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Specialized Systems for the Processing of Mnemonic Information within the Primate Frontal Cortex [and Discussion]

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Specialized systems for the processing of mnemonic information within the primate frontal cortex

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SUMMARY

The lateral frontal cortex is involved in various aspects of executive processing within short- and long-term memory. It is argued that the different parts of the lateral frontal cortex make distinct contributions to memory that differ in terms of the level of executive processing that is carried out in interaction with posterior cortical systems. According to this hypothesis, the mid-dorsolateral frontal cortex (areas 46 and 9) is a specialized system for the monitoring and manipulation of information within working memory, whereas the mid-ventrolateral frontal cortex (areas 47/12 and 45) is involved in the active retrieval of information from the posterior cortical association areas. Data are presented which support this two-level hypothesis that posits two distinct levels of interaction of the lateral frontal cortex with posterior cortical association areas. Functional activation studies with normal human subjects have demonstrated specific activity within the mid-dorsolateral region of the frontal cortex during the performance of tasks requiring monitoring of self-generated and externally generated sequences of responses. In the monkey, lesions restricted to this region of the frontal cortex yield a severe impairment in performance of the above tasks, this impairment appearing against a background of normal performance on several basic mnemonic tasks. By contrast, a more severe impairment follows damage to the mid-ventrolateral frontal region and functional activation studies have demonstrated specific changes in activity in this region in relation to the active retrieval of information from memory.

1. INTRODUCTION

What is the role in mnemonic processing of the large region of the lateral frontal cortex that, in the primate brain, extends in front of the precentral motor cortex as far as the frontal pole? Patients with damage to this lateral prefrontal cortical region perform well on several tests that are sensitive indicators of the memory disorder that follows damage to the limbic structures of the medial temporal region. Performance on these standard tests of memory, such as recognition and story recall, can be normal even when the lesions are bilateral, as several studies of patients who had undergone frontal lobotomies have clearly demonstrated (see Petrides 1989 for a review). In cases where a severe memory disorder has been reported after frontal lesions, there was involvement of the caudal orbito-medial limbic region of the frontal lobe and the immediately adjacent basal forebrain region (e.g. septal area, nucleus basalis of Meynert, etc.) or there has been significant damage outside the frontal cortex (see Petrides 1989 for a review). Indeed, there has never been a case of amnesia reported after lesions demonstrated to be restricted to the lateral frontal cortex.

Although damage to the lateral frontal cortex in both the human and the monkey brain does not result in a generalized memory disorder, mnemonic performance can be severely impaired under certain conditions of testing. In the monkey, a long line of studies that had its origin in the now classic demonstration by Jacobsen (1936) that lesions of the frontal cortex impair performance on the delayed response tasks has clearly established the involvement of the lateral frontal cortex in working memory (e.g. Mishkin 1957; Gross & Weiskrantz 1962; Butters & Pandya 1969; Mishkin *et al.* 1969; Goldman & Rosvold 1970; Goldman *et al.* 1971; Passingham 1975; Mishkin & Manning 1978; Funahashi *et al.* 1993). A precise characterization of the nature of this involvement has, however, proved elusive.

In the late 1970s, as part of our effort to capture the essential nature of the specific contribution of the human lateral frontal cortex to mnemonic processing, we developed a working memory task in which subjects were required to monitor their recent selections from a set of stimuli (Petrides & Milner 1982). Thus, in this self-ordered task, short-term memory was combined with one aspect of executive processing, namely monitoring. Patients with lateral frontal excisions were severely impaired on the self-ordered task, although they could perform well on several other memory tests, such as recognition memory and the digit span.

In the self-ordered task, the subjects are presented with different arrangements of the same set of stimuli and have to select a different stimulus, on each trial, until all the stimuli are selected. As soon as they start responding, the subjects must therefore be constantly comparing the responses that they have already made with those still remaining to be carried out, i.e. events in working memory must be closely monitored. Monitoring refers to the fact that each selection must

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be marked in the subject's mind and simultaneously considered in relation to the others that still remain to be selected Monitoring within working memory must not be confused with simple attention to a stimulus held in memory. For instance, there are many situations (e.g. recognition memory) in which a particular stimulus in memory is attended to and the other stimuli are not in the centre of current awareness. These situations do not challenge monitoring within working memory in the sense used here, although they demand attention to the stimulus that is being remembered (see Petrides 1995*a*).

