

Double dissociations of memory and executive functions in working memory tasks following frontal lobe excisions, temporal lobe excisions or amygdalo-hippocampectomy in man

Adrian M. Owen,² Robin G. Morris,³ Barbara J. Sahakian,² Charles E. Polkey⁴ and Trevor W. Robbins¹

Departments of ¹Experimental Psychology and ²Psychiatry, University of Cambridge, the ³Neuropsychology Unit, Institute of Psychiatry, University of London and the ⁴Neurosurgical Unit, The Maudsley Hospital, London, UK

Correspondence to: Adrian M. Owen, Department of Psychiatry, University of Cambridge, Box 189, Addenbrooke's Hospital, Cambridge CB2 2QQ, UK

Summary

Thirty-two neurosurgical patients with unilateral or bilateral frontal lobe excisions, 41 patients with unilateral temporal lobe lesions and 19 patients who had undergone unilateral amygdalo-hippocampectomy were compared with matched controls on a computerized test of spatial working memory. A significant deficit was observed in the frontal lobe group, even at the least challenging level of task difficulty and this impairment was found to relate to the inefficient use of a particular searching strategy shown to improve performance on this task. In contrast, deficits in the temporal lobe group and the amygdalo-hippocampectomy group were only observed at the most difficult level of the task and in neither group could the deficit be related to the inefficient use of

any particular searching strategy. In a follow-up study, the three patient groups were compared on analogous computerized tests of visual and verbal working memory. No deficits were observed in the frontal lobe group. By comparison, both the temporal lobe patients and the amygdalo-hippocampectomy group were significantly impaired in the visual working memory condition but not in the verbal working memory condition. These deficits were clearly evident at all levels of task difficulty and were not related to any particular searching strategy. The data are discussed in terms of the relative contributions of 'executive' and 'mnemonic' mechanisms to the contrasting, material dependent deficits observed in the frontal and temporal lobe groups.

Keywords: working memory; frontal cortex; temporal cortex; amygdala; executive functions

Abbreviation: rCBF = regional cerebral blood flow

Introduction

Working memory has been described as a 'brain system that provides temporary storage and manipulation of the information necessary for such complex tasks as language comprehension, learning and reasoning' (Baddeley, 1992). According to Baddeley's model, a limited capacity 'central executive' acts as a controller or scheduler of a number of slave systems. In the verbal modality the slave system is known as the 'articulatory loop', whilst the 'visuo-spatial sketch pad' is the name given to the analogous system responsible for the temporary storage of visuo-spatial material. The nature of the central executive has not been well defined either theoretically or experimentally, although

Baddeley has suggested that the frontal lobes may, at least partially, subserve the functions assigned to this control mechanism, and also that damage to the frontal cortex would therefore interfere with this component of working memory (Baddeley, 1986; Baddeley *et al.*, 1986).

Monkeys with bilateral damage to the area surrounding the sulcus principalis exhibit profound and selective deficits in spatial tasks that require memory for the location of objects in space (Gross and Weiskrantz, 1964; Goldman and Rosvold, 1970; Goldman *et al.*, 1971). Recently, Goldman-Rakic (1990) has argued that the mechanisms underlying working memory are similar, if not identical, to the processes measured

by the classic delayed response test. Using an elegant oculomotor variant of this task, impairments have been demonstrated in monkeys with sulcus principalis lesions, suggesting again, that this area plays a critical role in spatial working memory processing (Funahashi *et al.*, 1989). Furthermore, using the same oculomotor paradigm, neurophysiological studies have confirmed that prefrontal neurons spatially code the location of an object throughout the visual field (Funahashi *et al.*, 1989, 1990) in a manner analogous to the visual receptive fields of visual cortical neurons. This interpretation of working memory seems to be most closely related to the 'visuo-spatial sketch pad' component of Baddeley's model, especially given its emphasis on maintaining stimulus representations 'on-line'. However, it is not clear what executive functions are required for this class of delayed response test.

The problem of comparison between species is further compounded by Honig's (1978) definition of working memory, as used in Olton's radial arm maze, in which rats are required to self order a series of choices in order to maximize food reinforcement (Olton, 1982). This paradigm clearly requires memory for spatial location but, in addition, an executive or 'organizational' component of task performance to optimize the sequence of choices. Adaptations of the Olton procedure have been used to investigate spatial working memory in both humans (Owen *et al.*, 1990) and in primates (Passingham, 1985). In the former study, a computerized modification of this paradigm, originally developed by Morris *et al.* (1988), was used to assess spatial working memory in a group of neurosurgical patients with localized excisions of the frontal lobes (Owen *et al.*, 1990). Compared with controls, the frontal lobe patients made more returns to locations in which 'tokens' had already been found and were inefficient in the use of a repetitive searching strategy known to improve performance on this task.

Whilst these human and animal studies support the view that the prefrontal cortex plays an important role in spatial working memory, the precise nature of its involvement in executive, as well as mnemonic processes and its dependence on reciprocal connections with other neural structures, is unclear. Goldman-Rakic (1990) has described several multi-synaptic connections between the prefrontal cortex and the hippocampal formation and has speculated that these connections imply a reciprocal functional relationship between the hippocampus and the prefrontal cortex in working memory (Goldman-Rakic *et al.*, 1984). In keeping with this suggestion, it is well established that conventional lesions of the hippocampus or fornix in rats produce severe and enduring deficits in spatial working memory tasks (Olton *et al.*, 1978; Olton and Papas, 1979; Rawlins and Olton, 1982; Rawlins and Tsaltas, 1983; Aggleton *et al.*, 1986). Together, these studies suggest that spatial working memory involves a network of interconnected cortical and subcortical areas including, at the very least, the dorsolateral prefrontal cortex and the hippocampal formation.

A further question of interest is whether there are similar

networks associated with the executive and mnemonic components of non-spatial working memory. Monkeys with lesions of the inferior prefrontal convexity located ventrolateral to the sulcus principalis, or to the orbital prefrontal cortex, are impaired on tasks requiring memory for visual features of objects, but not for their location (Goldman *et al.*, 1971; Passingham, 1972, 1975; Bachevalier and Mishkin, 1986; Wilson *et al.*, 1993). More recently, Petrides (1991) has demonstrated that bilateral lesions limited to a specific area of the lateral prefrontal cortex in monkeys (cytoarchitectonic areas 46 and 9) give rise to severe and highly specific impairments in non-spatial (visual features) working memory performance. Petrides and Milner (1982) used a version of this self-ordered task, designed for human subjects, to compare working memory for various non-spatial stimuli in patients with neurosurgical excisions of the frontal or temporal lobes. The frontal lobe patients with left-sided removals were severely impaired in their ability to organize and monitor a sequence of pointing responses to both visual and verbal stimuli, whilst right-sided patients were less severely impaired and only in the nonverbal conditions. In contrast, no deficits were observed in the group of patients with temporal lobe excisions not extending posteriorly, on the medial side, beyond the pes of the hippocampus. However, material specific deficits related to the side of the lesion were observed in temporal lobe patients with more radical hippocampal involvement. The authors suggest that the pronounced deficits in the frontal lobe group may reflect 'poor organizational strategies, poor monitoring of responses or both' although no formal measures were employed to test this hypothesis (Petrides and Milner, 1982).

These results have recently been extended using PET combined with MRI to identify the neural loci of non-spatial working memory (Petrides *et al.*, 1993a, b). Using the same visual self-ordered working memory task mentioned above, significant increases in regional cerebral blood flow (rCBF) were observed within the left and particularly, within the right mid dorsolateral frontal cortex (area 46) and in the posterior part of the middle frontal gyrus on the left side (area 9). Furthermore, in a verbal analogue of this test, task related rCBF increases were observed bilaterally, within the mid dorsolateral frontal cortex (areas 46 and 9).

In summary, many previous investigations have suggested that the frontal lobes may play an important, yet not necessarily unique role in certain aspects of both spatial and non-spatial working memory performance. However, the precise contribution of mnemonic and strategic components of these tasks is unknown and is likely to depend upon the stimulus material used. Moreover, the role of the prefrontal cortex itself in this interaction between mnemonic and strategic components of performance is also unclear.

The present study was designed to investigate these issues further by comparing three groups of patients with well-localized neurosurgical excisions on analogous self-ordered tests of spatial, verbal and visual working memory. The spatial working memory paradigm used here has previously

been shown to be sensitive to the deficit in a single group of neurosurgical patients with frontal lobe damage (Owen *et al.*, 1990). In that study, a major contribution to the frontal lobe deficit was an inability to use a particular searching strategy shown to be related to superior performance in normal control subjects. The implication of this finding is that subjects with frontal damage will be relatively less impaired in tasks where there are no obvious strategies for improving performance. Consequently, in the frontal lobe patients, and in the other two patient groups studied, the approaches used to complete the three self-ordered working memory tasks were closely assessed, paying particular attention to the types of strategic or organizational deficits observed previously, in order to dissociate executive and mnemonic aspects of performance.

In addition, the role of the human hippocampal region in these tests of working memory was investigated by assessing two groups of patients with either a temporal neocortical excision (which typically includes a small amount of the hippocampus) or a selective amygdalo-hippocampectomy (which typically includes the entire hippocampus in one hemisphere). On the basis of the previous studies in rats, monkeys and humans described above, we predicted that spatial working memory deficits would be more severe in the patients with radical hippocampal excisions than in those with small hippocampal lesions and further, that similar patterns of impairment would be observed in analogous non-spatial working memory tasks (*see* Petrides and Milner, 1982).

Method

Patients

The three groups of neurosurgical patients included in this study were consecutive referrals with frontal lobe, temporal lobe or amygdalo-hippocampus excisions, performed at the Maudsley Hospital Neurosurgical Unit, London. Among the frontal lobe cases, three patients were tested, but later excluded from the analysis, since examination of their CT scans revealed some damage to subcortical structures. Three temporal lobe referrals were not tested since they had histories of affective disorder (two patients) and substance abuse (one patient). Since the number of patients within each group was limited, it was not possible to match the patients according to preoperative pathology. Testing was carried out either as part of the postoperative neuropsychological evaluation (*i.e.* within 3 months of surgery) or in long-term follow-up. The average time between surgery and testing was 4 years 10 months (range 3 months to 26 years) for the frontal lobe patients, 3 years 1 month (range 3 months to 10 years 1 month) for the temporal lobe patients and 1 year (range 3 months to 2 years) for the amygdalo-hippocampectomy patients. As this factor was not statistically related to performance on the working memory tests in any of the three patient groups, it will not be given further consideration in the main analyses of effects. In order to simplify the analysis

of laterality effects, only patients who were either right handed, or who were shown to be left hemisphere dominant during sodium amytal testing were included in this study.

