Pergamon

Neuropsychologia, Vol. 33, No. 1, pp. 1–24, 1995

0028–3932/95 $9.50 + 0.00

0028–3932(94)00098–0

VISUO-SPATIAL SHORT-TERM RECOGNITION MEMORY AND LEARNING AFTER TEMPORAL LOBE EXCISIONS, FRONTAL LOBE EXCISIONS OR AMYGDALO-HIPPOCAMPECTOMY IN MAN

ADRIAN M. OWEN,*† BARBARA J. SAHAKIAN,† JAMES SEMPLE,‡ CHARLES E. POLKEY§ and TREVOR W. ROBBINS†

†Department of Experimental Psychology, University of Cambridge, Cambridge, U.K.; ‡Smithkline Beecham Pharmaceuticals Ltd, Coldharbour Road, Harlow, U.K.; and §Neurosurgical Unit, The Maudsley Hospital, London, U.K.

(*Received* 15 *February* 1994; *accepted* 6 *July* 1994)

Abstract—Three groups of neurosurgical patients with temporal lobe excisions, frontal lobe excisions or unilateral amygdalo-hippocampectomy were assessed on a computerized battery of tasks designed to investigate visuo-spatial short-term recognition memory and learning. A double dissociation is reported between deficits of pattern recognition memory and spatial recognition memory which were observed in the two posterior groups and frontal lobe patients, respectively. In addition, both the temporal lobe and amygdalo-hippocampectomy patients were also impaired on a delayed matching-to-sample paradigm whilst frontal lobe patients performed at an equivalent level to controls. Finally, whilst the impaired performance of the three groups was indistinguishable on a test of paired-associate learning, quite different patterns of deficit were observed on a test of spatial *working* memory. These results are discussed with reference to recent suggestions that visual recognition memory is mediated by a neural system which includes, as major components, the inferotemporal cortex, the medial temporal lobe structures and particular sectors of the frontal lobe, and are compared to previous findings from patients with idiopathic Parkinson's disease and dementia of the Alzheimer type.

Key Words: visual memory; spatial memory; frontal lobe; temporal lobe; Parkinson's; Alzheimer's.

INTRODUCTION

A plethora of animal studies have now demonstrated that bilateral ablation of the inferotemporal cortex or medial temporal lobe structures produces impairments in tests of visual recognition memory [5, 32, 35, 36], although more recently particular sectors of the orbital and medial prefrontal cortex have also been implicated [2]. In human subjects, previous studies have suggested that both recognition and recall of visual patterns or objects are *particularly* sensitive to damage to the right temporal lobe [22, 29, 58]. The dominant left temporal lobe, in contrast, appears to play a critical role in the memory for verbal stimuli, but does not seem to contribute significantly to memory for non-verbal material [27, 28]. The challenge in recent years has been to relate these clinical phenomena to experimental

*To whom correspondence should be addressed at Neuropsychology Department, Montreal Neurological Institute, 3801 Rue University, Montreal, Quebec H3A 2B4, Canada.

findings, which depends heavily on utilizing a common theoretical, as well as empirical, approach to cross-species comparisons. In general, many of the complex neuropsychological paradigms commonly used to assess cognitive dysfunction in non-human primates have not been applied to human subjects with focal cortical lesions.

In the present study, spatial working memory, visuo-spatial recognition memory and visual–spatial paired-associate learning were assessed in groups of neurosurgical patients with unilateral temporal lobe excisions, unilateral or bilateral frontal lobe excisions and in patients in whom unilateral amygdalo-hippocampectomy had been performed. The design of these tests is based on the principle of bridging the neuropsychological gap that exists between man and experimental animals, such that direct comparisons of the cognitive deficits observed in brain damaged patients with those observed in animals bearing selective neurochemical or neuroanatomical lesions can be made. For example, matching-to-sample for complex coloured designs was tested using a procedure with randomly presented simultaneous presentation, 0 sec (immediate) presentation and delayed (4 or 12 sec) trials. In monkeys, delayed non-matching-to-sample is particularly sensitive to lesions of both the inferotemporal cortex [35] and the ventromedial frontal cortex [2]. A paired-associate learning task was also included in the present study which, importantly, required both visual pattern *and* visuo-spatial memory. However, this test also has aspects in common with delayed response [10] and conditional associative learning [50, 53] tasks, both of which are known to be impaired in patients and in monkeys [49, 51] with frontal lobe damage. Visual pattern recognition memory was also tested using a serial recognition task analogous to paradigms used by Gaffan [13] and Mishkin [35] to test visual memory for lists of objects in non-human primates. For comparison, a complementary test of visuo-*spatial* recognition memory was also included in the current study. Thus, several of these tests are designed to provide a componential analysis of those cognitive processes comprising particular forms of cognitive function; visual–spatial paired-associate learning, for example, requires both visual pattern recognition and visuo-spatial recognition which are, therefore, assessed individually using analogous paradigms.

For comparison with previous studies, a self-ordered searching task was also included in the current investigation to assess the efficiency of spatial *working* memory in the three patient groups. This task has certain aspects in common with the self-ordered searching tasks used previously by Petrides and Milner [57] to assess patients with frontal or temporal lobe damage, although importantly, in the current study, subjects were not required to remember objects by their specific features, only by their particular locations. Spatial working memory deficits have been widely reported, both in monkeys with frontal lobe damage [11, 15, 16, 18, 33, 48] and in rats with damage to hippocampal formation and related structures [1, 40, 41, 60, 61, 71]. In humans, differential patterns of impairment have previously been demonstrated using this task, in related, but not identical groups of patients with frontal lobe damage [42] and temporal lobe excisions or amygdalo-hippocampectomy [47].

Recent progress in defining the neurochemical and neuropathological correlates of Parkinson's disease (PD) and dementia of the Alzheimer type (DAT) has given impetus to the systematic analysis of the cognitive deficits associated with these neurodegenerative diseases. Visual memory and learning deficits have been consistently reported in patients with PD [14, 25, 38, 59, 62, 63, 72] although these results are by no means unequivocal. For example, several recent studies have reported normal visual recognition memory performance in PD patients medicated with L-Dopa and/or anti-cholinergic drugs [9], and in unmedicated patients with PD [24]. In contrast, the first, and most prominent symptom to

occur in patients with DAT is usually deterioration of memory and new learning [3, 4, 26, 37]. Substantial impairments in both verbal and non-verbal recognition memory and free recall have been reported which may be suggestive of temporal lobe dysfunction in these patients [3, 4]. We have recently assessed groups of medicated and non-medicated patients at different stages of PD [43, 45], and groups of patients with mild [65, 67] and moderate [67] DAT using similar and/or identical versions of the visuo-spatial recognition memory and learning tasks included in the current study. The results suggest that there are multiple memory impairments in PD which may differentially depend on the clinical severity of the disease. In particular, the test of spatial working memory described above was more sensitive in detecting deficits in these patients than tests of pattern and spatial recognition, delayed matching to sample and a test of visuo-spatial learning, which were relatively preserved in medicated and non-medicated patients with mild PD. In contrast, in DAT, profound deficits were observed across all the recognition memory tasks, even in the earliest stages of the disease [65, 67]. In assessing groups of neurosurgical patients with well documented excisions of the frontal and temporal cortices, the present study therefore has considerable significance for identifying the likely neural circuitry responsible for mediating these dissociable patterns of cognitive impairment in patients with PD and DAT.

METHOD

Subjects

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). Any patient with atypical (i.e. right hemisphere or bilateral) speech representation, as demonstrated by preoperative intracarotid sodium amobarbital tests was excluded. It was not possible to match the patients according to preoperative pathology because the number of patients within each group was limited. Testing was carried out either as part of the post-operative neuropsychological evaluation (i.e. within 3 months of surgery) or in long-term follow up. As this factor was not statistically related to performance on any of the neuropsychological tests used in the present study, it will not be given further consideration in the main analyses of effects.