2. MID-DORSOLATERAL FRONTAL CORTEX IS CRITICAL FOR MONITORING OF EVENTS IN WORKING MEMORY

In work with the monkey, where lesions can be restricted with precision within particular regions of the brain, it has now been shown that damage to the mid-dorsolateral part of the frontal cortex (i.e. the dorsal part of area 46 and area 9; figure 1) will result in a severe impairment on the self-ordered and the related externally ordered nonspatial working memory tasks (Petrides 1991, 1995*b*). Even more important, however, is the fact that it has been possible to analyse the nature of the impairment after lesions of this cortical region in isolation from the potentially additive/interactive effects of damage to other frontal areas. It is now clear that the impairment on the self-ordered and externally ordered working memory tasks after mid-dorsolateral frontal lesions occurs against a background of normal basic mnemonic processing. For instance, monkeys with such lesions (Petrides 1991, 1995*b*) or even larger dorsolateral frontal lesions (Bachevalier & Mishkin 1986) are able to perform normally on recognition memory tasks in which they have to identify the novel from the familiar stimuli. In addition, monkeys with dorsolateral frontal lesions perform well on delayed matching-to-sample tasks in which they have to recognize which one of two constantly recurring stimuli was most recently presented (Passingham 1975), as well as on the delayed object alternation task in which they have to alternate their responses between two stimuli (Mishkin *et al.* 1969; Petrides 1995*b*). In other words, mnemonic judgements based on the relative recency or primacy of stimuli need not be affected by dorsolateral frontal damage. This basic mnemonic processing, however, can quickly prove inadequate to sustain normal performance on more challenging non-spatial working memory tasks, such as the self-ordered and the externally ordered tasks.

The fundamental problem of animals with mid-dorsolateral frontal lesions on the self-ordered and on the externally ordered working memory tasks has been shown to stem from the monitoring requirements of the tasks, i.e. the number of stimuli that must be considered as responses are being made (Petrides 1995*b*). In one experiment, monkeys with lesions of the mid-dorsolateral frontal cortex were severely impaired when they were required to monitor which one of three possible stimuli they had previously selected, but they were not impaired in remembering which one of two stimuli was chosen, even when a long intertrial interval (60 s) was imposed (see Petrides 1995*b*, experiments 4 & 5). Thus, the number of possible alternative choices that must be considered (i.e. monitored) within working memory, and not the passage of time *per se*, is the critical factor determining whether or not an impairment will follow mid-dorsolateral frontal lesions.

The mid-dorsolateral part of the frontal cortex appears to be a specialized area of the cerebral cortex in which information can be held on-line for monitoring (in the sense described above) and manipulation of stimuli. It has been argued that it constitutes a specialized neural system where stimuli or events that are first interpreted and maintained in posterior

