletcher *et al.*, 1998b) is also compatible with this interpretation.

The final aspect of episodic retrieval concerns higher-level control processes. Such processes are ill-defined and even less fully explored. Nevertheless, it is clear that, in many of the tasks reviewed above, optimal retrieval depends upon the ability to engage and coordinate a series of subprocesses, such as switching between cueing and monitoring. Regions associated with such higher-level control processes will therefore be sensitive to interactions between several factors, including the nature of the retrieval task, the degree of experimental cueing and the nature of the information retrieved. The region that appears most regularly in association with these task features is AFC. In the meta-analysis of Duncan and Owen, AFC was one region that did appear to dissociate from other midlateral FC regions, being activated more often in episodic retrieval tasks than in WM tasks (Duncan and Owen, 2000). Our proposal assumes that this is nothing to do with retrieval *per se*, but rather with differences in the component processes of the WM and retrieval tasks typically used. Activation of AFC appears to be specific to intentional rather than incidental retrieval. There is evidence that this region is sensitive to target density in recognition memory tasks, but there are inconsistencies too, and these may reflect subtle differences in instructions that affect the degree of executive control. In particular, it is an unavoidable feature of blocked designs that subjects may engage in ‘metamemory’ processes, such as evaluating their overall performance and reviewing their strategies. Such processes will have their own haemodynamic correlates and may produce unpredicted effects. AFC activation is also sensitive to the nature of the retrieval task. As argued earlier, a role for AFC in the coordination of search and monitoring processes can explain the interactions between task type and target density (Rugg *et al.*, 1998), and between these retrieval tasks and the nature of prescan encoding (Buckner *et al.*, 1995; Schacter *et al.*, 1996a). It is difficult to account for the complex array of findings associated with AFC without

Table 3 Retrieval studies

	VLFC		DLFC		AFC	
	Left	Right	Left	Right	Left	Right
Squire <i>et al.</i> (1992)						
Stem cued recall	–	–	–	+	+	+
Buckner <i>et al.</i> (1995)						
Stem cued recall	–	–	–	–	–	+
Rugg <i>et al.</i> (1997)						
Intentional versus incidental	+	–	+	+	–	+
Shallice <i>et al.</i> (1994)						
Associate-cued recall	–	+	–	+	–	–
Fletcher <i>et al.</i> (1996)						
Semantic relatedness	–	–	–	+	+	+
Fletcher <i>et al.</i> (1998b)						
Free recall	–	–	–	+	–	–
Cued recall	–	+	–	–	–	–
Cabeza <i>et al.</i> (1997b)						
Recognition/cued recall	–	+	–	–	–	–
Cabeza <i>et al.</i> (1997a)						
Recency judgement	–	–	–	+	–	–
Henson <i>et al.</i> (1999b)						
Inclusion and exclusion	+	+	+	+	–	–
Exclusion versus inclusion	–	–	+	+	–	–
Nyberg <i>et al.</i> (1996)						
Source memory	–	+	–	–	–	–
Rugg <i>et al.</i> (1999)						
Source memory	+	–	–	–	+	–
Tulving <i>et al.</i> (1994b)						
Successful recognition	–	+	–	+	+	+
Kapur <i>et al.</i> (1995)						
Retrieval attempt	–	+	–	+	–	–
Nyberg <i>et al.</i> (1995)						
Retrieval attempt	–	+	–	–	–	–
Rugg <i>et al.</i> (1996)						
Successful recognition	–	–	–	+	+	+
Wagner <i>et al.</i> (1998a)						
Correct recognition	–	–	–	+	–	+
Schacter <i>et al.</i> (1997)						
True and false recognition	+	+	+	+	+	+
Buckner <i>et al.</i> (1998b)						
Shallow versus deep	+	+	+	–	–	–
Saykin <i>et al.</i> (1999)						
Old versus new	–	–	–	+	–	–
Henson <i>et al.</i> (1999a)						
Remember–know	–	–	–	–	+	–
Know–remember	–	–	–	+	–	–
Henson <i>et al.</i> (2000a)						
Low-confidence retrieval	–	–	+	+	–	–
Old versus new	–	–	+	–	+	+
Schacter (1996a)						
Low recall	–	–	–	–	+	+
Rugg <i>et al.</i> (1998)						
Cued recall versus recognition	–	–	+	–	+	+
Recognition: high target	–	–	–	–	–	+
Cued recall: zero target	–	–	–	–	+	+
Allan <i>et al.</i> (2000)						
Stem- versus fragment-cued	–	–	–	–	+	–
Stem-cued: high target	–	–	–	–	+	–
Fragment-cued: high target	–	–	–	+	–	–
Wagner <i>et al.</i> (1998b)						
Verbal retrieval	+	–	–	–	–	–
Non-verbal retrieval	+	+	–	–	–	–