Frontal lobe patients. The 16 frontal lobe patients included in this study had all undergone unilateral or bilateral frontal lobe surgery and were aetiologically heterogenous. Ten 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 and one case of astrocytoma removal.

All four patients with left-sided excisions had received unilateral lobectomies for the relief of intractable epilepsy. The remaining two patients had undergone bifrontal meningioma removal. In Fig. 1(i), representative diagrams are presented, showing the size and the site of the frontal lobe excision according to the neurosurgeon's drawings at the time of the operation. The frontal lobe group were tested on average 5 years, 6 months post-operatively (range = 3–240 months). Five were on anti-convulsant medication at the time of testing and all were seen as outpatients.

Temporal lobe patients. The standard "*en bloc*" resection [8] involves the removal of between 5.5 and 6.5 cm of the temporal lobe measured from the pole and typically includes a variable amount (less than 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 post-operative speech problems. Two typical post-operative temporal lobe resections are presented in Fig. 1(ii).

The 20 patients included in this group had all undergone unilateral temporal lobe surgery for the relief of intractable epilepsy. There were 11 cases where left-sided surgery had been performed and these included one 4.5 cm resection, six 6 cm resections, three 6.5 cm resections and one 7 cm resection (mean = 6.09 cm). In nine cases the neuropathological examination reported medial temporal sclerosis, in one case hippocampal sclerosis was reported and in one case, cortical dysplasia was diagnosed. In seven of these cases the neuropathological report was sufficiently detailed to include an estimate of the length of hippocampal removal and the mean value was 17.4 mm (range = 5–28 mm).

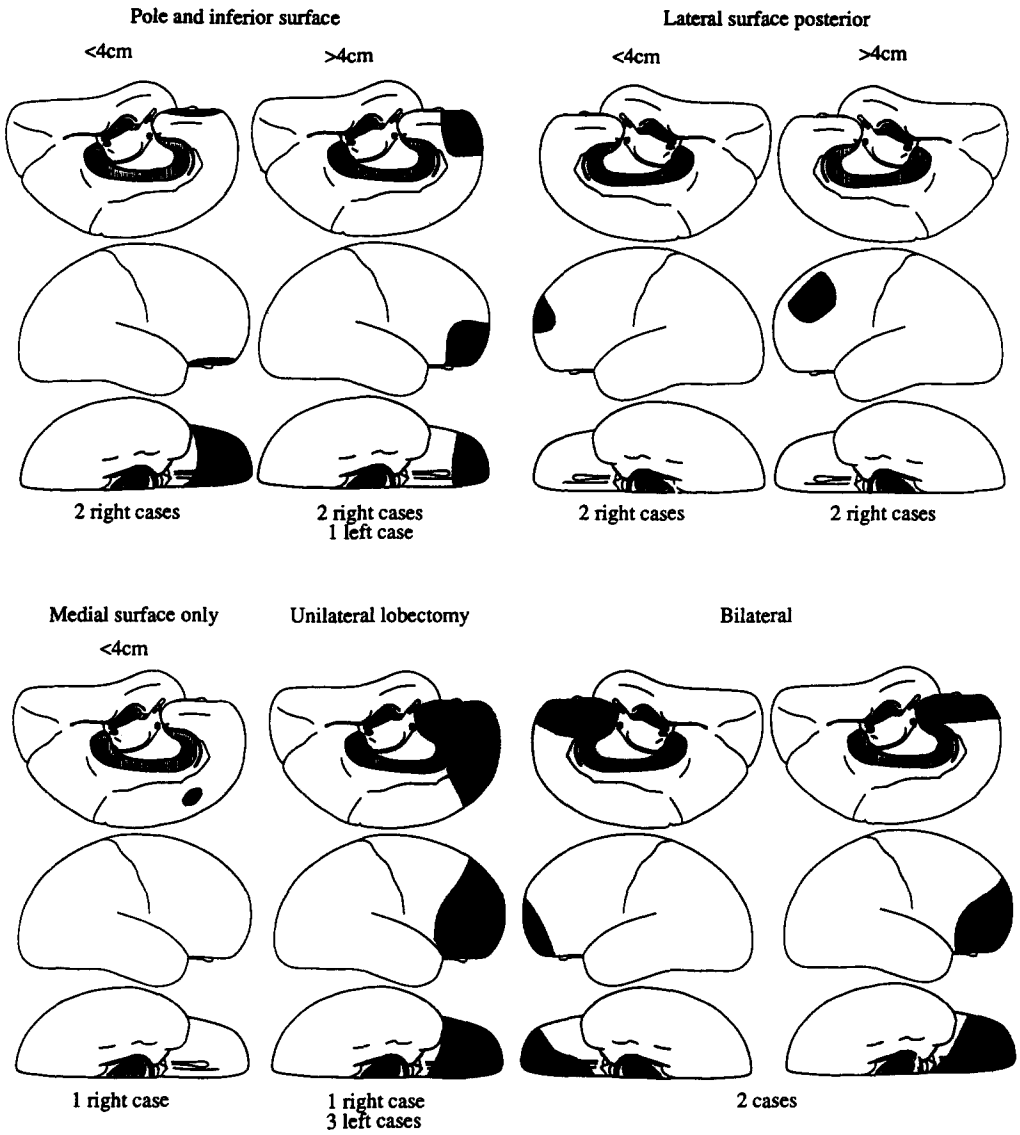
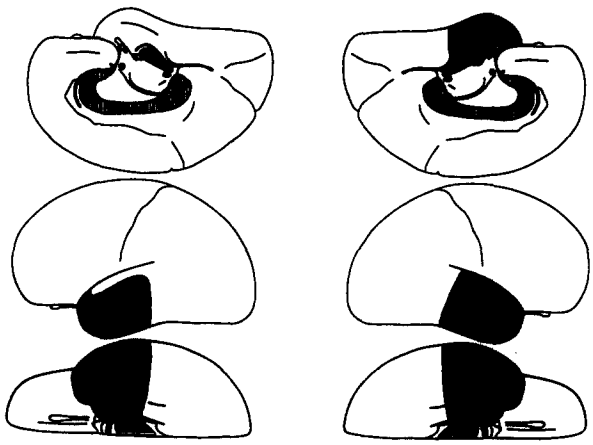


Fig. 1. (i) Diagrams based on the neurosurgeon's drawings at the time of surgery showing the extent of the frontal lobe excision in several representative cases.

Among the nine patients tested after a right temporal lobectomy there was one 5 cm resection, seven 6 cm resections and one 6.5 cm resection (mean = 5.94 cm). The mean length of hippocampal removal (reported in four of the patients) was 20.75 mm (range = 20–23 mm). In six cases medial temporal sclerosis was reported, one case of glial malformation was reported and for two patients no firm conclusions regarding the neuropathology were reached. The 20 temporal lobe patients were tested on average 35 months (range = 8–121 months) after surgery. All were seen as outpatients and all were on anti-convulsant medication at the time of testing.

Amygdalo-hippocampectomy patients. A variant of the "*en bloc*" temporal resection is the selective amygdalo-hippocampectomy [74]. This operation is performed in patients who have a known structural lesion in or near the medial temporal structures or when other investigations have suggested a medial temporal focus for seizures. In most cases the amygdala and hippocampus are removed entirely on one side without any permanent damage to the overlying cortical structures. The 11 patients (seven left-sided, four right-sided) included in this study had all



Left temporal lobectomy (11 cases) Right temporal lobectomy (9 cases)

Fig. 1. (ii) A typical left-sided and a typical right-sided temporal lobe resection again based on the neurosurgeon's drawings at the time of the operation. The blackened areas define the lesion site.

undergone unilateral amygdalo-hippocampectomy (A-H) for the relief of intractable epilepsy and were tested on average 11.6 months (range = 5–24 months) after surgery. All were seen as outpatients and all were on anti-convulsant medication.