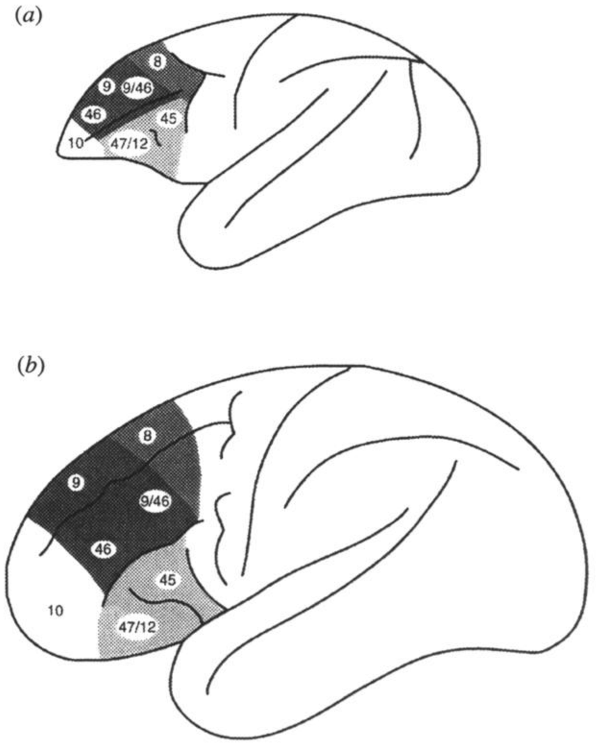

Figure 1. Lateral surface of the macaque monkey (*a*) and the human (*b*) frontal cortex illustrating the mid-dorsolateral frontal region (areas 46, 9, 9/46) and the mid-ventrolateral frontal region (areas 45 and 47/12). The term mid-dorsolateral frontal cortex is used to distinguish, in the rostro-caudal direction, this region from the frontopolar cortex (i.e. area 10) and the posterior dorsolateral frontal cortex (i.e. area 8 and rostral area 6). In the human brain, the mid-dorsolateral frontal cortex occupies the middle parts of the superior and middle frontal gyri. In the human brain, the ventrolateral frontal cortical areas 45 and 47/12 occupy the pars triangularis and pars orbitalis of the inferior frontal gyrus, respectively. In the macaque monkey brain, the ventrolateral frontal cortex lies below the sulcus principalis, occupying the inferior frontal convexity. It comprises architectonic areas 47/12 and 45. The term area 47/12 is used in both the human and the monkey brain to acknowledge the architectonic correspondence between the part of area 47 that lies on the pars orbitalis of the human inferior frontal gyrus and a large part of Walker's area 12 that occupies the inferior convexity of the macaque monkey (see Petrides & Pandya 1994).

association cortical areas can be recoded for the purpose of planned action or the monitoring of expected acts or events (Petrides 1994). It is a system for the on-line maintenance and monitoring of cognitive representations of intended acts (e.g. self-generated choices) and the occurrence of events from a given set. These specific functional contributions of the mid-dorsolateral frontal cortex, a region that is very well developed in the primate brain, make possible high-level planning and organization of behaviour.

3. A TWO-LEVEL HYPOTHESIS OF THE INVOLVEMENT OF THE LATERAL FRONTAL CORTEX IN MEMORY

It has been known for a long time that lesions restricted to the cortex lining the sulcus principalis in the monkey lateral frontal lobe result in severe impairments on certain spatial memory tasks, such as the classical delayed response and delayed alternation tasks (e.g. Mishkin 1957; Gross & Weiskrantz 1962; Butters & Pandya 1969; Goldman & Rosvold 1970). But lesions that spare the sulcus principalis and involve only the mid-dorsolateral frontal cortex that lies above it do not yield impairments on these standard spatial delayed response tasks (e.g. Mishkin 1957; Goldman & Rosvold 1970; Goldman *et al.* 1971) or on non-spatial analogues of these tasks (Mishkin *et al.* 1969). Performance on the latter non-spatial tasks is severely affected by lesions of the ventrolateral frontal cortex that extends below the sulcus principalis (Passingham 1975; Mishkin & Manning 1978).

The above evidence has often been taken to imply a dichotomy between the mnemonic processing of spatial information in the dorsolateral frontal cortex and non-spatial mnemonic processing in the ventrolateral frontal cortex. There are, however, a number of problems with this distinction. First, the recent demonstration of a severe impairment on the non-spatial self-ordered and externally ordered working memory tasks after lesions of the mid-dorsal part of the lateral frontal cortex (dorsal area 46 and area 9) of the monkey indicates that, at least for this part of the frontal cortex, the mnemonic demands of the task, rather than the modality of the material to be processed, determine whether an impairment will be observed after the lesions (Petrides 1991, 1995*b*). Second, it must be pointed out that lesions of the ventrolateral frontal cortex (areas 45 and 47/12) of the monkey impair severely performance of both the spatial and the non-spatial versions of the delayed alternation task (Mishkin *et al.* 1969). The above findings question the idea that the fundamental difference in the functional contribution of the mid-dorsolateral and the mid-ventrolateral frontal cortex can be adequately described as one of modality specificity, namely spatial for the dorsolateral and nonspatial visual for the ventrolateral frontal cortex.