+ = Significant activation detected; – = no significant activation detected. The label for each comparison is descriptive only; for more details see text.

recourse to such higher level descriptions. Moreover, the high mutual dependence of these hypothesized VLFC, DLFC and PFC processes during episodic retrieval may mean that a task intended to engage only a subset of them may inadvertently engage all of them. This may, in part, explain why the emergent pattern of findings is far from conclusive.

Lateralization of frontal cortex function in long-term memory

Before considering functional dissociations within the frontal lobes, it is important to draw attention to broader divisions of function between the left and right frontal lobes. The HERA theory (Tulving *et al.*, 1994a) suggested a functional lateralization of encoding and retrieval processes. It is often overlooked that the original formulation of Tulving and colleagues was specific to ‘verbal and verbalisable’ material, and they refrained from speculation as to whether this model would be apposite for other types of material. Some studies have suggested that encoding-related left FC activation may generalize to other types of stimuli. Studies involving semantic processing of pictorial stimuli, for example, have also produced left-sided activations (Vandenberghe *et al.*, 1996; Grady *et al.*, 1998). These pictures may have been verbalized, however, and subsequent studies have shown Tulving and colleagues’ caution to be well founded. Kelley and colleagues, for example, found that encoding nameable objects produced bilateral FC activation, and encoding unknown (unnameable) faces produced right rather than left FC activation (Kelley *et al.*, 1998; see also Wagner *et al.*, 1998b). This lateralization by material type is similar to that seen in WM tasks.

Our review of verbal LTM tasks supports part of the HERA theory, in that most studies involving verbal encoding have produced left-lateralized FC activations. It also appears true that right FC activations are more common during retrieval tasks than during encoding tasks (at least for those tasks that have been used to date). Thus, an encoding task that emphasizes the meaning of words almost invariably produces left VLFC activation, whereas simple recognition of words can produce solely right-sided FC activation. The HERA generalization may not be sufficient, however, in that our review includes many studies of verbal retrieval that activated both left and right FC, or even left FC alone (even in situations in which the control condition would appear to involve encoding).

We are thus left with two observations regarding left–right FC differences. The first is the influence of material on the laterality of activation. The second, less consistent observation is the nature of the verbal task, i.e. whether it involves mainly encoding into, or retrieval from, episodic memory. The latter observation may reflect differences in the types of processes engaged by typical ‘encoding’ and ‘retrieval’ tasks. One possible explanation that combines these two observations is that the sorts of cognitive processes associated with non-

verbal material are also those that are emphasized during the retrieval of episodic (but not semantic) memories, and these processes are lateralized to right FC. The left FC activation sometimes observed in more complex retrieval tasks (such as source retrieval or word-stem/fragment-cued recall) may then reflect additional demands to retrieve information from semantic memory, resulting in bilateral activation. One test of this possibility would be to examine whether the lateralization of FC activation switches when non-verbal material is processed in a way that is similar to verbal material, and vice versa. Such a cognitive manipulation may, however, prove difficult and at present we limit ourselves to the observation that both material and type of process appear to influence the lateralization of FC activation.