In total, 92 patients participated in the study and every patient completed the spatial working memory task. Each patient was paired with a normal control subject, matched as closely as possible with respect to age and verbal IQ. Among the patients, where a standard clinical neuropsychological assessment had been conducted, verbal IQ was derived directly using the revised Wechsler Adult Intelligence Scale. In all other cases, verbal IQ was estimated using the National Adult Reading Test (Nelson, 1982). In 15 of the frontal lobe patients (47%), 26 of the temporal lobe patients (63%) and 11 of the amygdalo-hippocampectomy patients (58%) the verbal IQ score was derived directly. All of the control scores were estimated using the National Adult Reading Test.

A subset of 51 of these patients also completed the tests of visual and verbal working memory. In all cases, each patient was matched with the same control subject across the three test conditions.

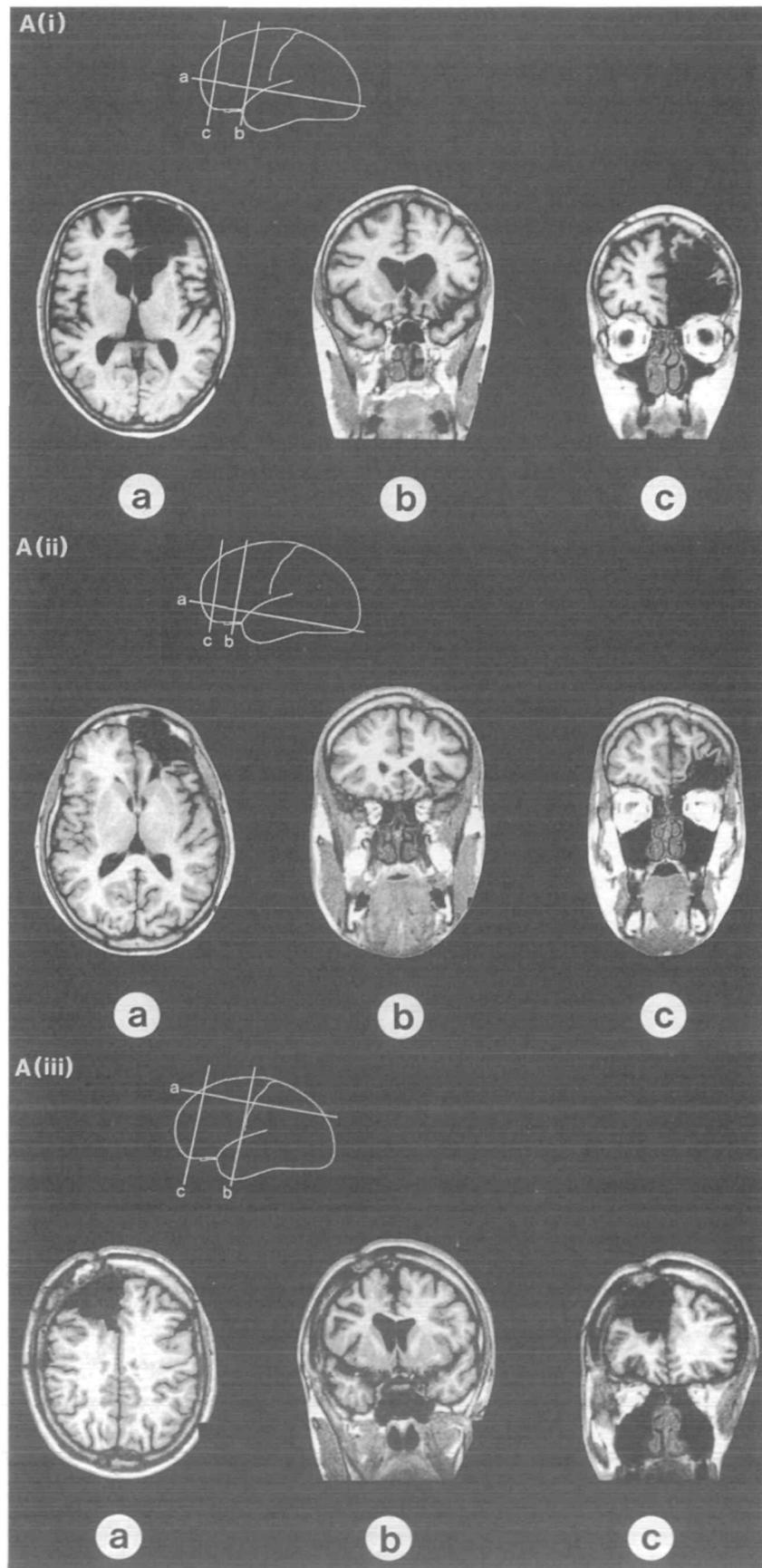
Frontal lobe patients

Thirty-two frontal lobe patients participated in this study and all completed the spatial working memory test. Three examples of representative lesions, examined using high-resolution MRI, are shown in Fig. 1A. Eighteen of these cases had right-sided frontal lobe excisions among which there were five cases of right frontal lobectomy, three cases where an aneurysm of the anterior communicating artery had been clipped, four cases where a right-sided meningioma had been removed, two cases of arterio-venous malformation removal, one case where a craniopharyngioma had been removed and three cases where an astrocytoma had been completely removed. Eleven patients had left-sided frontal lobe excisions among which there were seven cases of unilateral lobectomy for intractable epilepsy, one case of arterio-venous malformation removal and three cases where an astrocytoma had been completely removed. The remaining three patients had undergone bilateral frontal meningioma removal.

A sub-group of 18 of these frontal lobe patients also completed the visual and verbal working memory tests. Eleven of these patients had right-sided frontal lobe excisions among which there were four cases of right frontal lobectomy, two cases where an aneurysm of the anterior communicating artery had been clipped, three cases where a right-sided meningioma had been removed, one case of arterio-venous malformation removal, and one case where a benign astrocytoma had been removed. Five patients had left-sided frontal lobe excisions. All had undergone unilateral lobectomy. The remaining two patients had undergone bilateral frontal meningioma removal.

Temporal lobe patients

The standard 'en bloc' resection (Falconer, 1971) involves the removal of between 5.5 cm and 6.5 cm of the temporal



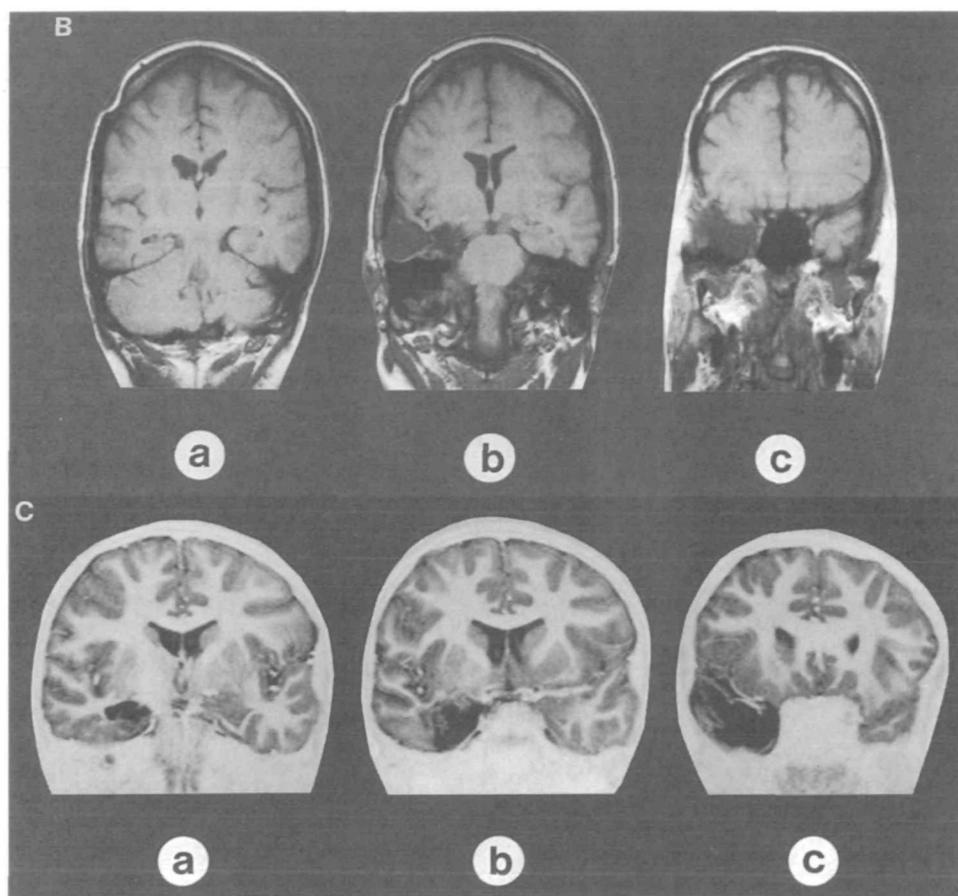


Fig. 1 (A) A series of single slice MRIs to show the extent of excision in three representative cases of the frontal lobe group (the positions of sections a, b and c are indicated schematically in each case): (i) left-sided unilateral lobectomy; (ii) left-sided inferior prefrontal excision; (iii) right-sided superior prefrontal excision. (B) A typical temporal lobe resection (right-sided). Coronal slice a is just caudal to the posterior limit of the excision. Coronal slices b and c are progressively more anterior. (C) A typical amygdalo-hippocampectomy (right-sided). Coronal MRI slices a-c show progressively more rostral sections through the temporal lobe.

lobe measured from the pole and typically includes a small amount (<3 cm) of the hippocampus and up to one-half of the amygdala. Since a standard operation was performed, the amount of the medial temporal lobe structures affected was relatively constant for all patients. In the dominant hemisphere, only the anterior 1–2 cm of the superior temporal gyrus is removed to minimize the risk of postoperative speech problems. A typical postoperative MRI following temporal lobe resection is shown in Fig. 1B. Forty-one temporal lobe patients completed the spatial working memory test. In this group, there were 19 patients where left-sided surgery had been performed and 22 cases where right-sided surgery had been performed. Twenty-three temporal lobe patients also completed the verbal and the visual working memory tests. In this group, there were 11 patients where left-sided surgery had been performed and 12 cases where right-sided surgery had been performed. All patients had undergone unilateral temporal lobectomy for the relief of pharmacologically intractable epilepsy.

Amygdalo-hippocampectomy patients

A variant of the 'en bloc' resection is the selective amygdalo-hippocampectomy (Yasargil *et al.*, 1985). This operation is performed on patients who have a known structural lesion in or near the medial temporal lobe structures, or when other investigations have suggested a medial temporal focus for seizures. In most cases, the amygdala and hippocampus are entirely removed on one side without any permanent damage to the overlying cortical structures. A typical postoperative amygdalo-hippocampectomy (MRI) is shown in Fig. 1C. Nineteen amygdalo-hippocampectomy patients completed the spatial working memory test. Of these, 12 had left-sided removals and seven had right-sided removals. Ten patients in this group also completed the visual and verbal working memory tests. Of these, six patients had left-sided removals and four patients had right-sided removals. In all cases, surgery was performed for the relief of pharmacologically intractable epilepsy.