An alternative hypothesis has recently been suggested that views the fundamental difference between the mid-dorsolateral and the mid-ventrolateral frontal cortex as one of distinct levels of involvement in memory rather than simply the result of modality specificity (Petrides 1994). According to this two-level hypothesis, the mid-ventrolateral frontal cortex, in interaction with posterior cortical association areas, subserves the expression within memory of various first-order executive processes, such as active selection, comparison and judgement of stimuli held in short-term and long-term memory (see Petrides 1994 for details; figure 2). This type of interaction is necessary

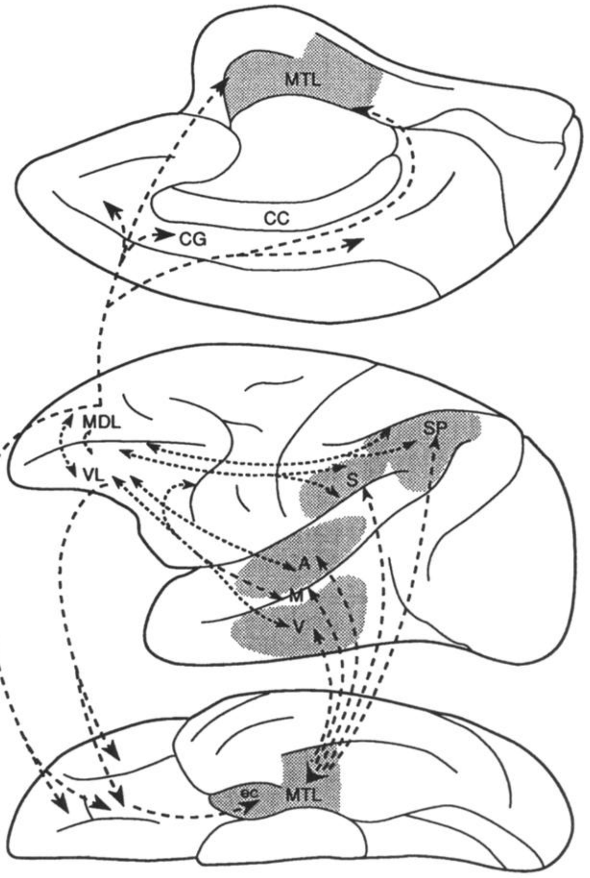

Figure 2. Schematic diagram of the brain of the macaque monkey to illustrate some of the functional interactions postulated by the two-level hypothesis of the role of the lateral frontal cortex to mnemonic processing. Somatosensory (S), spatial (SP), auditory (A), visual (V) and some aspects of multimodal (M) information are processed in posterior temporal and parietal association cortex. In the human brain, linguistic information is processed, primarily in the left hemisphere in the region of the parieto-temporal junction, i.e. supramarginal gyrus in parietal cortex and middle and posterior temporal cortex. Processing in these posterior association cortical areas is assumed by the present model to underlie not only perception and long-term storage, but also transient maintenance of information for further processing. These areas interact with ventrolateral (VL) frontal cortical areas when executive processing, such as decision making, comparison, or active retrieval of information held in memory, is involved. The mid-dorsolateral (MDL) frontal cortex, which is connected with the ventrolateral frontal cortex and with the memory system of the medial temporal lobe (MTL), both directly and indirectly, exercises a higher-order control of mnemonic processing when monitoring and manipulation of information in working memory is required. CC: corpus callosum; CG: cingulate gyrus; ec: entorhinal cortex.

for active (explicit) encoding and retrieval of information, i.e. processes initiated under conscious effort by the subject and guided by the subject's plans and intentions. The mid-dorsolateral frontal cortex (areas 9 and 46), on the other hand, constitutes another level of interaction and is involved when several pieces of information in working memory need to be monitored and manipulated on the basis of the requirements of the task or the subject's current plans. It must be emphasized that the two levels of mnemonic executive processing posited above are likely to be involved in several tasks and often simultaneously. The successful demonstration of the specific contribution of the different areas will therefore depend on selective lesion studies (e.g. in non-human primates) in which impaired performance on certain mnemonic tasks is contrasted with normal performance on other similar tasks and on neuroimaging studies with normal human subjects in which experimental tasks are differentially loaded with requirements thought to involve one or the other area.