Conclusions

Though a completely consistent picture is yet to emerge from the growing body of memory-related functional neuroimaging studies, a number of intriguing patterns are beginning to suggest themselves. But first it is worth while to consider the possible sources of inconsistency between studies. We suggest that they arise at a number of levels: foremost, we are applying the techniques to poorly defined cognitive processes. Our incomplete understanding may produce inappropriate characterizations of function and thereby inconsistent PET and fMRI observations across studies. Secondly, the adoption of some frontally mediated functions may be subject-specific. As many of the earlier studies used low numbers of subjects, differences in strategies and performance across the small subject samples may have produced relatively large effects. Thirdly, the relationship between the macro- and microstructure of FC is highly variable (Roland *et al.*, 1997). This variability means that activations in microstructurally similar regions across subjects may be localized to apparently different macrostructural regions, and vice versa. Fourthly, the question of whether a given activation is actually present (‘significant’) is normally determined by prespecified statistical thresholding. Thus, the failure of a given region to survive such thresholding does not mean that we can exclude it from consideration. That is, the presence of a significant activation in one region and the absence of significant activation in another is only weak evidence for functional specialization. More powerful evidence is the observation of significant double dissociation between regions and tasks. Such dissociations are rarely reported in functional neuroimaging studies, however. Finally, and more generally, we must bear in mind that attempts to understand localized correlates of cognitive processes often fail to emphasize a more global picture of integrated systems in the brain. Despite clear evidence of functional specialization in the brain, the widespread connections of FC remind us that overemphasis on localization of function may prove detrimental to an understanding of functional integration of FC with other brain regions (Fuster, 1997).

With these caveats in mind, we return to the question of

whether the postulated functional dissociations between AFC, DLFC and VLFC have proved useful in reviewing FC activations in memory. We suggest that the body of evidence points towards these regions subserving three broadly distinct functions, all of which may be engaged to a greater or lesser extent in each of the three memory domains. We describe these processes as (i) updating and maintaining the contents of WM, (ii) selecting, manipulating and monitoring the contents of working memory, and (iii) selecting processes, goals and subgoals. We suggest that these three functions map onto VLFC, DLFC and AFC, respectively. Apart from the possible lateralization of these processes for verbal and spatial material, we do not further differentiate these processes by left or right FC (see previous section).

Before characterizing these functions in greater detail, we note that the processes described, and the terms used, draw on existing models of executive function (Shallice and Burgess, 1998) and functional neuroanatomical dissociations (Petrides, 1994). There are also similarities with an existing view of FC contributions to WM and LTM (Wagner, 1999), although our model differentiates the functional roles of DLFC and AFC and avoids the specification of these functions to any particular stage of LTM. Here, we postulate abstract executive processes that we believe are common to WM and LTM tasks, and emphasize the interactive nature of these processes.

Updating and maintaining the contents of working memory

All of the tasks that we have described in this review require subjects to examine the contents of WM in order to make a decision. An early step in each involves bringing information into WM (updating), and holding it on-line (maintaining) in the service of further processing of that material. In the WM tasks described in the first section, the information is, typically, provided externally. In other tasks, the information must be retrieved from long-term semantic or episodic memory, reflecting the reinstantiation of stored (passive) information into active WM. With reference to the terminologies used in the three previous subsections, this step corresponds to the active 'rehearsal' (rather than passive storage) discussed in relation to WM tasks, the 'generation' (often of individual or shared semantic attributes) discussed in relation to encoding tasks, and the cue 'specification' discussed in retrieval tasks. In deep encoding tasks, for example, subjects are required to retrieve information from long-term semantic memory into WM in order to make a response. In paired associate-cued retrieval tasks, the cue must be maintained in WM together with possible responses retrieved from long-term episodic (and perhaps semantic) memory. One of the clearest pictures to emerge from the literature reviewed above is the activation of VLFC in such cases, whether in the context of tasks considered as WM, LTM encoding or LTM retrieval.