Control subjects. For the tests of visuo-spatial recognition memory and learning, a single group of 44 normal, healthy control subjects (control group 1), were chosen to match the three patient groups as closely as possible with respect to age *and* pre-morbid verbal IQ estimated using the National Adult Reading Test (NART) [39]. For the spatial working memory task, a slightly smaller group of 37 control subjects (control group 2) were selected using the same criteria. Both groups were drawn from a large pool of control volunteers in London, Cambridge, Harlow and at the North East Age Research panel in Newcastle Upon Tyne. Informed consent was obtained from all control subjects prior to the neuropsychological testing session.

Table 1 shows a summary of characteristics for the three patient groups and the two groups of normal controls. For the tests of visuo-spatial memory and learning, one-way analysis of variance confirmed that, whilst the four groups did not differ significantly in terms of estimated pre-morbid verbal IQ [$F(3, 87) = 2.64$, $P > 0.05$], they did differ significantly in terms of age [$F(3, 87) = 6.64$, $P < 0.001$]. Orthonormal contrasts between the four groups confirmed that only the frontal lobe patients were significantly older than the group of normal controls [$t(87) = 4.24$, $P < 0.001$]. Similarly, for the spatial working memory task, the groups differed significantly with respect to age [$F(3, 77) = 4.19$, $P < 0.01$] but not IQ [$F(3, 77) = 1.49$, $P > 0.05$]. Contrasts between the groups again confirmed that the frontal lobe patients were significantly older than the normal controls [$t(77) = 2.63$, $P = 0.01$]. In a large control study of over 800 normal control volunteers, we have found no relationship between age and any of the tests included in the current study in subjects less than 50 years of age [64]. However, to control for any affect of age difference in this study, this factor was treated as a covariate throughout all analyses of performance.

Table 1. Subject characteristics

	N	M/F	Age	Verbal IQ	L/R/Bi
Frontal	16	8/8	46.63(4.52)	108.5(2.89)	4/10/2
Temporal	20	13/7	33.40(2.13)	106.4(2.50)	11/9
Amygdalo-hippocampectomy	11	5/6	31.55(1.92)	103.0(2.40)	7/4
Control group 1 (Vis-sp memory and learning)	44	21/23	32.32(1.55)	110.7(1.03)	
Control group 2 (Spatial working memory)	37	21/16	36.18(2.24)	108.9(1.34)	

M/F = male/female; L/R/Bi = Laterality Left/Right/Bilateral (S.E.M. in brackets).

Procedure

The main testing procedures were taken from the Cambridge Neuropsychological Test Automated Battery (CANTAB), a series of computerized paradigms run on an IBM PS/2 Model 30 286 personal computer with a high resolution Taxan 770+ colour monitor fitted with a Mellordata touch sensitive screen. Subjects were seated at a comfortable height approximately 0.5 m from the monitor. It was explained that they would have to respond to stimuli by touching the screen. They were introduced to the apparatus by way of a "motor screening task" in which they were asked to respond to a series of 10 flashing crosses on the screen by placing the index finger of their preferred hand on the centre point of each cross. After satisfactorily completing the introductory motor screening task, subjects were given the following tests in the order described below.

Pattern recognition [Fig. 2(i)]. This test was presented in two phases. Initially, subjects were shown a series of 12 simple, but abstract, coloured visual patterns (set 1) appearing one at a time inside a white box located in the centre of the screen (presentation phase). The stimuli were not difficult to verbalize [see Fig. 2(i)], although no encouragement was given to the subjects to use verbal labels. Each of these "target" patterns was presented for 3 sec, the screen was then cleared and the next pattern appeared. In the second (recognition) phase, 12 pairs of coloured patterns appeared on the screen (one pair at a time) and the subject was required to respond to each pair by touching the pattern they had already seen during the presentation phase. Each of the target patterns was presented in reverse order and paired with distractor patterns that differed in form but not in colour from the targets. Each response was accompanied by an auditory tone and visual feedback was automatically provided by the computer in the form of green ticks (for correct responses) and red crosses (for incorrect responses). This procedure was then repeated with 12 new patterns (set 2) and the subject's total score (maximum possible = 24) was expressed as a percentage correct.

Spatial recognition [Fig. 2(ii)]. This procedure was also presented in two phases. In the presentation phase, subjects were shown a series of 5 unfilled 1 in. white squares, appearing one at a time, at different locations on the screen. Each square was presented for 3 sec before the screen was cleared and the next square appeared. In the second (recognition) phase, two squares appeared simultaneously on the screen and the subject had to select which location had been used before in the presentation phase. The target squares were presented in reverse order and paired with distractor squares which appeared in novel locations which had never been used as target locations. Again, each response was accompanied by an auditory tone and visual feedback was provided in the form of green ticks and red crosses. This procedure was then repeated three more times using new target and distractor locations on each occasion. The subject's total score (maximum possible = 20) was expressed as a percentage correct.

Simultaneous and delayed matching to sample [Fig. 2(iii)]. At the beginning of each trial, a complex abstract (sample) pattern consisting of four quadrants, each differing in colour and form, appeared in the centre of the screen for a presentation period of 4.5 sec. Subjects were told to study the pattern, since they would later be required to

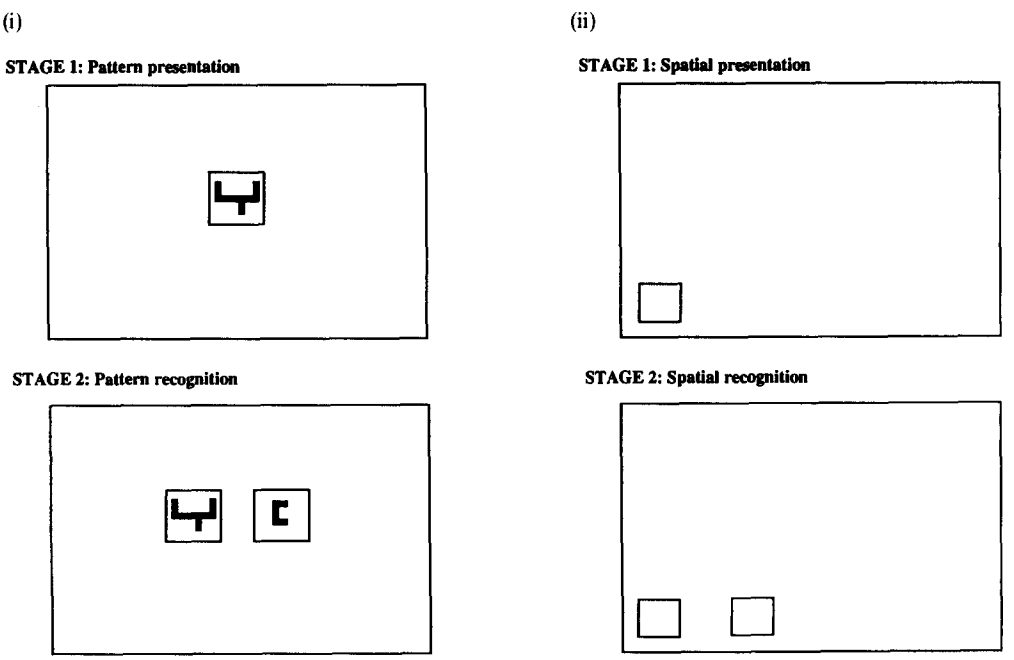


Fig. 2. (i) The pattern recognition memory test. (ii) The spatial recognition memory test.

identify it from among three "distractor" patterns. In the *simultaneous* condition, four choice patterns then appeared, located under the sample pattern. The subject was required to respond by touching the choice pattern that corresponded exactly (in both colour and form) to the sample pattern above. Only one of the choice patterns was identical to the sample. One of the other choice patterns was a novel distractor, differing in both colour and form from the sample. The remaining two choice patterns were "partial distractors" in that one had the colours of the sample but the form of the novel distractor whilst the other was the same shape as the sample but had the colours of the novel distractor. In addition, each of the four choice patterns had one (random) quadrant in common to discourage mnemonic strategies based on remembering the colour and shape of a single quadrant [see Fig. 2(iii)]. The subject's response was accompanied by an auditory tone and visual feedback was provided in the form of green ticks and red crosses. After an incorrect response, the subject had to continue to choose until the correct (target) stimulus had been touched.