It should be pointed out here that the two-level hypothesis is fundamentally different from another current theoretical position which suggests that the various prefrontal areas perform a similar role in working memory, but that each will process different types of information (Goldman-Rakic 1995).

4. FUNCTIONAL ACTIVATION OF THE HUMAN MID-DORSOLATERAL FRONTAL CORTEX

In studies with positron emission tomography (PET) it has been possible to extend to the human brain the demonstration from the animal work that the mid-dorsolateral frontal cortex constitutes a specialized region for the monitoring, within working memory, of self-ordered and externally ordered responses (Petrides *et al.* 1993*a*, *b*). In one study, the distribution of cerebral blood flow (i.e. a marker of local neuronal activity) was measured in normal volunteer subjects as they performed a non-spatial visual self-ordered task, a visual matching control task and a visual conditional task (Petrides *et al.* 1993*a*). The same eight visual stimuli (abstract designs) were used in all three tasks and these stimuli were presented in a different random arrangement on each trial. The subjects were required to indicate their response by pointing to particular stimuli. Thus, the only difference between the three tasks lay in their cognitive requirements. In the self-ordered task, the subjects were required to select a different stimulus on each trial until all had been selected. The subjects were therefore required to consider actively (i.e. monitor) their earlier selections as they were preparing their next response. In the matching control task, the subjects had to search and find the same stimulus on each trial. This task therefore involved the same visual stimuli and searching behaviour as the self-ordered task, but did not require that the subjects consider their earlier responses in relation to the current one. In the conditional task, the subjects had learned, prior to scanning, associations between the stimuli and particular colour cues. During scanning, they were required to select the stimulus that was appropriate for the colour cue presented. Thus, the searching among the stimuli was the same as in the self-ordered task, but since the stimulus to be selected, on each trial, was completely determined by the colour cue presented, no monitoring within working memory of prior selections was required. Performance of the self-ordered task, in comparison with either the matching control or the conditional task, resulted in significantly greater activity within the mid-dorsolateral frontal cortex (areas 46 and 9), particularly within the right hemisphere. There was no activation in this region when cerebral blood flow in the conditional task was compared with that of the control task, although there was now significant activity within the posterior dorsolateral frontal cortex in area 8, a region that is known to be critical for visual conditional learning. The contrast in the activation patterns between the self-ordered and the conditional tasks emphasizes the specificity of activation within the mid-dorsolateral frontal cortex in relation to the monitoring requirements of the self-ordered task.

A related study demonstrated bilateral activation of the mid-dorsolateral frontal cortex in relation to the performance of a verbal self-ordered task and a verbal externally ordered task (Petrides *et al.* 1993*b*). With regard to spatial working memory, activation of either the ventrolateral frontal cortex (area 47/12; Jonides *et al.* 1993) or the mid-dorsolateral frontal cortical area 46 (McCarthy *et al.* 1994) has been reported. We have also observed activation of the mid-dorsolateral or the mid-ventrolateral frontal cortex or both, depending on whether the monitoring or the retrieval of specific information from spatial working memory was taxed (Owen *et al.* 1996). When the task required the execution of a sequence of moves previously shown, the ventrolateral frontal cortex was activated. When, however, the task required in addition active monitoring and manipulation of spatial information within working memory, activation was also observed in the mid-dorsolateral frontal cortex.