Table 1 Subject characteristics

	<i>n</i>	M/F	Age (years)	Verbal IQ	L/R/Bi
Spatial working memory					
Frontal	32	17/15	42.38 (3.15)	99.19 (2.17)	11/18/3
Control	32	22/10	41.97 (3.17)	100.2 (1.65)	
Temporal	41	20/21	29.83 (1.41)	93.67 (2.11)	19/22
Control	41	24/17	36.34 (2.37)	99.57 (1.41)	
Amygdalo-hippocampectomy	19	8/11	32.58 (1.88)	88.86 (5.50)	12/7
Control	19	5/14	32.11 (3.09)	93.92 (1.53)	
Visual and verbal working memory					
Frontal	18	9/9	44.27 (4.29)	99.72 (3.07)	5/11/2
Control	18	11/6	46.88 (4.56)	99.72 (2.55)	
Temporal	23	6/17	26.86 (1.67)	89.45 (1.76)	11/12
Control	23	8/15	39.04 (3.92)	98.32 (2.67)	
Amygdalo-hippocampectomy	10	5/5	34.30 (3.14)	83.60 (10.6)	6/4
Control	10	8/2	33.10 (4.93)	93.70 (2.24)	

M/F = male/female; L/R/Bi = laterality left/right/bilateral; SEM in brackets.

Control subjects

Spatial working memory task

Since the three patient groups differed in terms of age and estimated verbal IQ, three groups of normal control subjects were chosen to match the patient groups as closely as possible with respect to these variables. The control subjects were drawn from a large pool of volunteers in Cambridge, London and at the North-East Age Research Panel in Newcastle upon Tyne. Exclusion criteria included any history of neurological or psychiatric illness, substance abuse or head injury. A summary of the main characteristics for the six patient and control groups is presented in Table 1.

One-way ANOVAs revealed that both the frontal lobe group and the amygdalo-hippocampectomy group were well matched with their respective control groups in terms of both age [frontal, $F(1,62) = 0.008$; amygdalo-hippocampectomy, $F(1,36) = 0.017$] and estimated verbal IQ [frontal, $F(1,62) = 0.14$; amygdalo-hippocampectomy, $F(1,36) = 0.79$]. The temporal lobe group were both significantly younger than their controls [$F(1,80) = 5.5$, $P < 0.05$] and scored slightly lower in terms of estimated verbal IQ [$F(1,80) = 5.86$, $P < 0.05$]. To correct for these differences, age and verbal IQ were therefore treated as covariates during all subsequent analyses of performance.

Visual and verbal working memory tasks

As the patient and control subjects described above had been matched on a one-to-one basis, the three sub-groups of neurosurgical patients were compared with their corresponding sub-groups of normal, healthy controls. A summary of the main characteristics for the six patient and control sub-groups is presented in Table 1. One-way ANOVAs revealed that both the frontal lobe group and the amygdalo-hippocampectomy group were again well matched with their respective control groups in terms of age [frontal, $F(1,34) = 0.18$; amygdalo-hippocampectomy, $F(1,18) = 0.046$] and estimated verbal IQ [frontal,

$F(1,34) = 0.00$; amygdalo-hippocampectomy, $F(1,18) = 0.96$]. Again, since the temporal lobe patients were significantly younger than their controls [$F(1,44) = 8.3$, $P < 0.01$] and scored significantly lower in terms of estimated verbal IQ [$F(1,44) = 8.2$, $P < 0.01$], these variables were treated as covariates in all subsequent analyses.

All patients and control subjects gave their informed consent to participate in this study, which was approved by the Ethics Committee of the Institute of Psychiatry, London.

Procedure

Spatial working memory task

This test has been described in detail elsewhere (Morris *et al.*, 1988; Owen *et al.*, 1990, 1992, 1993, 1995). Subjects were required to 'search through' a number of boxes presented on the screen by touching each one with the result that it 'opened up', revealing what was inside (Fig. 2A). The object of the task was to collect 'blue tokens' hidden inside the boxes and once found, to use them to fill an empty column at the side of the screen. At any one time, there would be a single token hidden inside one of the boxes and the subjects were required to search until they found it, at which point the next token would be hidden. The key instruction was that once a blue token had been found within a particular box, then that box would never be used again to hide a token. Consequently, two types of search error were possible. First, a subject may return to open a box in which a blue counter has already been found during the same trial (a 'between search' error). Secondly, a subject may return to a box already opened and shown to be empty earlier in the same search sequence (a 'within search' error). Subjects could search the boxes in any order, but for control purposes, the number of empty boxes visited (excluding errors), before a token was found was determined by the computer. After four practice trials with three boxes, there were four test trials with each of four, six and then eight boxes. The task

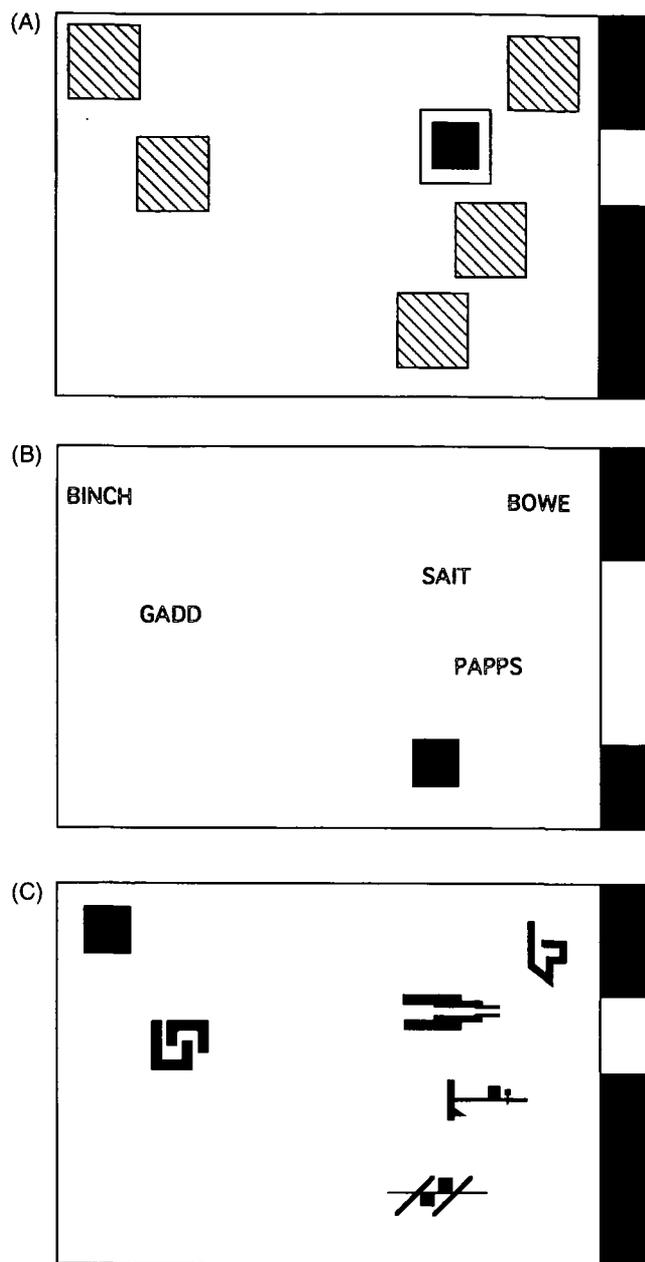


Fig. 2 (A) The spatial working memory task. (B) The verbal working memory task. (C) The visual working memory task. In each case, subjects are required to search through each stimulus to find square 'tokens' and then to collect them on the right side of the screen.

was scored according to the number of 'between' and 'within' search errors at each level of difficulty.

Verbal working memory task

The test was formally similar to the spatial working memory task described above. The subject was required to 'search through' a number of monosyllabic surnames presented on the screen by touching each one to 'find' hidden tokens (Fig. 2B). Each name was trial unique and occurred with a

similar frequency in the Greater London telephone directory. Names which were considered 'common' (e.g. 'Smith' or 'Jones'), or which were associated with a famous person were avoided, as were names with obvious semantic or visual properties (e.g. 'Green' or 'Long').

Again, the object of the task was to collect blue tokens hidden 'behind' the name and, once found, to use them to fill an empty column at the side of the screen. The subjects were instructed that at any one time there would be a single token hidden behind one of the names. Their task was to search until they found it, at which point the next token would be hidden. Again, once a blue token had been found behind a particular name, then that name would never be used again to hide a token. Since every name was used once, on every trial the total number of blue tokens to be found corresponded to the number of names on the screen. In this sense, the task was very similar to the spatial working memory task in that subjects were required to conduct a systematic search through an array, avoiding items in which tokens had previously been found. However, the crucial difference between the two tasks was that in the verbal task, the items to be searched (i.e. the names) altered their spatial locations after each response. Within any given trial, the same fixed number of spatial locations were always used, although after each selection every name moved randomly to a new location. This provision ensured that the test could not be solved using spatial cues.

A small pilot study of 24 control subjects, revealed that this test was considerably more difficult than the spatial working memory task. Therefore, after four practice trials with three names, all of the patient and control groups were given four test trials with each of four and six names. The frontal lobe patients and their control group were also given four additional problems with eight names. The task was scored according to the number of 'between search' and 'within search' errors at each level of difficulty.

Visual working memory task

This task was very similar in design to the verbal working memory task described above, although instead of surnames, simple coloured shapes were used as the sample stimuli. Each shape was trial unique and could not easily be described verbally. Within each trial, all the shapes were the same colour, although with each new trial, a different colour was always used (Fig. 2C).

Again, subjects were required to collect 'blue tokens' hidden 'behind' the shapes and to avoid shapes behind which a blue token had previously been found. As in the verbal working memory task, the items to be searched (i.e. the shapes) altered their spatial locations after each selection. Again, this provision ensured that the test could not be solved using spatial cues. The number of incorrect shapes selected (excluding errors), before a token was found was determined by the computer.

As with the verbal memory task, a pilot study of 24 control

subjects had shown this version of the working memory paradigm to be more difficult than the spatial condition and so, in most of the groups studies, task difficulty was varied only between three and six stimuli. Thus, after four practice trials with three shapes, all of the patient and control groups were given four test trials with each of four and six shapes. The frontal lobe patients and their controls, however, were also given four additional problems, with eight shapes. As in the spatial and verbal analogues of this task, performance was assessed according to the number of 'between search' and 'within search' errors at each level of difficulty.