The *delay* condition was identical to the *simultaneous* condition in every way except that after the initial 4.5 sec presentation period, the sample stimulus disappeared from the screen. There then followed a 0 sec, 4 sec or 12 sec delay before the four choice stimuli appeared and the subject was required to make their selection. Following three practice trials (one each of simultaneous, 0 sec and 12 sec), there were a total of 10 test trials in each of the four conditions presented in a pseudo random order (total test trials = 40).

Each subject was scored according to the number of trials correct on the first choice in each of the simultaneous and delay conditions. In addition, mean response latencies in each condition were also calculated, including only those trials in which the first choice was the correct one.

Paired-associate learning [Fig. 2(iv)]. In this test, subjects were required to remember up to eight pattern–location associations. Initially, six white boxes were presented around the screen [see Fig. 2(iv)] and subjects were told that each of them would "open up" in turn, showing them what was inside. Their task was to look for coloured patterns in the boxes and to remember which pattern belonged in which box. Each of the boxes opened up (i.e. became "unfilled") for 3 sec and then closed again in a randomized sequence. In the first trial, only one of the boxes contained a coloured pattern. Immediately after the last box had opened, this pattern was presented in the centre of the screen and the subject was required to respond by touching the box in which it had appeared. Feedback was *not* provided after each response although if the choice was correct, the words "ALL CORRECT" appeared in the centre of the screen and the subject proceeded to the next trial. If the choice was incorrect, the boxes were successively reopened (*reminding* phase) for 2 sec each, and the subject was then given a second attempt to locate the

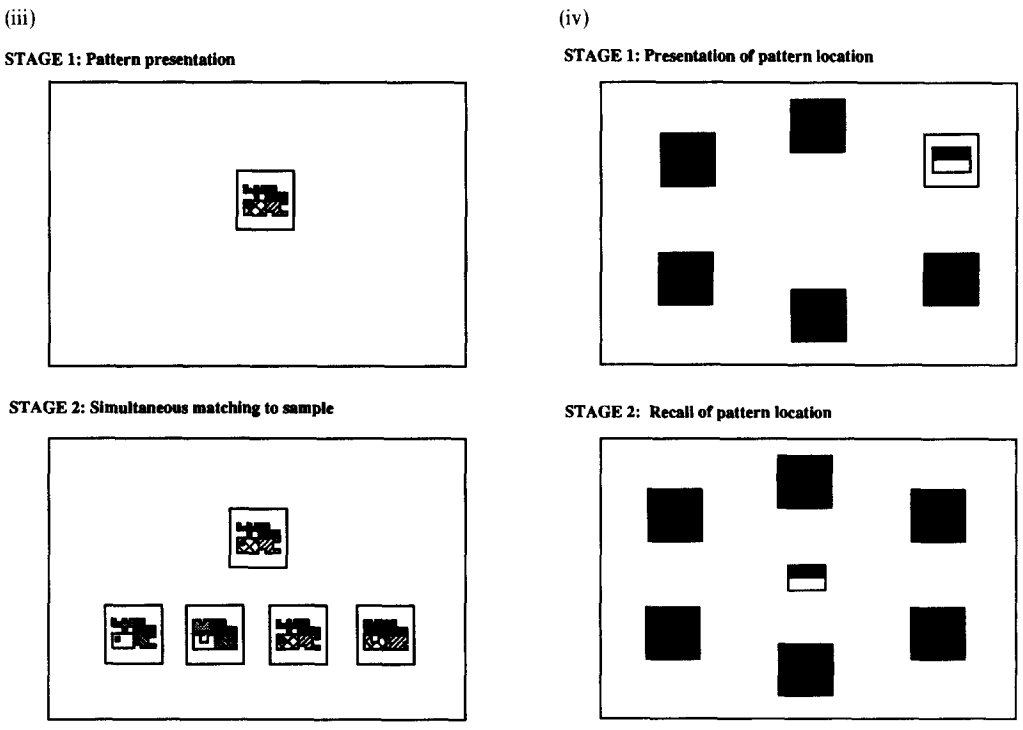


Fig. 2. (iii) Simultaneous and delayed matching to sample. (iv) Paired-associate learning.

pattern correctly. On each trial, the subject was allowed up to nine *reminding* phases, making 10 attempts in all, before the test was terminated. After the initial trial with one pattern, there was one more trial with a single pattern, then two trials with two patterns each, two trials with three patterns each and then one trial with six (one in every box) patterns to locate. Finally, two extra boxes were added to the array on the screen and the subject was required to locate a total of eight patterns correctly. The subject automatically moved from one trial to the next by locating all of the patterns correctly, either after the initial *presentation* phase or after one of the nine *reminding* phases. Performance was assessed according to three main measures. (i) *Trials* represented the total number of presentations required (maximum score = 10 presentations per trial) to locate all the patterns correctly, summed across each of the eight trials. Subjects were assigned the maximum score of 10 for trials not attempted due to failure at an earlier stage. (ii) *Errors* represented the total number of errors (incorrect placements) summed across the eight trials. Subjects not reaching a particular set, were assigned the worst score obtained by a subject actually attempting that set. (iii) The *memory* score was calculated according to the total number of patterns located correctly after the first presentation, summed across the eight trials (range = 0 to 26).

Spatial working memory. This test has been described in detail elsewhere [42, 43]. Subjects were required to "search through" a number of boxes presented on the screen in order to collect "blue tokens" hidden inside. At any one time, there would be a single token hidden inside one of the boxes and subjects were 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. On each trial, every box was used once to hide a token such that the total number of blue tokens to be found corresponded to the number of boxes on the screen. Errors were scored according to the number of occasions on which a subject returned to open a box in which a blue counter had already been found. After four practice trials with three boxes, there were four test trials with each of four, six and eight boxes making a total of 12 test trials in all.

The relevance of repetitive searching strategies on this test has previously been investigated in patients with frontal lobe damage [42]. An efficient strategy for completing this task is to follow a predetermined search sequence, beginning with a particular box and then returning to start each new sequence with that same box as soon as a token has been found. The extent to which this repetitive searching pattern was used as a strategy for approaching the problem was estimated from the number of search sequences starting with the same box, within each of the more difficult six and eight box problems. The total of these scores 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.

RESULTS

Pattern and spatial recognition

Mean values and corresponding standard errors for the pattern and spatial recognition tests are shown in Fig. 3 for the three patient groups and the group of controls. One-way analyses of variance showed that there was a statistically significant difference between the four groups on both the pattern recognition memory [$F(3, 86) = 4.29$, $P < 0.01$] and the spatial recognition memory [$F(3, 86) = 2.94$, $P < 0.05$] tasks. A between group, orthonormal contrast analysis confirmed that both the temporal lobe patents [$t(86) = 3.19$, $P < 0.01$] and the amygdalo-hippocampectomy group [$t(86) = 2.39$, $P < 0.05$] were significantly impaired on the pattern recognition memory task but neither group was impaired on the spatial recognition memory task [$t(86) = 1.8$, $P > 0.05$ and 0.46, $P > 0.05$, respectively]. In contrast, the frontal lobe group was severely impaired on the spatial recognition memory task [$t(86) = 2.74$, $P < 0.01$], whilst pattern recognition memory was relatively preserved [$t(86) = 1.2$, $P > 0.05$].