5. FUNCTIONAL CONTRIBUTION OF THE MID-VENTROLATERAL FRONTAL REGION: INVOLVEMENT IN ACTIVE RETRIEVAL BUT NOT AUTOMATIC RETRIEVAL

The two-level hypothesis presented above makes a distinction between active (strategic) retrieval, which requires ventrolateral frontal cortex, and automatic retrieval which does not (Petrides 1994, 1995*a*). According to this hypothesis, automatic retrieval is the by-product of the triggering of stored representations in posterior cortical association regions either by incoming sensory input that matches pre-existing representations or by recalled events that trigger stored representations of related information on the basis of strong pre-existing associations or other relations, such as thematic context. This kind of automatic retrieval occurs as long as the connections between the posterior temporal and parietal association areas, where sensory processing is carried out, and subcortical structures are intact. The ventrolateral frontal cortex interacts with posterior temporal and parietal association cortex (via strong bi-directional connections) when active retrieval of specific information held in these posterior association areas is required. Active retrieval implies conscious (i.e. willed) effort to retrieve a specific piece of information guided by the subject's intentions and plans. This attempt at retrieval may be self-generated or set up by the instructions given to the subject.

The above hypothesis provides an adequate explanation of why lateral frontal lesions do not cause a generalized memory disorder. Performance on several standard memory tests can be normal after such lesions because it can be the automatic result of processing in the posterior temporal and parietal perceptual systems. For instance, when a stimulus that was seen before is again experienced through the visual modality, the novel processing matches (i.e. triggers) pre-existing representations in posterior association cortex; this reactivation is sufficient to carry knowledge that the stimulus had been experienced before. Thus, performance on several basic recognition tasks that simply require awareness of familiarity of the stimulus can be normal after lateral frontal lesions. Similarly, when a subject reads or listens to a narrative story and that subject is subsequently asked to relate this story, the thematic relations between the various components of the story automatically trigger related pieces of information in posterior association cortex. Thus, the story is recalled even if the subject has suffered damage to the lateral frontal cortex. By contrast, when the subject is asked to recall specific pieces of information that are not automatically triggered by current sensory input or thematic and other strong relations, an active retrieval must be initiated to search for and retrieve the particular piece of information. According to the two-level hypothesis presented above, this type of search does require interactions between the ventrolateral frontal cortex and the posterior temporal and parietal association cortex.

In a recent series of studies with positron emission tomography, we attempted to test the prediction from the two-level hypothesis that the mid-ventrolateral frontal cortex (i.e. areas 45 and 47/12) is involved in the active explicit retrieval of specific information (Petrides *et al.* 1995; Doyon *et al.* 1996). In the first study, the aim was to establish whether the human mid-ventrolateral frontal cortex, in the left hemisphere, is involved in the strategic retrieval of verbal information from long-term memory (Petrides *et al.* 1995). To engage the subject in active retrieval of specific verbal information from long-term memory, the main experimental condition involved, during scanning, the free recall of a list of arbitrary words that had been studied before scanning. It is well known from experimental psychological studies that free recall under these conditions is the result of active strategic retrieval processes. Note that performance on such a free recall task cannot be simply the result of recognizing familiar words that are presented again, nor can it be the result of retrieving information by thematic relatedness, as in a logical story. The subject is now asked to recall a specific set of arbitrary words from his/her lexicon that were presented on a particular recent occasion under particular conditions, namely the specific set of words studied just before scanning.

As any recall task will require some degree of monitoring within working memory of the output from long-term memory, it was to be expected that during the performance of the above free recall task there should be significant activity in the mid-dorsolateral region of the frontal cortex, in addition to any ventrolateral activity that might be observed. Note that in our earlier work with PET (Petrides *et al.* 1993*b*), the mid-dorsolateral region of the frontal cortex, but not the ventrolateral, was shown to be specifically activated in relation to the monitoring, within working memory, of self-generated and externally generated verbal responses. Two control conditions were therefore employed to reveal any specific contribution of the left mid-ventrolateral frontal cortex to the active retrieval of verbal information. One of these scanning conditions required the simple repetition of auditorily presented words and was designed to control for processes involved in the listening, understanding and production of words. The other control condition was designed to involve easy verbal retrieval (i.e. at a level that would be significantly easier than that of the free recall task) but monitoring, within working memory, of the retrieved verbal output at about the same level as that in the free recall task. For this purpose, a verbal paired-associate task was used in which the pairs were very well learned before scanning and were therefore very easy to retrieve in comparison with the free recall task (Petrides *et al.* 1995).