A further dissociation between anterior and posterior VLFC may also exist. The rehearsal-related VLFC activations in simple WM tasks tend to be more posterior, whereas the semantic generation-related VLFC activations in encoding tasks tend to be more anterior. This may reflect a further difference between the process of maintaining information in WM and the process of updating (reinstantiating) information in WM from LTM.

Selecting, manipulating and monitoring the contents of working memory

For many of the more complex memory tasks used in imaging experiments, simple updating and maintenance processes are insufficient for optimal performance. Rather, these tasks require selection from, or refinement of, information that is maintained on-line, together with ongoing evaluation of the sufficiency of that information for the current task. Referring once more to the terminology in the previous sections of this paper, this function corresponds to 'manipulation' in WM tasks, 'organization' in encoding tasks and 'monitoring' in retrieval tasks. The terms 'organization' and 'manipulation' may be used interchangeably in that they refer to any process whereby presented or retrieved material is modified. The term 'selection' is used in our formulation because it is frequently the case that tasks require not merely the rearrangement of material held on-line but also the selection of the most appropriate stimuli before a response can be made. This use is different from that for VLFC; VLFC is involved in selecting information from LTM (to instantiate in WM), whereas DLFC is involved in selecting information that is already active in WM.

Monitoring processes are loosely grouped with organization and manipulation for two reasons. First, it is difficult to envisage successful selection and manipulation processes being performed in the absence of continual monitoring of the appropriateness of the resulting changes. Secondly, existing functional imaging tasks have used paradigms that do not differentiate between these processes. It is thus more parsimonious to group them together loosely and to observe that a most likely candidate for their anatomical implementation is DLFC, activation of which is, for example, increased when information must be reordered in WM tasks, decreased by divided attention during demanding encoding tasks, and increased when information is inconclusive or uncertain in retrieval tasks.

We view the relationship between VLFC and DLFC function in a similar way to previous formulations (Petrides, 1994). Their functions are highly interactive, in that DLFC monitors processes that often result in the updating of information maintained (by VLF processes) in WM; any new information in turn forms the substrate for further selection and manipulation processes subserved by DLFC. With this in mind, a strong prediction in all memory tasks is of co-activation of these regions. Indeed, this has often been the

case, dissociations being found only when tasks make different relative demands on maintenance and manipulation processes.

Selecting processes, goals and subgoals

Efficient interaction between DLFC and VLFC is often necessary to meet the demands of the task. The model would therefore be incomplete without the postulation of 'metaprocesses', i.e. processes that are involved in setting goals and coordinating the DLFC and VLFC processes employed to achieve these goals. The need for this higher-order level of control would be greatest when subjects were required to switch between concurrently performed tasks. An example is the branching task of Koechlin and colleagues, in which successful performance depends upon the subject's ability to switch frequently between a number of operations and to hold in mind the subgoals associated with each (Koechlin *et al.*, 1999). More complex episodic memory retrieval tasks might also be expected to maximize the extent to which subjects must coordinate VLFC and DLFC functions in the engagement of iterative search and monitoring processes (nonetheless, even what appear to be simple recognition tasks might engage complex metamemory or switching strategies, as discussed above in the section headed Concluding section on retrieval). The lack of AFC activation in typical 'encoding' tasks probably reflects the fact that such tasks differ little in their requirement for selecting between different executive processes.

We attribute this control function to AFC. [In another review (Christoff and Gabrieli, 2000), AFC was associated with the monitoring of self-generated information, as distinct from DLFC, which was associated with the monitoring of externally generated information. While we prefer our orthogonal distinction, we accept that the evidence in support of one or other view is far from decisive.] Thus, if VLFC and DLFC form a functional unit concerned with updating/maintenance and selection/manipulation/monitoring, respectively, then perhaps controlling influences from AFC regions enable optimal switching between these processes in order to maximize task performance. The role of AFC can thus be viewed as a third use of selection: the selection between processes or goals (rather than between information maintained in WM and stored in LTM). It can also be viewed as another type of monitoring, in which it is the interaction between VLFC and DLFC processes that is being monitored rather than the information being maintained/manipulated *per se*. While this idea of high level function is frustratingly vague, we believe that it is necessary in order to capture the complex pattern of AFC activation reviewed here.