Simultaneous and delayed matching to sample

Data for this test were analysed separately for the simultaneous and delayed matching conditions. Since performance accuracy was expressed as a proportion correct score (maximum possible in each condition = 10), an arcsin transformation of the data was performed before one- and two-way analyses of variance were conducted. The (transformed) proportion correct scores for the three patient groups and the combined control group

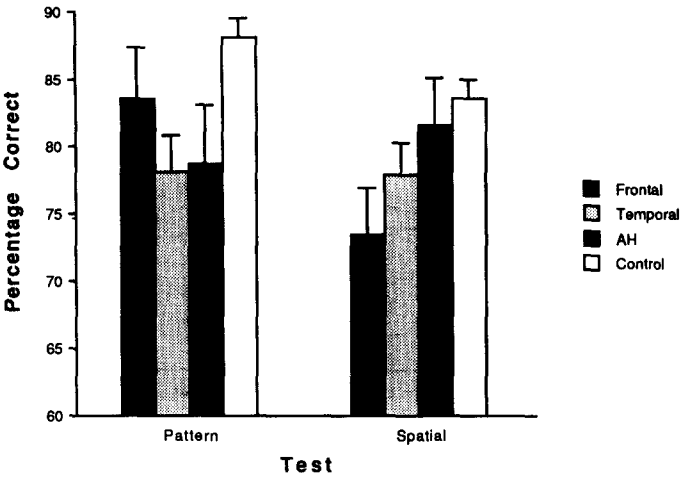


Fig. 3. The mean percentage correct scores for the pattern and spatial recognition memory tests. Bars represent standard errors.

within each of the four conditions are presented in Fig. 4. In general, control performance was high with normal subjects scoring above 85% correct at all levels of difficulty.

There was no significant difference between the patient and control groups when the stimuli were presented simultaneously [$F(3, 84) = 0.43$, $P > 0.05$]. In the delay conditions however, there was an overall effect of group [$F(3, 84) = 4.42$, $P < 0.01$] and delay [$F(2, 170) = 11.11$, $P < 0.0001$] but no significant interaction between the two factors [$F(6, 170) = 1.29$, $P > 0.05$]. Thus, whilst these main effects indicated a significant overall impairment in one or more of the patient groups, the non-significant interaction confirmed that this deficit was not related to the length of the delay within the range tested. An orthonormal contrast analysis of these effects confirmed that both the temporal lobe patients [$t(84) = 3.36$, $P \leq 0.001$] and the amygdalo-hippocampectomy patients [$t(84) = 2.43$, $P < 0.025$] were significantly impaired, whilst no significant deficit was observed in the patients with frontal lobe damage [$t(84) = 1.47$, $P = 0.14$].

Response latencies for the simultaneous and delayed conditions were also analysed using separate one and two-way analyses of variance (Fig. 4). In all cases, latencies were recorded in milliseconds and then transformed into logarithms (Base 10) to reduce skewness in the distribution. There was a highly significant main effect across the patient and control groups in the simultaneous matching condition [$F(3, 84) = 7.79$, $P < 0.0001$]. Orthonormal contrasts revealed that both the temporal lobe patients [$t(84) = 3.62$, $P < 0.001$] and frontal lobe group [$t(84) = 4.06$, $P < 0.0001$] were significantly slower than controls in this condition, although this effect only approached significance in the amygdalo-hippocampectomy group [$t(84) = 1.91$, $P = 0.06$].

In contrast, across delay conditions, the main effect of group did not reach significance [$F(3, 83) = 2.43$, $P > 0.05$] and there was no significant interaction between the group and delay factors [$F(6, 168) = 1.24$, $P > 0.05$]. There was however, a highly significant main effect of delay [$F(2, 168) = 66.17$ $P < 0.0001$].

A comprehensive analysis of error types was undertaken in order to ascertain whether any particular type of error was associated with poor performance on this task. The three patient and control groups were compared in terms of the proportion of errors that were "colour

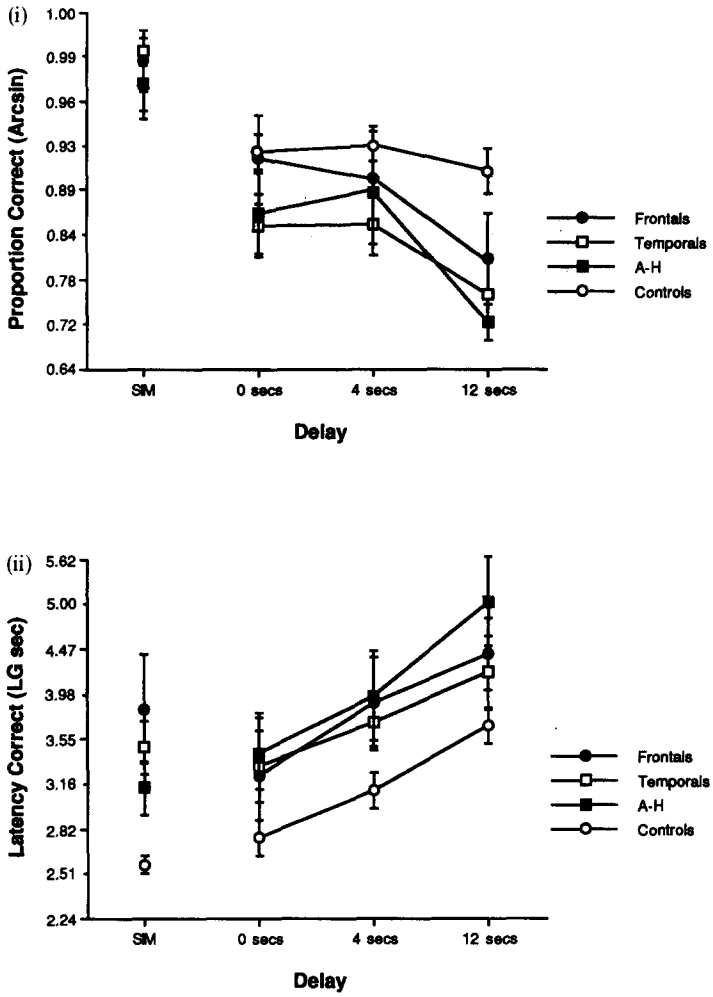


Fig. 4. Simultaneous and delayed matching to sample (i) proportion correct and (ii) mean latency for correct solutions. Bars represent standard errors.

errors" (e.g. selecting the shape which was the same colour as the target but the wrong form), "form errors" (e.g. selecting the shape which was the same form as the target but the wrong colour) or "distractor errors" (incorrect colour *and* form). In general, the subject groups made more errors of "colour" (55–83% of total errors) than of either "form" (13–28% of total errors) or "distractor" (3–9%). However, no significant differences were observed between the groups.

Together, these results confirm that whilst none of the three patient groups were impaired in the simultaneous matching to sample task, in terms of their accuracy of performance, all three groups were generally slower to respond in this condition. In the delayed matching to sample task, there were *no* significant delay-dependent deficits although overall, both the temporal lobe group and the amygdalo-hippocampectomy patients were significantly less accurate than controls. Latencies were, in general, not significantly increased in the patient groups across the three delayed matching conditions. Impaired accuracy of performance in

the two posterior patient groups did not appear to be related to a relative increase in any particular type of selection error.

Paired-associate learning

The three patient groups and their respective control groups were compared in terms of three indices of learning and memory; total *trials* to criterion, total *errors* committed and total number of patterns correctly located after a single presentation (*memory score*). The data are presented in Fig. 5.