Strategy measures: rationale and computation of strategy scores

The spatial working memory task described above requires a self-ordered, well-organized search to maintain high levels of performance, which presumably depends, to some extent, upon spatial memory capacity. A purely 'mnemonic' deficit, involving reduced capacity, would be expected to affect performance preferentially at those levels of task difficulty where spatial capacity or 'span' were exceeded. However, previous studies have also shown that, in control subjects, performance on this task can be facilitated by the adoption of a repetitive searching strategy, beginning each search with a particular box and then returning to start each new sequence with that same box as soon as a token has been found (e.g. Owen *et al.*, 1990). The optimal strategy is then to repeat the previously employed order of choices until a reinforced location is encountered when it is necessary to sample a novel location. Such strategies, when applied to self-ordered search tasks of this type, may serve to reduce the load on active working memory and would, presumably, enhance performance at all levels of task difficulty. The deficit in patients with frontal lobe damage on this task has previously been shown to be related to an inefficient use of this particular searching strategy (Owen *et al.*, 1990), suggesting that the contribution of both 'strategic' (or 'executive') and 'mnemonic' factors to efficient performance can be differentiated. In the present study, a similar approach was used to estimate the extent to which a systematic searching pattern was adopted as a strategy for approaching the spatial working memory problems. The strategy measure was derived by adding up the number of different boxes that were used to initiate search sequences within each of the more difficult six- and eight-box problems. Thus, if half of the searches in one of the most difficult eight-box problems were started with one particular box and the other half were started with a different box, then the strategy score for that problem would be two (two different boxes used to initiate sequences). The total of these eight scores (four six-box problems and four eight-box problems), provided a single measure of strategy for each subject, with a high score (many sequences beginning with a different box) representing low use of the strategy, and a low score (many sequences starting with the

same box) representing more extensive usage. The estimate was rescaled in the range 1–38, the best possible score of one being obtained when, within each problem, the same box was used to initiate each search sequence. Conversely, if every search started with a different box, the maximum score of 38 was obtained.

By focusing on the first response in a given search, this method provides only an estimate of the extent to which the entire search is systematically organized, but one which is clearly maximally independent of the main measure of task performance; between search errors. Thus, if more information concerning the entire sequence of choices is incorporated into the strategy measure, this would inevitably lead to a confounding of the mnemonic (between search errors), and strategic scores resulting in artifactual correlations between the two measures. The method of using the first response within each search to derive the strategy measure would not be useful, of course, unless it accurately assessed the tendency to use effective strategies. However, the previous finding that there are highly significant correlations, in normal control subjects, between mnemonic score and this 'first response' strategy measure indicates that it is indeed an effective strategy. Further evidence that this correlation cannot be artifactual comes from the finding that an unimpaired strategy can accompany an impaired memory score in certain groups, e.g. in patients with Alzheimer's disease (Sahgal *et al.*, 1992).

Since our previous investigation has shown that an efficient, repetitive spatial strategy may be developed to solve the spatial working memory test (Owen *et al.*, 1990), analogous strategies were monitored in the verbal and visual working memory tests. Thus, for all the four and six stimuli problems, the extent to which subjects began each search with a particular name (for the verbal working memory task) or a particular shape (for the visual working memory task), and then returned to start each subsequent sequence with that same name or shape, was calculated. The estimate was then rescaled in the range 1–27 with lower scores representing more extensive use of the strategy. The range of scores differed from that in the spatial working memory task since fewer searches are required to complete the four- and six-box problems than to complete the six- and eight-box problems. The best possible score of one was obtained when, within each problem, the same stimulus (name or shape) was used to initiate each search sequence. Conversely, if every search within each of these problems started with a different stimulus, the maximum score of 27 was obtained. Since the frontal lobe patients and their control group were also given four eight-box problems in the verbal and visual working memory tasks, it was possible, in these groups, to recalculate an equivalent strategy score (e.g. based on the six- and eight-box problems: range 1–38), to that calculated for the spatial working memory test. A supplementary analysis of visual and verbal strategies at six- and eight-box levels of difficulty is therefore included for these two groups.

The repetitive serial ordering of choices, as assessed by

this strategy measure is, by far, the most plausible approach to solving these non-spatial memory tasks. Other possible strategies based, for example, on semantic coding (in the verbal working memory task) are clearly ruled out by the stimulus material. Similarly, in the visual working memory task, the stimuli were not easily verbalized. Finally, in the verbal working memory task, strategies based on alphabetic sequences of the first letters were discouraged by including names beginning with the same first letter within each trial (see Fig. 2B). Even if such strategies were adopted, one would expect them to manifest as repetitive serial ordering of choices which, therefore, would be detected by the strategy measure described above.

Data analysis

Since the number of subjects performing each of the working memory tasks varied and since the tasks differed with respect to the number of difficulty levels included, the data were analysed within task. Thus, for each of the working memory tests, comparisons were drawn between each of the patient groups and their matched control group. The main variables were the total number of 'between search' errors and the total number of 'within search' errors (summed across the four trials within each level of difficulty) and the single measure of 'strategy' described above. Given the complexity of this design, the analysis of error scores required calculation of both main effects and interactions between the two critical variables, group (frontal versus control, temporal versus control and amygdalo-hippocampotomy versus control) and difficulty (four boxes, six boxes and for spatial working memory only, eight boxes). Since the frontal lobe patients and their control group were also given four visual and verbal working memory problems with eight boxes, a supplementary analysis was also conducted on these groups to include these more difficult problems. Standard tests of normality and homogeneity of variance across groups confirmed that the data were ideally suited for a parametric analysis. Therefore, for error scores, a two-way ANOVA procedure was employed to assess the relationship between group and difficulty, covarying, where appropriate (see above) for the effects of age and verbal IQ. Where significant interactions between the group and difficulty factors were identified (usually indicating that a patient group were disproportionately affected by increasing task difficulty), simple main effects were calculated at each level of difficulty and are reported separately. Within each of the working memory tasks, the single 'strategy score' was analysed using one-way ANOVA, covarying, where appropriate, for the effects of age and verbal IQ. Two supplementary analyses were made: (i) the spatial working memory data were re-analysed including only those subjects who completed the verbal and visual working memory tasks and the results are reported; (ii) the effects of laterality of lesion were assessed using a three-way ANOVA (group × difficulty by side of lesion) and the results are reported.

Results

Spatial working memory

The mean numbers of 'between search' errors made by the six patient and control groups at each level of difficulty are presented in Fig. 3.

Among the frontal lobe patients and their control group (Fig. 3), the number of 'between search' errors increased significantly with search set size [$F(2,124) = 129.25$, $P < 0.0001$] and there was a highly significant group main effect with the patients making many more errors than the controls [$F(1,62) = 25.35$, $P < 0.0001$]. There was also a highly significant interaction between the group and difficulty factors [$F(2,124) = 8.72$, $P < 0.0001$]. Further analyses of simple main effects revealed that the frontal lobe patients were significantly impaired in terms of the number of errors at all levels of task difficulty [four boxes, $F(1,62) = 9.39$, $P < 0.005$; six boxes, $F(1,62) = 24.03$, $P < 0.0001$; eight boxes, $F(1,62) = 15.19$, $P < 0.0005$]. The mean numbers of 'within search' errors (or returns to boxes which have previously been checked and shown to be empty earlier in the same search sequence) made by the six patient and control groups at each level of difficulty are presented in Table 2. The frontal lobe group were significantly impaired relative to their controls [$F(1,62) = 6.13$, $P < 0.05$], although there was no significant interaction between the group and difficulty factors [$F(2,124) = 1.59$, $P > 0.05$]. Again, there was a highly significant effect of task difficulty [$F(2,124) = 9.13$, $P < 0.0001$].

Spatial working memory impairments were also observed in the temporal lobe patients (Fig. 3). Thus, although the patients and their controls did not differ overall in terms of the number of between search errors [$F(1,77) = 2.73$, $P > 0.05$], there was a highly significant interaction between the group and difficulty factors [$F(2,158) = 7.11$, $P = 0.001$]. Further analysis of this interaction revealed that the temporal lobe patients made significantly more errors than controls only at the most difficult (eight boxes) level of task difficulty [$F(1,80) = 6.43$, $P < 0.025$]. In both groups, the number of 'between search' errors increased significantly with search set size [$F(2,158) = 185.87$, $P < 0.0001$]. In terms of 'within search' errors (Table 2), the temporal lobe group were not significantly impaired relative to their controls [$F(1,77) = 3.27$, $P = 0.074$] and there was no significant interaction between the group and difficulty factors [$F(2,158) = 0.33$, $P > 0.05$]. Again, there was a highly significant effect of task difficulty [$F(2,158) = 15.31$, $P < 0.0001$].

Spatial working memory impairments were also observed in the amygdalo-hippocampotomy patients (Fig. 3). Thus, although there was no overall increase in the number of between search errors in these patients when compared with their matched control group [$F(1,36) = 2.32$, $P > 0.05$], there was a significant interaction between the group and difficulty factors [$F(2,72) = 5.74$, $P = 0.005$]. Further analysis of this

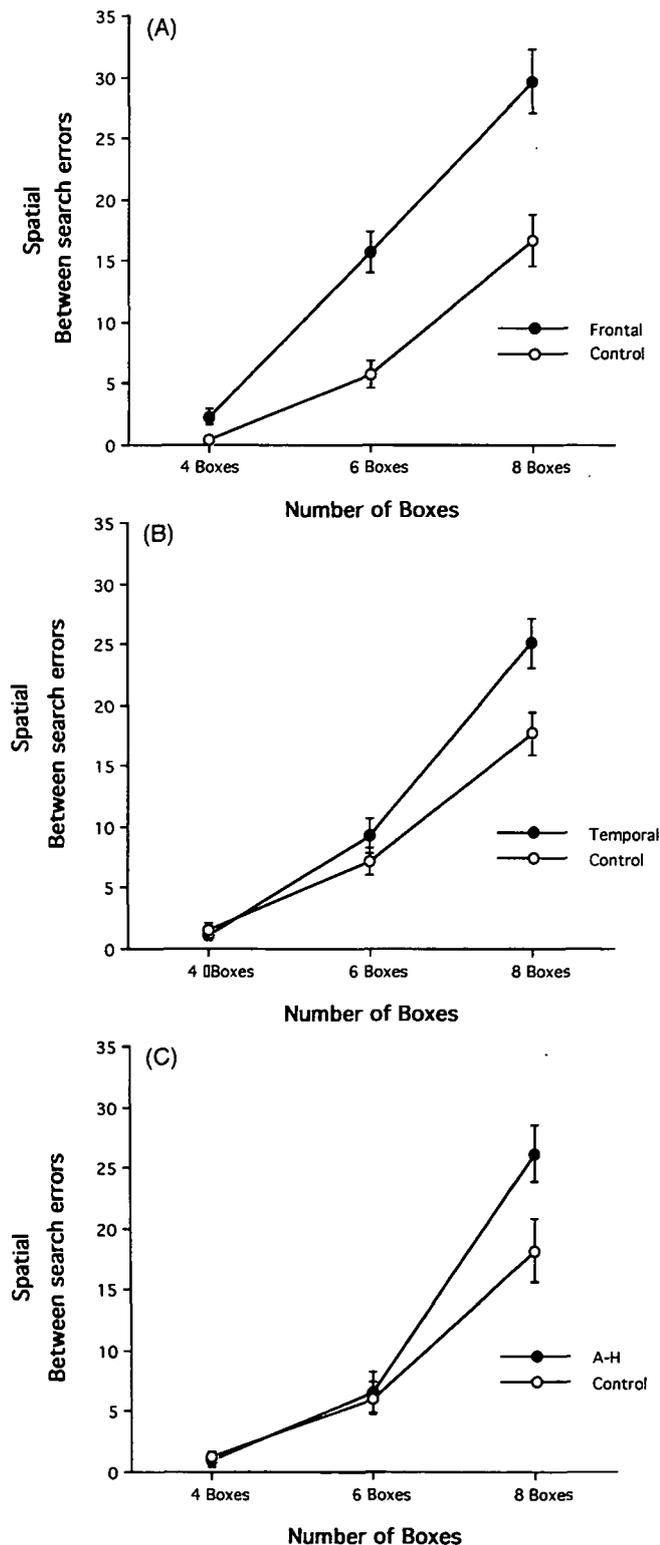


Fig. 3 Spatial working memory. The mean number of 'between search' errors at each level of difficulty in frontal lobe patients and controls (A), temporal lobe patients and controls (B) and amygdalo-hippocampectomy (AH) patients and controls (C).