Theoretical predictions

Part of the value of a theory is its capacity to make predictions that can be tested empirically. For example, central to our proposal is the potential involvement of all three frontal areas

in any of the different memory domains. That is, we suggest that the involvement of any area will depend upon the subprocesses engaged by the task rather than whether that task is defined experimentally as encoding, retrieval or WM. Thus, while Table 2 indicates that AFC has rarely been activated in studies of memory encoding, one can envisage learning situations that would engage this region. The encoding tasks used typically are largely stimulus-driven, requiring subjects to make similar decisions on stimuli presented successively. Such tasks are unlikely to involve the higher-order control processes that are suggested here to be reflected by AFC activation. However, an encoding task that included the requirement not only to process individual stimuli but also to learn, for example, a set of rules that govern the relationship between the stimuli, would be predicted to show AFC activation.

A further prediction concerns the temporal patterns of activation in different FC regions (as revealed by recent event-related fMRI studies). In most of the studies reviewed here, VLFC and DLFC have been dissociated according to the level of activation across different tasks. If these regions reflect maintenance and manipulation demands respectively, we can make further predictions about the temporal profile of activity. In the reordering task developed by D'Esposito and colleagues, for example, subjects either maintain or alphabetically reorder a sequence of letters (D'Esposito *et al.*, 1999). In the alphabetize condition, once the sequence has been reordered, only subsequent maintenance of the reordered sequence is required during the period before the probe appears. This would suggest a briefer period of DLFC activation superimposed upon a VLFC activation that lasts throughout the delay period. Similar arguments could be applied to the temporal profiles of AFC and DLFC activity in more complex episodic encoding and retrieval tasks.

Another area of prediction concerns changes in the functional or effective connectivity between the three FC regions. These changes can be detected even in the absence of any overall difference in mean regional activity across two tasks. Furthermore, by modelling the predicted covariance between activity in different regions, one can detect not only task-related changes in the connectivity between two regions, but also changes in the modulation of the connectivity between two regions by a third region (Büchel and Friston, 1997). Our theory of FC function suggests that a task involving manipulation of information in WM would increase the effective connectivity or coupling between DLFC and VLFC, whereas a task involving further control of the timing or nature of this manipulation (e.g. in task-switching) would increase the effective modulation of the VLFC-DLFC coupling by AFC. Such proposals regarding effective connectivity between different FC regions have been little tested to date.

Summary

Notwithstanding remaining uncertainties and difficulties, there is no doubt that functional neuroimaging has produced

a resurgence of interest in structure–function relationships within the frontal lobes. First, the techniques have generated a host of results and hypotheses that deserve further neuropsychological investigation of localized FC lesions. Secondly, the results of imaging studies have prompted theorists to develop new terminologies with which to distinguish different executive functions (e.g. maintenance of information, selection between competing responses, monitoring of task relevance). Indeed, if one does assume a one-to-one mapping between function and anatomy, imaging results may even be used to further inform psychological models. For example, a model may be called into question if it makes the assumption that two tasks involve identical executive processes but are found to activate different FC regions, or if two tasks are assumed to engage different executive processes but activate the same FC regions. Finally, imaging studies have also introduced a number of novel WM tasks (such as the *n*-back task) that were developed with the constraints of scanning in mind but which deserve further behavioural investigation.

Most importantly, functional imaging has highlighted the inadequacies of our current understanding of the range of ‘executive functions’ subserved by FC. The possibility of rooting what will necessarily be a high-level (and often metaphorical) terminology in objective measurements of brain activity is likely to prove valuable. In particular, the observation of dissociations across different FC regions is likely to focus theoretical distinctions between the various terminologies surrounding the executive control of memory processes. This, perhaps, will be the most valuable contribution of these techniques.

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