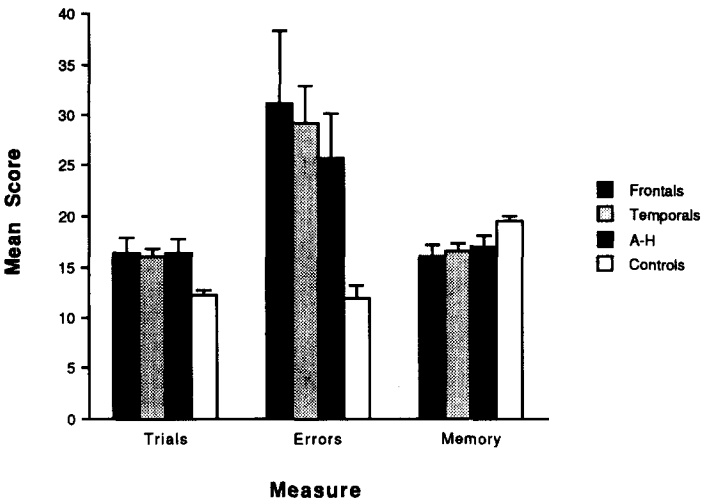


Fig. 5. The paired-associate pattern–location learning task. Bars represent standard errors.

In terms of the total number of trials required to reach criterion, there was a highly significant difference between the four groups [$F(3, 85) = 8.00$, $P < 0.0001$]. Orthonormal contrasts were performed and confirmed that compared to controls, the temporal lobe patients [$t(85) = 3.71$, $P < 0.0001$], the amygdalo-hippocampectomy patients [$t(85) = 3.27$, $P < 0.01$] and the frontal lobe patients [$t(85) = 3.37$, $P = 0.001$] required significantly more trials to complete the task. A similar group main effect was found for total number of errors [$F(3, 85) = 8.45$, $P < 0.0001$] and again, all three groups were impaired [$t(85) = 4.05$, $P < 0.0001$, $t(85) = 2.60$, $P < 0.025$ and $t(85) = 3.79$, $P < 0.0001$, respectively]. Similarly, a significant group effect was found for memory score [$F(3, 85) = 4.92$, $P < 0.005$] and again, all three groups were impaired [$t(85) = 2.97$, $P < 0.005$, $t(85) = 2.06$, $P < 0.05$ and $t(85) = 2.98$, $P < 0.005$, respectively].

In summary, deficits in visuo-spatial paired-associate learning were clearly evident in all three patient groups although it was not possible to dissociate the patients on any particular measure of performance.

Spatial working memory

The mean number of errors at each level of the spatial working memory test are shown in Fig. 6 for the three patient groups and the group of normal controls. Two-way analyses of variance conducted across the three difficulty conditions revealed a significant group

difference [F (3, 76) = 10.71, $P < 0.0001$], a significant effect of task difficulty [F (2, 154) = 204.19, $P < 0.0001$] and a highly significant interaction between the two factors [F (6, 154) = 6.01, $P < 0.0001$]. An orthonormal contrast analysis confirmed that although the temporal lobe group was not impaired overall [t (76) = 1.82, $P > 0.05$] deficits were observed in *both* the frontal lobe group [t (76) = 5.40, $P < 0.01$], and the patients with amygdalo-hippocampectomy excisions [t (76) = 2.81, $P < 0.01$]. Among temporal lobe patients, the interaction between the group and difficulty factors also just failed to reach significance [t (154) = 1.87, $P = 0.064$] although significant interactions were observed in both the frontal [t (154) = 4.5, $P < 0.0001$] and amygdalo-hippocampectomy groups [t (154) = 2.44, $P < 0.025$]. For these two groups, simple main effects were therefore, calculated. Compared to the control group, the frontal lobe patients made significantly more errors at the easiest four box level of task difficulty [t (76) = 3.47, $P = 0.001$] as well as at the more difficult six [t (76) = 4.76, $P < 0.0001$] and eight box levels [t (76) = 15.78, $P < 0.0001$]. In contrast, the amygdalo-hippocampectomy group was only significantly impaired at the most difficult, eight box level of difficulty [t (76) = 2.77, $P < 0.01$].

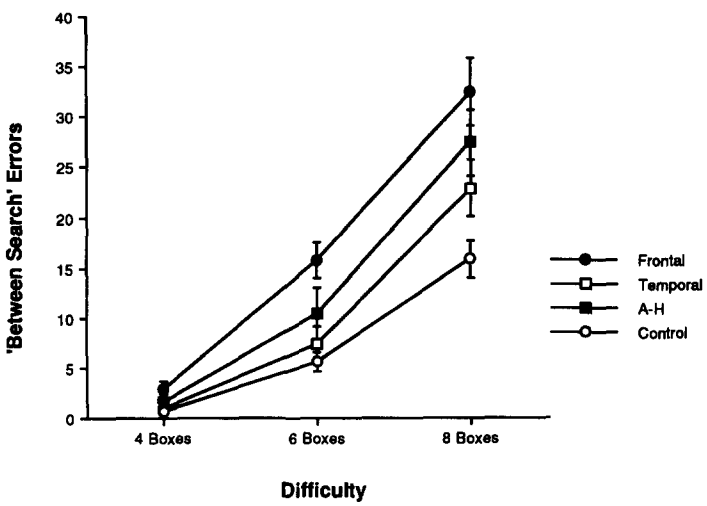


Fig. 6. Search errors in the spatial working memory test. Bars represent standard errors.

The estimate of strategy employed in this task was scored on a scale of 1–37 with lower scores representing more extensive use of the strategy. The best possible score of 1 was obtained when, within each of the more difficult six and eight problems, the same box was used to initiate each search sequence. Conversely, if every search within each of these problems started with a different box, the maximum score of 37 was obtained. This particular strategy is known to improve performance on this task [42] and has been discussed in detail by Owen *et al.* [47]. The mean spatial "strategy scores" (± S.E.M.) for the temporal lobe patients, the amygdalo-hippocampectomy patients, the frontal lobe patients and the group of normal control subjects were 14.67(1.25), 15.9(0.96), 17.81(1.44) and 12.73(0.83), respectively. There was a significant difference between the groups [F (3, 76) = 0.05] in the extent to which this strategy was adopted. Orthonormal contrasts confirmed that, according to this measure, the frontal lobe group approached this task in a less systematic way than the controls [t (76) = 2.56, $P < 0.025$] although no significant deficits were observed in either

the temporal lobe patients [t (76) = 1.30, $P > 0.05$] or the patients with amygdalo-hippocampectomy excisions [t (76) = 1.72, $P > 0.05$].

In summary, these results demonstrate qualitatively and quantitatively different patterns of impaired spatial working memory in sub-groups of neurosurgical patients. In the frontal lobe group, profound deficits were observed even at the simplest level of task difficulty. Furthermore, this deficit was found to relate to the inappropriate use of a repetitive searching strategy shown to improve performance in all of the patient and control groups tested. In contrast, in the amygdalo-hippocampectomy group, deficits were only observed at the most challenging level of difficulty and these patients were unimpaired in terms of their strategy for approaching the task. The temporal lobe group were not significantly impaired ($P = 0.064$) compared to the control group according to either measure although examination of Fig. 6 suggests some impairment in this patient group at the most difficult, eight box level.

Interrelationships among cognitive tests

To test the general relationships among the five tests described here, Pearson's product moment correlation coefficients were calculated between several indices of performance, derived from the main variables described above. Specifically, pattern recognition, spatial recognition, simultaneous matching, total delayed matching, total spatial working memory errors and paired-associate, total trials and memory score were intercorrelated. As the pattern of deficits in the temporal lobe and amygdalo-hippocampectomy groups was identical across tasks and since the number of patients in the latter group was small, they were collapsed into a single patient group for the purposes of this correlational analysis.