In relation to the repetition control task, both the free recall task resulted in greater activation within both the mid-ventrolateral and mid-dorsolateral frontal cortex. The comparison between the free recall (i.e. difficult retrieval) and the highly learned paired-associate recall (i.e. easy retrieval) revealed significantly greater activity in the left mid-ventrolateral frontal cortex in the free recall task, but no difference between the tasks in the mid-dorsolateral frontal cortex (Petrides *et al.* 1995).

Significant activity in the dorsolateral frontal cortex had been previously observed in a number of other PET studies that examined retrieval from verbal episodic memory (Grasby *et al.* 1993; Shallice *et al.* 1994; Tulving *et al.* 1994; Buckner *et al.* 1995). In these studies, with the exception of Buckner *et al.* (1995), no activation of the ventrolateral frontal cortex was observed. The present results suggest that the earlier failure to observe activation in ventrolateral frontal cortex from retrieval of verbal episodic memory was due to the fact that the control tasks used also activated, to the same extent, ventrolateral frontal cortex. The results presented above indicate that the mid-dorsolateral and the mid-ventrolateral frontal cortex are involved in the performance of tasks requiring retrieval from verbal episodic long-term memory, but their

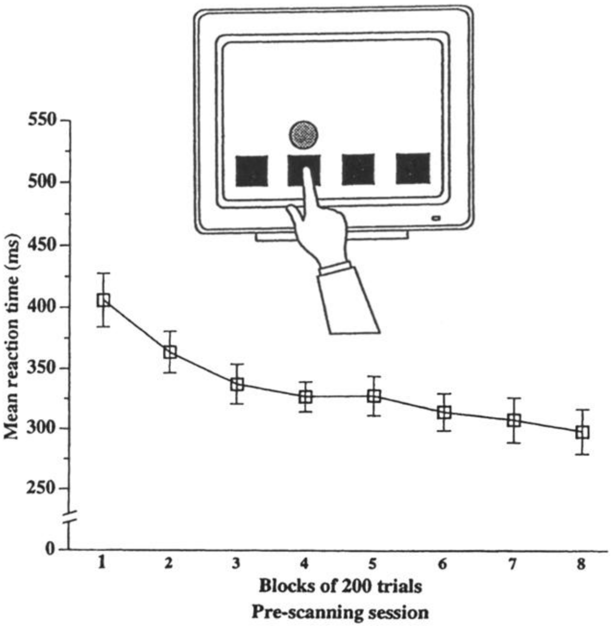

Figure 3. Schematic diagram of the experimental arrangement in the visuospatial sequence task. On each trial, a red circle appeared above one of four blue response boxes. The subject's task was to touch that box as quickly as possible. The graph shows the mean reaction time data of the subjects tested in the visuospatial sequence task. Note the gradual reduction in reaction time implying implicit learning of the sequence as a result of the pre-scanning training session. Each data point in the training session corresponds to the reaction time averaged over two blocks of 100 trials (i.e. 200 trials). At the end of this training session, the subjects were scanned while they performed this task. Although behaviourally the subjects demonstrated learning of the sequence, they did not have explicit knowledge of the sequence when tested after scanning.

contributions differ. The mid-dorsolateral frontal region participates in free recall by virtue of its role in the on-line monitoring, within working memory, of the output from long-term memory, whereas the mid-ventrolateral frontal cortex is more directly involved in active retrieval mechanisms (Petrides *et al.* 1995).

In another PET study, we tested the prediction that the right mid-ventrolateral frontal cortex would be involved in the active explicit retrieval of specific information in a visuospatial task (Doyon *et al.* 1996). The aim of this study was to compare neuronal activation between a condition in which the subjects performed a highly automatized visuospatial sequence under implicit control with a condition in which the subjects performed the same sequence but now with explicit knowledge and thus explicit retrieval of each move in the sequence. The prediction from the two-level hypothesis was that, in comparison with the automatic performance of the visuospatial sequence, explicit performance of the sequence should involve activity in the ventrolateral frontal cortex.