interaction revealed that the amygdalo-hippocampectomy group made significantly more errors than controls only at the most difficult (eight boxes) level of task difficulty

[$F(1,37) = 5.35, P < 0.05$]. In both groups, the number of 'between search' errors increased significantly with search set size [$F(2,72) = 130.17, P < 0.0001$]. In terms of 'within search' errors (Table 2), the amygdalo-hippocampectomy group were not impaired overall, relative to their controls [$F(1,36) = 0.75, P > 0.05$], although there was a significant interaction between the group and difficulty factors [$F(2,72) = 3.70, P < 0.05$]. Further analysis of this interaction again revealed that the patient group only made significantly more 'within search' errors at the most difficult (eight boxes) level of task difficulty [$F(1,37) = 6.49, P < 0.05$]. There was a significant main effect of task difficulty [$F(2,72) = 7.2, P = 0.001$].

The estimate of strategy employed in this task was derived by adding up the number of different boxes used to initiate a search within each of the six- and eight-box problems (eight problems in total). The estimate was then rescaled in the range 1–38 with lower scores representing more extensive use of the strategy (see Owen *et al.*, 1990). The mean spatial 'strategy scores' for each of the patient groups and the controls are presented in Table 2 and illustrated in Fig. 4. There was a highly significant difference in the extent to which this strategy was adopted in the frontal group and their matched controls [$F(1,62) = 8.5, P < 0.005$], with the patient group tending to approach the task in a less systematic way. In contrast, there was no significant difference between the temporal lobe group and their controls [$F(1,38) = 0.53, P > 0.05$], or between the amygdalo-hippocampectomy group and their controls [$F(1,38) = 0.114, P > 0.05$] in terms of this strategy measure. There was however, a significant correlation between the spatial strategy measure and the number of 'between search' errors on six- and eight-box problems in the frontal lobe patients and their controls [$r(32) = 0.59, P < 0.001$; $r(32) = 0.53, P < 0.01$, respectively], the temporal lobe group and their controls [$r(41) = 0.66, P < 0.001$; $r(41) = 0.53, P < 0.001$, respectively] and the amygdalo-hippocampectomy patients and their controls [$r(19) = 0.55, P < 0.01, r(19) = 0.73, P < 0.001$, respectively].

Importantly, the same general pattern of results was observed when the spatial working memory data were reanalysed, including only those patients from the three neurosurgical groups who also completed the visual and verbal working memory tasks. Thus, the frontal lobe patients were significantly impaired in terms of 'between search' errors [$F(1,34) = 24.67, P < 0.0001$] and there was a significant interaction between the task difficulty and group factors [$F(2,68) = 11.36, P < 0.001$]. In contrast, in the temporal lobe and amygdalo-hippocampectomy groups, there were significant interactions between the task difficulty and group factors [$F(2,86) = 6.13, P < 0.01$ and $F(2,36) = 7.13, P < 0.01$, respectively] but no significant main effects of group [$F(1,41) = 2.05$ and $F(1,18) = 0.3$, respectively]. Furthermore, only the frontal lobe group was significantly impaired in terms of their spatial strategy score [$F(1,34) = 4.12, P < 0.05$], although, in all groups, this measure correlated with total 'between search' errors on six-

Table 2 Mean performance data for 'within search' errors and strategy scores

	Within search errors			Strategy score
	4 boxes	6 boxes	8 boxes	
Spatial working memory				
Frontal	0.78 (0.40)*	4.16 (1.35)*	5.19 (1.35)*	36.5 (0.98)**
Control	0.22 (0.07)	0.91 (0.54)	2.53 (0.83)	32.7 (0.85)
Temporal	0.00 (0.00)	0.93 (0.39)	2.24 (0.43)	32.6 (0.88)
Control	1.20 (0.46)	1.73 (0.54)	2.90 (0.60)	32.2 (0.95)
Amygdalo-hippocampectomy	0.00 (0.00)	0.47 (0.29)	3.74 (1.16)*	35.0 (1.13)
Control	1.16 (0.83)	0.26 (0.15)	1.42 (0.57)	33.8 (0.76)
Verbal working memory				
Frontal	7.78 (1.78)	16.9 (4.46)		23.3 (1.11)
Control	6.41 (0.95)	13.7 (2.98)		24.6 (0.96)
Temporal	4.39 (0.60)	10.0 (1.84)		26.2 (0.65)
Control	6.45 (0.74)	14.1 (2.39)		24.3 (0.76)
Amygdalo-hippocampectomy	4.50 (1.21)	12.2 (4.10)		25.6 (1.20)
Control	7.89 (1.25)	11.1 (3.47)		25.0 (0.91)
Visual working memory				
Frontal	6.39 (0.86)	11.1 (2.14)		23.6 (1.41)
Control	2.94 (0.65)	10.4 (2.15)		23.8 (0.56)
Temporal	6.13 (1.02)	15.6 (2.29)		26.0 (0.65)
Control	4.91 (0.80)	12.1 (1.83)		24.3 (0.52)
Amygdalo-hippocampectomy	5.70 (1.81)	12.8 (2.89)		23.5 (1.25)
Control	2.90 (0.69)	9.9 (2.62)		24.7 (0.56)

SEM in brackets; **P* < 0.05; ***P* < 0.01.

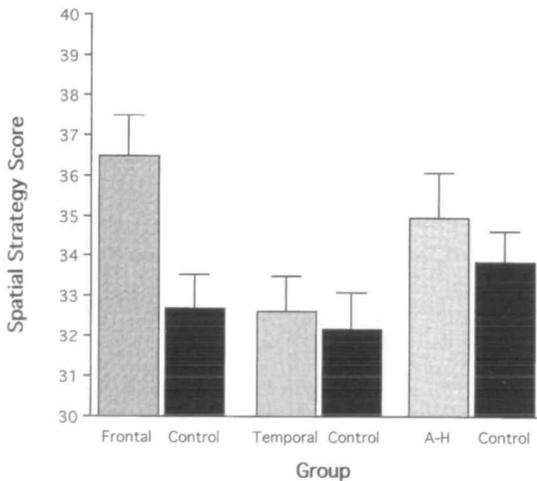


Fig. 4 Mean total strategy scores on the spatial working memory task in frontal lobe patients and controls; temporal lobe patients and controls and amygdalo-hippocampectomy (AH) patients and controls.

and eight-box problems. The mean strategy scores for this subset of frontal lobe patients and their controls were 36.39 (SEM = 1.49) and 33.89 (SEM = 0.80), respectively.

In summary, these results demonstrate that all three neurosurgical groups were impaired on the spatial working memory task, although in qualitatively different ways. In the frontal lobe group, deficits in the number of between search errors were observed even at the simpler levels of difficulty involving four and six boxes, whilst deficits in the temporal lobe and amygdalo-hippocampectomy groups were only observed at the most difficult, eight-box level of the task.

Figure 3 clearly illustrates this difference between the frontal lobe patients and the two groups with more posterior excisions. Thus, the frontal lobe patients make nearly three times more errors than their controls at the six-box level of difficulty, whilst the temporal lobe and amygdalo-hippocampectomy patients make almost identical numbers of errors to their control groups. Moreover, the absolute number of errors made by the frontal patients at this level is much greater than that made by the other two patient groups. In contrast, when the task involved eight boxes all three patient groups were impaired relative to their control groups and made similar numbers of between search errors (Fig. 3).

In all six patient and control groups, measures of performance (errors), were found to relate to the extent to which subjects adopted a systematic strategy to search among the boxes in the more difficult six- and eight-box problems. Thus, subjects who tended to use a repetitive searching method, as indexed by our 'strategy score', also tended to make fewer errors during the search. Importantly, however, relative to controls, only the frontal lobe patients were significantly impaired in the extent to which this method was used. Examination of Fig. 4 clearly shows that the frontal lobe patients had a strategy score that was higher (less systematic searching) than their control group and also substantially higher, for example, than the patients with temporal lobe excisions.