Among control subjects, total trials score on the paired-associate learning test correlated significantly with pattern recognition [r (43) = −0.49, $P < 0.001$] and less so with spatial recognition memory score [r (43) = −0.29, $P < 0.05$]. Memory score did not correlate significantly with either test. In the temporal lobe/amygdalo-hippocampectomy group, the paired-associate task, trials score was most closely associated with the pattern recognition memory task [r (31) = −0.53, $P = 0.001$], whilst the relationship between the paired-associate task and spatial recognition memory only approached significance [r (31) = −0.28, $P = 0.06$]. In this group, the memory score also correlated highly with performance on the pattern recognition task [r (31) = 0.50, $P < 0.005$], but not the spatial recognition memory task [r (31) = 0.1, $P = 0.28$]. In contrast, in the frontal lobe group both pattern recognition memory [r (16) = −0.73, $P = 0.001$ and r (16) = 0.55, $P < 0.025$] and spatial recognition memory [r (16) = −0.63, $P = 0.005$ and r (16) = 0.54, $P < 0.025$] correlated with the trials *and* memory scores from the paired-associate learning task.

Finally, spatial working memory score among frontal lobe patients correlated with performance on the spatial recognition memory test [r (16) = −0.69, $P < 0.0025$], but did not among the other patient groups [r (27) = −0.008, $P = 0.48$] or among the control subjects [r (18) = −0.162, $P = 0.26$].

Effects of laterality

In the current study, the initial analysis combined left, right and bilateral frontal lobe patients into a single group. A supplementary examination of the data was performed therefore, to look at the possible effects of laterality of lesion in this patient group. Our own previous studies, have revealed no significant differences relating to the side of the excision in slightly larger groups of frontal lobe patients on tests of spatial working memory, planning

[42] and attentional set-shifting [44, 46]. In the present study, there were clearly *no* differences between the patients with left- and right-sided excisions although the small sample size in the former group ($N=4$) precluded any formal statistical analysis of this comparison. Notably however, the performance of the two bilateral frontal lobe patients was particularly poor, although only in terms of certain performance measures. For example, in the test of pattern recognition memory, the bilateral patients scored 69% correct, compared with 82 and 84% in the left- and right-sided cases. This dissociation was *not* evident however, in the complementary test of spatial recognition memory. Thus, the bilateral patients scored 75% which is well above chance levels and compares very favourably with the 71 and 73% scores of the left- and right-sided unilateral groups. In the simultaneous matching to sample task, the bilateral patients performed well (95%) although their score with just 0 sec delay was dramatically inferior (both patients attained only 60% correct) to that observed in *any* of the other patient groups. Importantly however, this impairment was not exacerbated at longer delays and these patients scored at the same level, or better, than other groups at both 4 sec (75%) and 12 sec (75%). In the paired-associate learning task, the two bilateral patients were somewhat worse than either the left or right frontal lobe groups in terms of both measures of learning (trials = 22.23, errors = 56.9) but were not correspondingly poor in terms of their mean memory score (15.4). Finally, at all levels of task difficulty, performance on the spatial working memory task was equivalent or better to that of either of the unilateral frontal lobe groups.

These results confirm that the deficits observed in tests of spatial working memory, visuo-spatial memory and learning in frontal lobe patients are not disproportionately related to damage to one or other hemisphere. However, the pattern of performance observed in two patients suggests that certain aspects of visuo-spatial memory and learning may depend critically on bilateral damage to the prefrontal cortex.

For the purposes of the initial analysis, the left and right temporal lobe patients and the left and right amygdalo-hippocampectomy patients were also combined to form two composite groups. However, because previous evidence has suggested that visuo-spatial recognition memory may be particularly susceptible to damage in the non-dominant hemisphere [22, 29] a supplementary analysis was performed, to look at the possible effects of laterality of lesion in these patient groups. As the pattern of deficits in the temporal lobe and amygdalo-hippocampectomy groups was similar across tasks and because the number of patients in the latter group was small, they were collapsed into a single patient group and then split according to the side of the removal. The left ($N=18$), and right ($N=13$), temporal/amygdalo-hippocampectomy sub-groups were indistinguishable on every single measure of performance across each of the spatial working memory, visuo-spatial memory and learning tasks. For example, visual pattern recognition scores were 78% (left) and 79% (right), whilst corresponding scores in the spatial recognition memory task were 79% and 79%. Across delays, overall matching to sample performance was also equivalent for left (78%)- and right (80%)-sided cases and a similar pattern was found in the paired-associate learning task (memory score = 17.0 and 16.94, respectively). Finally, the groups did not differ in terms of their performance on the spatial working memory test, a pattern similar, in fact, to that reported in much larger groups of temporal lobe and amygdalo-hippocampectomy patients [47].

These results unequivocally suggest that impaired performance on these test of visuo-spatial recognition memory and learning in patients with temporal lobe or amygdalo-hippocampectomy excisions is unrelated to the side of the removal.

Visuo-spatial recognition memory: Comparisons with other neuropsychological tests

The frontal lobe group included in this investigation were drawn from a larger sample of neurosurgical patients with prefrontal excisions who have been studied, in detail, in related papers [42, 44, 46, 47]. It is however, important to consider the deficits observed in the temporal lobe and amygdalo-hippocampectomy groups in terms of their performance on tasks not generally associated with the temporal lobe region. For example, these same patients have been assessed on the computerized version of the Tower of London test of planning [42, 69]. The number of moves (above the minimum) required by the temporal lobe patients to complete the 2, 3, 4 and 5 move Tower of London problems were 0.0(0.0), 0.08(0.04), 1.01(0.19) and 1.33(0.34), respectively. For the amygdalo-hippocampectomy group, the corresponding figures were 0.0(0.0), 0.09(0.02), 1.63(0.24) and 1.84(0.39). In all cases, these scores are similar or better than those of a control group described previously by Owen *et al.* [42] and considerably better than the group of frontal lobe patients, included in that study. Similar patterns were observed for the other measures of performance on the Tower of London task. Thus, initial thinking or "planning" times in the temporal lobe and amygdalo-hippocampectomy groups varied in the range 3.52(1.94)–12.59(2.64) sec and 1.98(0.57)–15.69(2.3) sec, respectively. Like the frontal lobe patients reported by Owen *et al.*, [42], these scores are within the normal range. In terms of subsequent thinking time, which *was* impaired in the frontal lobe group, scores varied in the range 0.96(0.21)–2.03(0.1) sec, for the temporal lobe patients and 0.92(0.31)–2.32(0.13) sec for the amygdalo-hippocampectomy group, which are again, comparable with normal control scores. On a computerized test of short-term spatial span based on the block tapping task devised by Corsi [30], the mean scores for the temporal lobe and amygdalo-hippocampectomy patients included in the present study were 5.72(0.27) and 5.0(0.26), respectively. Again, these scores are within the normal range [42].

DISCUSSION

In this study, three groups of neurosurgical patients with temporal lobe excisions, frontal lobe excisions or unilateral amygdalo-hippocampectomy were assessed on a computerized battery of tasks designed to investigate visuo-spatial short-term recognition memory and learning. Double dissociations were observed between the temporal lobe and amygdalo-hippocampectomy groups and the patients with frontal lobe damage on tests of pattern and spatial recognition memory. Specifically, whilst pattern recognition memory was impaired in the two posterior groups, deficits in spatial recognition memory were only observed in the frontal lobe patients.

Whilst all three patient groups performed accurately in a test of simultaneous matching to sample, both the temporal lobe and amygdalo-hippocampectomy patients were significantly impaired when a short delay was introduced. In contrast, in a test of paired-associate learning, requiring both visual pattern and visuo-spatial memory, impairments of learning and memory were evident in all three patient groups. The performance of the three groups was however, clearly dissociable on a self-ordered searching task designed to assess spatial working memory. Specifically, a highly significant deficit was observed in the frontal lobe group at all levels 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 were only observed in the amygdalo-hippocampectomy and (non-significantly) in the temporal lobe group at the most challenging level of task difficulty and in

neither group could the deficit be related to the inefficient use of any particular searching strategy.