In this task, the subjects were faced with a touch-sensitive screen on which four blue response boxes were displayed. During testing, a red circle would appear above one of the response boxes and the subject was simply required to touch that box as quickly as possible (figure 3). As soon as the subject had touched the appropriate box, the red circle disappeared and, after a fixed interval (800 ms), the red circle would again appear above one of the boxes, thus initiating the next trial. As before, the subject's task was merely to touch the box that lay under the red circle as fast as possible. In every block of ten trials, the red circle moved in a predetermined fixed sequence, but the subject was not informed of this. The subjects were extensively trained on this task just before scanning. As expected, the result of this training was to reduce significantly the subject's reaction time on each trial, indicating learning of the repeating sequence (figure 3). The subjects were then scanned with PET as they performed this highly automatized visuospatial sequence of movements.

After the above training and scanning, the subjects were asked whether they had noticed that there was a sequence in the task and whether they knew the sequence. Although all subjects were aware that there was a repeating sequence of moves, none of them was able to generate the repeating sequence from memory. The subjects were then given explicit training on the sequence in the following manner. Instead of simply being required to press the box below which the red circle appeared, as in the implicit training, they were now asked to press the box where they thought the next stimulus in the visuospatial sequence would appear. This training procedure was continued until the subjects reached the learning criterion. The subjects were then scanned with PET under testing conditions that were identical to those of the implicit sequence performance.

Note that in both the implicit and the explicit conditions, the subjects performed the same visuospatial sequence and made the same number of movements, as each response was guided by the appearance of the red circle every 800 ms. Thus, there was only one difference between the two conditions: In the explicit condition, the subject had explicit knowledge of the sequence and, after each response, would actively retrieve the next location where the red circle would appear; by contrast, in the implicit condition, although there was implicit anticipation of the next response (as indicated by the reaction times), the subject was not able to retrieve explicitly specific information about the next move. When activity in the two conditions was compared, there was greater activity within the right ventrolateral frontal cortex during the performance of the explicit sequence, in accordance with the predictions of the two-level hypothesis. Note that no other part of the frontal cortex exhibited increases in blood flow in the explicit condition in comparison with the implicit condition. It is also interesting to note that the increase was observed only in the right ventrolateral frontal cortex, as would be expected from the fact that the stimulus material was visuospatial.

In conclusion, the data reviewed above show that within the mid-lateral part of the frontal cortex, two systems can be distinguished: one centered on the mid-dorsolateral frontal cortex and the other on the mid-ventrolateral frontal cortex. The fundamental distinction between these two regions of the frontal lobe appears to be in terms of the nature of the executive processing that is being carried out, although within the dorsolateral and ventrolateral frontal regions there may be further specialization according to the sensory modality of the information processed.

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Discussion

A. Baddeley (*Department of Psychology, University of Bristol, 8 Woodland Road, Bristol BS8 1TN, U.K.*). Random generation is a task that is particularly good at interfering with executive activities. In one particular study involving random pressing of keys at the same time as remembering a sequence of digits we have shown that the randomness of the output reduces as the digit span increases. As these two processes interact in a lawful linear way, a simple explanation for this finding is that these two processes are in some sense occupying the same system. However, it would seem from your functional imaging studies that you are suggesting that the storage system and the generation system are occupying two different regions within the prefrontal cortex, namely dorsolateral and ventrolateral regions respectively. Am I right in drawing that conclusion and if so, does that suggest that we need some other sort of explanation before we can fully understand both our behavioural data and your scanning data?

M. Petrides. I have argued that the ventrolateral frontal cortex is critical for active retrieval of information from memory storage and the mid-dorsolateral frontal cortex is critical for monitoring within working memory. We know that these two parts of the frontal cortex are anatomically connected and, presumably, these two frontal regions are in close functional interaction. In this sense, I should be inclined to say that, assuming that your two tasks tap on resources of both the ventrolateral and the dorsolateral frontal regions, although perhaps in a different manner, the lawful linear way in which these two tasks interact reflects, at least partially, the close functional interaction of these two frontal regions.