Verbal working memory

In terms of 'between search' errors (Fig. 5), the frontal lobe patients were unimpaired overall in terms of their

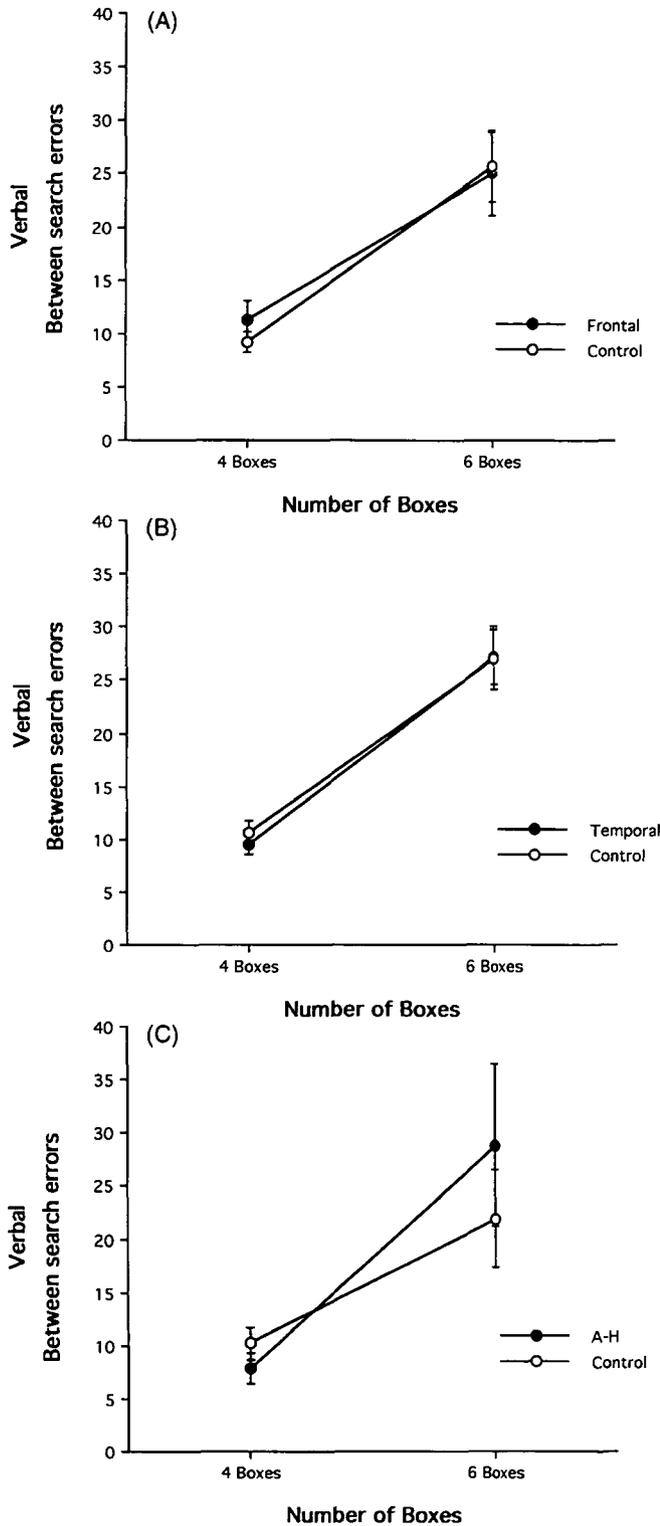


Fig. 5 Verbal working memory. The mean number of 'between search' errors at each level of difficulty in frontal lobe patients and controls (A); temporal lobe patients and controls (B) and amygdalo-hippocampectomy patients and controls (C).

performance on the verbal working memory task [$F(1,33) = 0.04, P > 0.05$] and there was no interaction between the group and difficulty factors [$F(1,33) = 0.37, P > 0.05$].

There was however, a significant effect of task difficulty [$F(1,33) = 44.6, P < 0.0001$]. A qualitatively and quantitatively similar pattern was observed for 'within search' errors (Table 2).

Since the frontal lobe patients and their control group were also given four problems with eight names, a supplementary analysis was conducted to included these more difficult problems. The number of between search errors at this level were 47.27 (SEM = 6.40) for the frontal lobe patients and 40.76 (SEM = 5.32) for the control subjects. When these data were included in the main analysis there was still no significant main effect of group [$F(1,33) = 0.51, P > 0.05$] and no significant interaction between the group and difficulty factors [$F(1,33) = 0.46, P > 0.05$]. Within search errors at the eight-name level of difficulty were 23.47 (SEM = 4.89) and 16.24 (SEM = 4.58) for the patients and controls. Again, no significant differences between the two groups were observed.

The temporal lobe group was also unimpaired in all aspects of the verbal working memory test (Fig. 5). Thus, 'between search' errors were not significantly increased in this group [$F(1,40) = 0.12, P > 0.05$] and there was no interaction between the group and the difficulty factors [$F(1,42) = 0.3, P > 0.05$]. There was again, a significant effect of task difficulty [$F(1,42) = 86.67, P < 0.0001$]. A qualitatively and quantitatively similar pattern was observed for 'within search' errors (Table 2).

The amygdalo-hippocampectomy group was also unimpaired in all aspects of the verbal working memory test (Fig. 5). 'Between search' errors were not significantly increased [$F(1,17) = 0.19, P > 0.05$] and there was no interaction between the group and the difficulty factors [$F(1,17) = 1.25, P > 0.05$]. There was a significant effect of task difficulty [$F(1,17) = 15.26, P = 0.001$]. As in the other groups, a qualitatively and quantitatively similar pattern was observed for 'within search' errors (Table 2).

The estimate of strategy employed in this task was analogous to the spatial strategy score and was derived by adding up the number of different stimuli used to initiate a search within each of the four- and six-box problems (eight problems in total). The estimate was then rescaled in the range 1–27 with lower scores representing more extensive use of the strategy. A correlational analysis among the three control groups revealed that this strategy measure did not correlate with error performance on the verbal working memory task [$r(17) = 0.21, r(23) = 0.19$ and $r(10) = 0.40$, respectively], suggesting that, unlike the spatial working memory task, this approach does not constitute an effective strategy for approaching the verbal task. This correlation was similarly non-significant when, for the frontal lobe control group, the strategy measure was recalculated (including all the six- and eight-name problems), to be equivalent to that used in the spatial working memory analysis [$r(17) = 0.27, P = 0.145$].

Compared with their matched controls, none of the three patient groups were significantly impaired in terms of the

verbal strategy measure [frontal, $F(1,30) = 0.61$, $P > 0.05$; temporal, $F(1,38) = 1.13$, $P > 0.05$; amygdalo-hippocampectomy, $F(1,18) = 0.152$, $P > 0.05$] (Table 2).

In summary, these results demonstrate that, unlike the spatial working memory task, deficits were not observed in any of the three neurosurgical groups on an analogous test of verbal working memory.

Visual working memory

In terms of 'between search' errors, the frontal lobe patients were unimpaired overall in terms of their performance on the visual working memory task [$F(1,34) = 2.14$, $P > 0.05$] and there was no interaction between the group and difficulty factors [$F(1,34) = 1.12$, $P > 0.05$]. There was, however, a significant effect of task difficulty [$F(1,34) = 39.06$, $P < 0.0001$]. A qualitatively and quantitatively similar pattern was observed for 'within search' errors (Table 2).

Since the frontal lobe patients and their control group were also given four problems with eight shapes, a supplementary analysis was conducted to include these more difficult problems. The number of between-search errors at this level were 37.83 (SEM = 4.86) for the frontal lobe patients and 28.44 (SEM = 4.26) for the control subjects. When these data were included in the main analysis there was still no significant main effect of group [$F(1,34) = 2.55$, $P > 0.05$] and no significant interaction between the group and difficulty factors [$F(1,34) = 1.06$, $P > 0.05$]. Within search errors at the eight-shape level of difficulty were 16.28 (SEM = 2.25) and 10.06 (SEM = 2.54) for the patients and controls. Again, no significant differences between the two groups were observed.

Significant visual working memory deficits were observed among the temporal lobe patients, although these were qualitatively different from those observed in the spatial working memory task (Fig. 6). Thus, there was a significant overall increase in the number of 'between search' errors [$F(1,41) = 7.82$, $P < 0.01$], but no significant interaction between the group and task difficulty factors [$F(1,43) = 2.24$, $P > 0.05$]. The effect of task difficulty was highly significant [$F(1,43) = 100.4$, $P < 0.0001$]. Although there was a similar trend in the 'within search' errors measure [main effect, $F(1,41) = 3.21$, $P = 0.081$], only the effect of task difficulty reached statistical significance [$F(1,43) = 33.44$, $P < 0.0001$] (Table 2).

The amygdalo-hippocampectomy patients were also impaired on the visual working memory task (Fig. 6). Thus, there was a significant overall increase in the number of 'between search' errors [$F(1,18) = 5.69$, $P < 0.05$] but no significant interaction between the group and task difficulty factors [$F(1,18) = 1.2$, $P > 0.05$]. The effect of difficulty was highly significant [$F(1,18) = 42.62$, $P < 0.0001$]. In the 'within search' errors measure (Table 2) only the effect of difficulty was significant [$F(1,18) = 16.74$, $P = 0.001$].

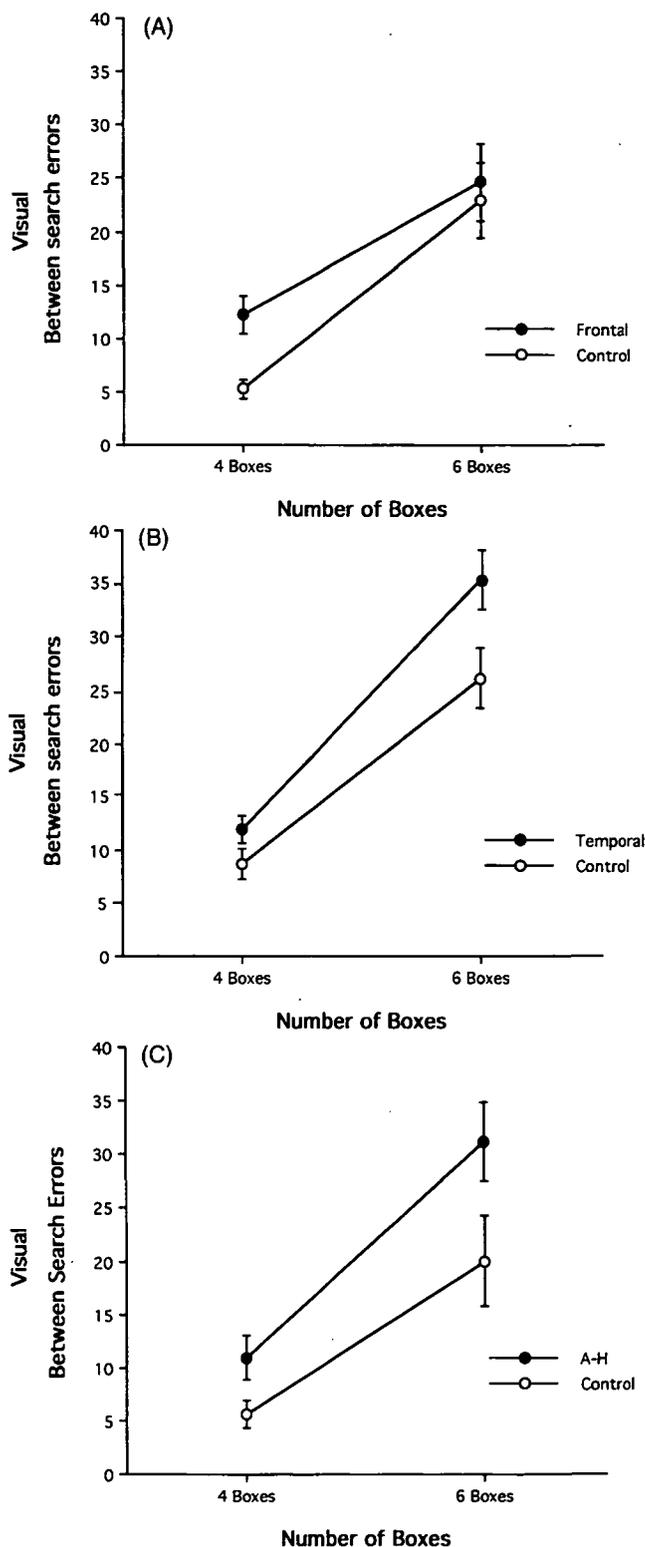


Fig. 6 Visual working memory. The mean number of 'between search' errors at each level of difficulty in frontal lobe patients and controls (A); temporal lobe patients and controls (B) and amygdalo-hippocampectomy patients and controls (C).

The estimate of strategy employed in this task was analogous to the spatial strategy score and was derived by adding up the number of different shapes used to initiate a

search within each of the four- and six-box problems (eight problems in total). A correlational analysis among the three control groups revealed that this strategy measure did not correlate with error performance on the visual working memory task [$r(17) = 0.33$; $r(23) = 0.34$ and $r(10) = 0.18$, respectively], suggesting that, unlike the spatial working memory task, this approach does not constitute an effective strategy for approaching the visual task. This correlation was similarly non-significant when, for the frontal lobe control group, the strategy measure was recalculated (including all the six- and eight-name problems), to be equivalent to that used in the spatial working memory analysis [$r(17) = 0.29$, $P = 0.124$].

Compared with their matched controls, none of the three patient groups were significantly impaired on the visual strategy measure [frontal, $F(1,28) = 0.048$, $P > 0.05$; temporal, $F(1,38) = 1.99$, $P > 0.05$; amygdalo-hippocampectomy, $F(1,18) = 0.53$, $P > 0.05$] (Table 2).

In summary, these results confirm that, relative to their matched control groups, only the temporal lobe group and the amygdalo-hippocampectomy group were significantly impaired on this test of visual working memory. Thus, both patient groups made significantly more between-search errors than their controls when the task involved six boxes. Moreover, Fig. 6 clearly demonstrates that these posterior groups also tended to make more between search errors than the frontal lobe patients, who were unimpaired at this level, and even at the more difficult eight-box level of difficulty. No differences existed between the groups at the simpler four-box level of difficulty; in fact, examination of Fig. 6 suggests that the frontal lobe patients may have been performing rather more poorly, relative to their own control group, than either of the other two groups at this stage, although this difference did not reach statistical significance.

The effects of laterality

In the current study, the initial analysis combined left, right and (in the cases of three frontal lobe patients) bilateral patients within each of the three neurosurgical groups. A supplementary analysis was performed, however, to look at the possible effects of laterality of lesion on performance in the three patient groups. In a previous study, no differences relating to side of lesion were observed in a smaller group of frontal lobe patients on the test of spatial working memory (Owen *et al.*, 1990). In Table 3, the mean total 'between search' error scores for the left, right and bilateral frontal, temporal and amygdalo-hippocampectomy patients in all three working memory tests are presented for comparison. Since each of the 92 patients included in the study was paired with a normal control subject matched for age and estimated verbal IQ, the entire patient and control population was split according to both pathology and laterality of lesion. Thus, for each of the spatial, verbal and visual working memory tests, three-way ANOVAs were calculated, comparing the effects of task difficulty, pathology (frontal versus control,

Table 3 Mean total 'between search' error scores for left, right and bilateral patients performing the spatial, verbal and visual working memory tests

Pathology	<i>n</i>	Spatial	<i>n</i>	Verbal	Visual
Frontal					
Left	11	48.64 (6.3)	5	85.80 (20.9)	73.00 (28.3)
Right	18	45.00 (5.8)	11	73.10 (11.3)	69.36 (6.76)
Bilateral	3	61.00 (5.5)	2	144.0 (40.0)	108.5 (12.5)
Temporal					
Left	19	32.08 (4.5)	11	32.33 (10.8)	38.00 (7.60)
Right	22	36.71 (5.8)	12	43.00 (14.9)	48.00 (5.59)
Amygdalo-hippocampectomy					
Left	12	33.58 (5.3)	6	37.55 (3.33)	51.73 (4.79)
Right	7	37.14 (4.2)	4	35.67 (4.82)	43.08 (4.53)

SEM in brackets; *n* = number of patients; Amygdalo-hippocampectomy.

temporal versus control and amygdalo-hippocampectomy versus control) and side of lesion. No significant main effects of laterality were observed in any of the three working memory tests. Similarly, there were no significant two-way interactions between the laterality and task difficulty factors and no significant three-way interactions between laterality, difficulty and pathology. Notably, however, in all three tasks, the performance of the bilateral frontal lobe group was far worse than that of any of the other patient groups tested, although the relatively small group size precluded any formal statistical analysis of this effect. Similar three-way analyses were carried out separately for the 'within search' error score and for the strategy score. Again, no significant differences between any of the sub-groups were observed.

These results unequivocally suggest that the deficits observed in tests of spatial and visual working memory in patients with frontal lobe, temporal lobe or amygdalo-hippocampectomy excisions are not disproportionately related to damage to one or other hemisphere.

Discussion

In this study, three analogous self-ordered searching tasks with mnemonic and strategic components were used to compare spatial, verbal and visual working memory in patients with frontal lobe excisions, temporal lobe excisions, or in whom selective amygdalo-hippocampectomy had been performed.

In the frontal lobe group, deficits were only observed in the spatial working memory task. Thus, in these patients, significant increases were observed in both the number of 'between search' and 'within search' errors. In addition, whilst the degree of impairment appeared to depend, to some extent, on the difficulty of the task (i.e. the number of boxes), significant deficits were detectable even at the simplest level of task difficulty. Moreover, this increase in errors was shown to relate to the inefficient use of a particular repetitive searching strategy, known to improve performance on this task. In contrast, in formally similar tests of visual and verbal

working memory, no deficits were observed in the frontal lobe group.

Significant spatial working memory deficits were also observed in the group of patients with unilateral temporal lobe damage. Compared with matched control subjects, these patients were significantly impaired in the spatial working memory condition, although this deficit was restricted to the 'between search' errors measure and was only evident at the most challenging level of task difficulty. Moreover, this increase in errors was not accompanied by an impairment in the extent to which an organized searching pattern was adopted, although the measure of 'strategy' employed did correlate with the number of errors made in both the temporal lobe patients and their control group. Profound deficits were also observed among the temporal lobe patients in the visual working memory condition. Thus, significant increases in the number of 'between search' errors were detected in this group, even at the simplest level of task difficulty. However, this increase in errors was not related to any detectable impairment in the extent to which the repetitive searching strategy was employed to solve the task. No deficits were observed in the temporal lobe group in the verbal working memory condition.

The pattern of impairment observed in the group of patients in whom selective amygdalo-hippocampectomy had been performed was qualitatively similar to, but not identical to, that seen in the temporal lobe patients. Thus, in the spatial working memory condition these patients were impaired in terms of both 'between search' and 'within search' errors, although these deficits were only evident at the most difficult level of task difficulty. In addition, the amygdalo-hippocampectomy patients were not impaired in their use of a repetitive searching strategy known to improve performance on this task. In the visual working memory task, deficits were also observed in the amygdalo-hippocampectomy group, although these impairments were relatively independent of task difficulty. Finally, no deficits were observed in the verbal working memory condition.

Spatial working memory: anatomical considerations

The results of the present investigation both confirm and extend those of a previous study in which a smaller subset of the neurosurgical patients with localized excisions of the frontal lobes were shown to be impaired on the spatial working memory task (Owen *et al.*, 1990). Using the same paradigm, the present study has shown that spatial working memory impairments may also be observed following temporal lobectomy or unilateral amygdalo-hippocampectomy, although, importantly, these deficits are both qualitatively and quantitatively different from those seen after frontal lobe damage. Whilst these results support the view that both frontal and temporal lobe structures play important roles in spatial working memory, the precise neural circuitry

responsible for this apparent functional relationship is unclear. In general, spatial working memory deficits are associated, in primates at least, with bilateral damage to the area surrounding the sulcus principalis (e.g. Passingham, 1985; Funahashi *et al.*, 1989). In work with patients, it is impossible to establish which areas of frontal cortex are critically involved in spatial working memory, or in any other type of cognitive processing, because the lesions are rarely confined to specific cytoarchitectonic areas. However, a recent investigation has addressed the issue of localization within the frontal cortex directly with PET and MRI, using a modified version of the spatial working memory task used in the present study (Owen *et al.*, 1996a). When normal control subjects performed the task with eight boxes, significant changes in rCBF were observed in the right mid-dorsolateral frontal cortex (cytoarchitectonic areas 46 and 9) and bilaterally, in the ventrolateral frontal region (area 47). Thus, there appear to be functionally distinct sub-divisions within the human lateral frontal cortex which may subservise different aspects of spatial working memory processing during this task (*see* Owen *et al.*, 1996a).

Regarding the role of more posterior regions, it is well established that damage to the hippocampus or fornix in rats produces severe and long-lasting deficits in spatial working memory tasks which are formally similar to the paradigm adopted in the current study (Olton *et al.*, 1978; Olton and Papas, 1979; Rawlins and Olton, 1982; Rawlins and Tsaltas, 1983; Aggleton *et al.*, 1986). In addition, in a recent functional imaging study using PET in normal control subjects, a significant increase in blood flow was observed in the right hippocampus during a task that required spatial working memory (Owen *et al.*, 1996b). The present findings concur fully with these results and demonstrate that, in patients, relatively small medial temporal lobe removals from either hemisphere can also impair performance on a test of spatial working memory. Thus, significant deficits were observed after either a temporal neocortical excision (which typically includes a small amount of the hippocampus) or a selective amygdalo-hippocampectomy (which typically includes the entire hippocampus in one hemisphere), although importantly, the more restricted impairment in the former group ('between search' errors only) compared with that observed in the latter group ('between search' errors and 'within search' errors) may reflect the relative sparing of the medial temporal lobe structures in the temporal lobectomy patients. Together, these results clearly support the view that spatial working memory involves a network of interconnected and functionally related cortical and subcortical areas including, at the very least, the prefrontal cortex and the hippocampus (Goldman-Rakic, 1990).

Spatial working memory: psychological considerations

Although it has been possible to implicate specific neural structures in spatial working memory, the relative contribu-

tions of these different areas, in functional terms, is less clear. The fact that the increase in errors among frontal lobe patients was shown to relate to the inefficient use of a particular searching strategy known to improve performance on this task, clearly implicates deficient 'strategic' or 'executive' functions in this patient group. The rationale for using this measure of strategy, based on a simple pattern of initial responses across searches, has been provided in the Method section. Again, its use has been vindicated by the now consistent observation that there is a highly significant correlation between this measure of strategy and overall memory performance that cannot occur artifactually. Thus, for example, this correlation is not invariably present: in the case of patients with Parkinson's disease, increased 'between search' errors have been observed in the absence of changes in the strategy score (Owen *et al.*, 1992). Moreover, a negative relationship between strategy and memory scores has been found in patients with Alzheimer's disease (Sahgal *et al.*, 1992). These results suggest that the spatial working memory task has separable executive and short-term memory components.

It is unlikely that the strategy deficit in frontal lobe patients is merely a consequence of impaired short-term spatial memory for two reasons. First, in a previous study, an unimpaired spatial span of 4.9 was observed in a group of frontal lobe patients which included many of those included in the present study. Spatial span provides an unambiguous measure of spatial memory capacity (Owen *et al.*, 1990). The average spatial span for the frontal lobe patients included in the present study was 5.0 (SEM = 0.22). (A. M. Owen, unpublished observations). Secondly, this measure of spatial span does not correlate significantly with the strategy score in the frontal lobe group [$r(27) = -0.29$, $P = 0.1364$]. Therefore, it is unlikely that the deficits in strategy and between search errors arise from a common impairment in short-term spatial memory. A more obvious explanation is that the frontal lobe patients are impaired in finding a strategy that alleviates the load on working memory imposed by the task. This conclusion substantiates previous suggestions by other investigators that the behaviour of frontal lobe patients on tasks which require working memory, reflects 'poor organizational strategies, poor monitoring of responses or both' (Petrides and Milner, 1982; *see also* Gershberg and Shimamura, 1995). Poor 'cognitive strategies' have also been described in relation to the deficits that are observed in frontal lobe patients performing tasks which require 'estimates' or 'logical reasoning' (Shallice and Evans, 1978; Smith and Milner, 1984). Organizational 'strategies', when applied to self-ordered searching tasks of the type employed in the present study, may serve to reduce the overall load on working memory, and would, presumably, improve performance at all levels of task difficulty. It is notable in this regard that, as a group, the frontal patients were clearly impaired in terms of errors, when the task involved six boxes, whilst the temporal lobe and amygdalo-hippocampectomy groups were clearly not impaired at this level (Fig. 3). On the other hand,

all three groups made significantly more errors than their controls at the most difficult (eight-boxes) level of task difficulty. Importantly, whilst performance in the temporal lobe and amygdalo-hippocampectomy groups was shown to relate to the extent to which a systematic strategy was adopted by the subjects, neither of these patient groups was impaired in the use of this strategy. This pattern of impairment, which has been observed previously in patients with probable Alzheimer's disease (Sahgal *et al.*, 1992, 1995), suggests intact executive function accompanied by a more fundamental disruption of mnemonic processes in patients with damage to the medial temporal lobe region. The results of this investigation, therefore, extend our previous findings (Owen *et al.*, 1990) and suggest that the 'mnemonic' and 'executive' components of spatial working memory may be dissociable at the neural level.

Spatial versus non-spatial working memory

The results of the present study would seem to suggest a relatively specific impairment of spatial working memory in patients with frontal lobe damage. Thus, no impairments were observed in the frontal lobe group in the analogous tests of visual and verbal working memory even when they were tested at very demanding (e.g. eight-box) levels of task difficulty. On the face of it, this is a truly surprising result which, if substantiated, shows that frontal lobe patients are not necessarily impaired in difficult working memory tasks, suggesting that they do not suffer from some generalized reduction in cognitive resources (Duncan, 1995). In evaluating this potentially important result, care must be taken to ensure that the null effects do not arise, for example, from 'ceiling effects' in which the task is so difficult that both control subjects and frontal lobe patients respond essentially randomly. This interpretation is refuted, however, by the results of our own computer simulation in which random selections were generated across the entire set of problems 300 times. According to this simulation, random responding on this task would lead to mean (\pm SEM) between search error scores in the four-, six- and eight-box levels of difficulty of 26.34 (0.89), 61.42 (1.69) and 93.16 (0.75), respectively. These scores hold true, of course, for all three tasks and show that, even at the most difficult levels, none of the patient or control groups were responding randomly.

A second possible explanation for the pattern of impaired spatial and intact non-spatial working memory in the frontal lobe group is that it relates to the particular location of damage in the prefrontal cortex in this particular group of patients. However, on the basis of the heterogeneity of excisions assessed from the neurosurgeon's drawings and exemplified by the MRIs in Fig. 1, it does not appear to be the case that there was more frequent damage, for example, in the dorsolateral frontal region, than in any other region. Furthermore, an explanation based on modality specific frontal areas is not supported by recent activation studies which have used PET/MRI co-registration to identify similar

neural loci for spatial (e.g. Owen *et al.*, 1996a) and non-spatial working memory (Petrides *et al.*, 1993a, b).

In a previous study (Petrides and Milner, 1982) verbal and visual working memory deficits were reported in frontal lobe patients, whilst in later studies (Petrides *et al.*, 1993a, b) using similar tasks, relatively specific increases in rCBF were observed bilaterally, within the mid-dorsolateral frontal cortex. The most parsimonious explanation for the apparent incongruity of these results with those of the present study concerns differences in the executive and mnemonic requirements of the tasks used, particularly in the types of strategies available for approaching the different paradigms and in the abilities of patients to take advantage of these strategies. For example, in the tasks used by Petrides and Milner (1982) and later by Petrides *et al.* (1993a), subjects were required to select a different item from an array, each time the complete set of available stimuli was presented. The emphasis of these tasks lies in organizing and monitoring a sequence of responses to a given array. Accordingly, the deficits observed in frontal lobe patients may reflect the inefficient use of organizational strategies to guide responding, a view consistent with the hypotheses of those authors (Petrides and Milner, 1982). The requirements of the tasks used in the present study were very different. Thus, since only one 'token' was hidden at any one time, subjects were required to remember which stimuli had been reinforced, rather than all of the stimuli that had been selected. This requirement adds a level of complexity not present in the study by Petrides and Milner (1982) and, according to their terminology, substantially increases the monitoring demands of the tasks. In the spatial task used in the present study, this difficulty can be overcome, at least partially, by following a repetitive searching strategy as shown by the relationship between strategy and superior performance among control subjects. However, in the visual and verbal working memory tasks, no such relationship exists, suggesting that repetitive serial searching strategies are less useful where abstract, non-spatial stimuli are used. It may be, for example, that in our tasks, a repetitive strategy in which the 'map' or 'plan' can be continually and visually monitored (e.g. in the spatial condition), may be more useful than an analogous strategy in which the 'map' has to be generated and then manipulated by reference to an internal representation (e.g. in the visual and verbal conditions). Thus, in the present study, and in the previous study by Petrides and Milner (1982), a deficit was only observed in frontal patients under circumstances where an obvious strategy exists to facilitate performance. Presumably then, in tests where no simple strategy exists to improve the efficiency of working memory (such as the non-spatial conditions used in the present study), subjects rely more heavily on mnemonic processes and under these circumstances, frontal lobe patients are unimpaired.

Unlike the frontal lobe group, both the temporal lobe and the amygdalo-hippocampectomy patients were also significantly impaired in the visual working memory condition. This finding is consistent, in a general sense, with the conclusions

of Petrides and Milner (1982). In the former study, right temporal lobe patients with extensive damage to the hippocampus were significantly impaired on two visual self-ordered working memory tasks. Importantly, the present study confirms that a similarly striking non-spatial working memory deficit can be produced by unilateral, selective amygdalo-hippocampectomy; a procedure which leaves the overlying cortical structures largely intact (Yasargil *et al.*, 1985). In addition, comparable deficits were also found in the temporal lobe group (with restricted hippocampal involvement) in the present study, which adds to the growing list of memory tasks on which a temporal neocortical excision is sufficient, in itself, to cause a deficit which may not necessarily be exacerbated by damage to the medial temporal region (Milner, 1978, 1980). The fact that these deficits were less clearly lateralized than in the investigation by Petrides and Milner (1982), most likely reflects the fact that, in the present study, simple coloured shapes were used as stimuli which may have been easier to verbalize than the more complex abstract designs employed in the previous investigation.

In contrast to the profound visual working memory deficits observed in both the temporal and amygdalo-hippocampectomy patients, neither group was significantly impaired in the verbal working memory condition. It is unlikely that this pattern of results can be explained by reduced sensitivity of the verbal working memory test to impairment in the patient groups, since performance among controls (in terms of errors) was comparable to performance in the visual working memory condition, in which deficits were observed. Furthermore, significant verbal working memory deficits have recently been observed in patients with Parkinson's disease using this same paradigm (Owen *et al.*, 1996c). In the previous study by Petrides and Milner (1982), a mild, but significant, deficit was demonstrated in left temporal lobe patients with extensive hippocampal involvement on a difficult self-ordered task involving low-imagery words. The difference between these results suggests that the type of stimulus material selected may be a most critical variable in determining whether non-spatial working memory deficits are observed following damage to the medial temporal structures. For example, in the former study (Petrides and Milner, 1982), the words in the 'low imagery' condition were nevertheless familiar to the subjects and were, in fact, selected on the basis of their medium to high frequency ratings. In contrast, in the present study, the 'words' or names were specifically chosen so as to be unfamiliar (or 'uncommon') and may therefore have the semantic properties of meaningless 'non-words' (see Fig. 2B). Taken together, the results of these two studies suggest that the involvement of the medial temporal lobe structures in other verbal working memory tests (e.g. Petrides and Milner, 1982), may not depend on the stimulus material being 'verbal' *per se*, but rather that the task involved, requires the manipulation of 'familiar' or 'previously encoded' verbal stimuli such as real words, phrases or digits.

In the present study, no consistent relationship was found

between the pattern of cognitive deficits and laterality of excisions in any of the three patient groups, although, in general, more profound deficits were observed in those frontal lobe patients with bilateral damage than in any patient group with damage restricted to one or other hemisphere. This latter result is particularly interesting given that, experimentally, the relationship between working memory processes and damage to the prefrontal cortex is most often investigated in animals with bilateral frontal lobe lesions (Passingham, 1985; Funahashi *et al.*, 1989; Petrides, 1991). These results also concur in a general sense, with the more recent PET/MRI studies of Petrides *et al.* (1993a, b) and Owen *et al.* (1996a). In those investigations, significant increases in rCBF were observed bilaterally using both spatial and non-spatial material. With respect to the more posterior lesion groups, the present results also confirm that deficits in tests of both spatial and non-spatial working memory may not be as closely associated with damage to one or other hemisphere as other, more traditional, tests of mnemonic function (Milner, 1971; 1974; Jones-Gotman *et al.*, 1993).

In summary, these results show that patients with frontal lobe damage are capable of normal levels of performance in certain types of difficult working memory task. The results suggest that both 'executive' (or 'strategic') and 'mnemonic' mechanisms may contribute differentially to performance in tests of spatial and non-spatial working memory. Moreover, these dissociable mechanisms appear to depend most heavily on the frontal cortex and the medial temporal lobe structures respectively.

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