Taken together, these results suggest that tests of pattern recognition memory and delayed matching to sample are more sensitive to deficit in patients with temporal lobe or amygdalo-hippocampectomy damage than in patients with frontal lobe excisions. In contrast, tests of spatial recognition memory and spatial working memory were more affected by frontal lobe damage than by lesions of the temporal lobe structures although spatial working memory deficits were evident in the posterior groups. Finally, visuo-spatial paired associate learning appears to involve contributions from both frontal and temporal lobe regions since the performance of the three patient groups was indistinguishable on this task.

The test of visual pattern recognition memory employed in this study is analogous to the types of serial recognition test used by Gaffan [13] and Mishkin [35] for testing visual memory for lists of objects in non-human primates. In those studies, performance was disrupted by lesions of both the inferotemporal cortex [35] and the structures of the mesial temporal lobe [13, 34, 70]. The present findings concur with these experimental findings and demonstrate that recognition memory for serially presented, complex visual designs may be similarly disrupted by *both* temporal lobe or the selective amygdalo-hippocampectomy in *either* hemisphere. The task also has certain aspects in common with the recurring "nonsense" figures test described by Kimura [22]. In that study, impairments were most evident in a group of neurosurgical patients with right temporal lobe removals although like the current study, no clear differences were found between the left- and right-sided groups. This may be due, at least in part, to the fact that the stimuli used in both studies, although formally visual, are not difficult to label verbally. Thus, both verbal and non-verbal mnemonic mechanisms may contribute to performance on this task. The findings from the test of spatial recognition memory fully concur with recent evidence from positron emission tomography (PET) studies of spatial memory processing in humans (e.g. [20]). In that PET study, subjects were required to remember the location of three dots presented simultaneously on a computer screen for a delay period of 3 sec and then to decide whether or not a probe circle was presented in one of those same three locations. Significant areas of activation were reported in the right prefrontal, occipital, parietal and premotor cortices but not in the temporal or mesial temporal areas. Both of these tasks were similar to paradigms which have been developed recently to examine the neural basis of spatial *working* memory in the primate [11, 12, 15]. Although none of these tasks places the same emphasis on the retention and *manipulation* of spatial material as more traditional tests of spatial working memory (e.g. [48]), they do, nevertheless, require the simultaneous retention of several items of spatial information for a short period of time. It is of some interest therefore, that in the current study, performance on this test of spatial recognition memory correlated significantly with performance on the self-ordered, spatial working memory task among patients with frontal lobe damage. The present findings therefore provide further evidence, implicating the prefrontal cortex in the maintenance of spatial information for short periods of time, and extend research in non-human primates [11, 12, 15, 16, 18, 33].

This double dissociation, between impaired performance on the pattern and spatial recognition memory tasks in temporal/amygdalo-hippocampectomy patients and patients with frontal lobe damage respectively, is interesting given that these two tasks were designed to be closely analogous. One possible interpretation is that the frontal lobe patients are specifically impaired on tasks which require the manipulation of spatial, rather than visual or verbal material. This seems unlikely, however, in view of the many studies which have

demonstrated a significant association between the prefrontal cortex and performance on tests of non-spatial memory (e.g. [54–57]). Task difficulty would not account for the observed double dissociation between the patient groups and is therefore, also unlikely to play a significant role. A more parsimonious explanation for the pattern of deficits observed concerns subtle differences between the two tasks which may have differentially affected the patient groups in ways not directly related to the stimulus modality *per se*. For example, in the pattern recognition memory task, all the stimuli were clearly distinguishable and in this sense, they were truly trial unique. Importantly, dorsolateral prefrontal lesions do not affect recognition memory in primates when trial unique stimuli are used [2, 21, 54]. Although the stimuli used in the spatial recognition task were also formally trial unique, the extent to which they were truly distinguishable was constrained by the physical dimensions of the computer screen upon which they were presented. Given that 40 locations were used over 20 trials (20 correct, 20 incorrect) in this study, it is possible that subjects approached the task as though a smaller number of stimuli were being presented repeatedly across trials. It is precisely on tasks such as this, in which one has to choose from a small set of repeated items, that frontal lobe patients (e.g. [57]) and dorsolateral prefrontal monkeys [54], are impaired.

The simultaneous and delayed matching to sample task adopted in this study was derived directly from paradigms that have been used to define the neural substrates of visual memory in the monkey [35]. The monkey tasks used by Mishkin differed from the present ones largely in their use of objects rather than two-dimensional stimuli and a non-matching rather than a matching rule, but were similar in not including a distractor task during the delay interval and in using trial-unique stimuli. In monkeys, visual recognition and delayed matching (or non-matching) to sample performance has been disrupted by lesions which include damage to the inferotemporal cortex [35, 68], hippocampus, amygdala, various combined lesions of these structures and also of structures they innervate, such as the anterior thalamic nucleus and the mediodorsal nucleus of the thalamus [35]. These deficits, unlike those of the present study, are generally delay-dependent. One possible reason for this apparent discrepancy is that, for human neurosurgical subjects with unilateral removals, longer delays than those employed in the current study (i.e. 12 sec) may be necessary to elicit a delay dependent deficit. There is certainly some, albeit non-significant ($P=0.08$), evidence from Fig. 4, that the impairment in the amygdalo-hippocampectomy group *is* relatively more severe with increasing delay. Delay dependent deficits *have* previously been observed using this task, in patients with mild DAT [65, 67], although the neuropathological changes which characterize this disease are rarely restricted to one or other hemisphere and the concurrent deterioration of intellectual function is rather more severe than that observed in any of the patient groups included in the present study. The fact that deficits in patients with temporal lobe or amygdalo-hippocampectomy damage were *not* evident in the simultaneous matching to sample task, confirms that these impairments are mnemonic rather than perceptual in nature, a view consistent with the conclusions of previous animal and human studies (e.g. [29]). As it is difficult to label the matching to sample patterns, it is also unlikely that an impairment of verbal rehearsal underlies the deficits in the temporal lobe and amygdalo-hippocampectomy groups. It was possible to name the four colours used in each sample although a "colour distractor" was specifically employed to discourage such strategies. In this regard, it is important to note that the proportions of different types of error in the impaired patient groups were not significantly different from those of controls. These results therefore extend the findings from previous primate studies (e.g. [34]) in several ways. First, visuo-spatial recognition memory, assessed using the trial unique, delayed matching to

sample procedure, is sensitive to deficits in patients with temporal lobe damage to either hemisphere. Importantly however, the present study also demonstrates that a similarly striking impairment can be produced in man, by unilateral selective amygdalo-hippocampectomy, a procedure which leaves the overlying cortical structures largely intact [74].

Impairments in matching to sample performance using trial unique stimuli, have also been reported following lesions of orbital and adjacent medial portions of the frontal cortex [2], although, unlike the more posterior lesions, performance is affected, even at short delays [2]. In the present study, no significant deficit in accuracy was observed in the frontal lobe group in either the simultaneous or the delayed matching conditions. However, examination of Fig. 4 clearly suggests some impairment (albeit non-significant) in these patients, although this appears to be largely restricted to the longest, 12-sec delay. There are several possible reasons for this apparent discrepancy. First, it is plausible that for human subjects, unlike primates, 0–4 sec intervals are too brief to elicit the expected deficits at "short" delays. However, this explanation seems unlikely since the temporal lobe group were clearly impaired at these shorter delays. A second possibility, is that whilst all 16 frontal patients had excisions of one, or other, or both frontal lobes, too few had damage to the "critical area" required to elicit the expected deficit. This is an important consideration given that damage to the dorsolateral prefrontal cortex in primates does *not* impair (non) matching-to-sample using trial unique stimuli [2, 12, 54]. In the current study, no clear relationship was observed between the site of excision within the frontal lobe and the precise pattern of impairment observed, although post-operative magnetic resonance imaging in these patients, may help to clarify this issue. An important finding from this group, however, was the disproportionately impaired performance of two of the frontal lobe patients with bilateral removals, in the shortest, 0 sec delay condition. Both subjects scored only 60% correct which, whilst well above chance levels (25%), was substantially lower than any of the three patient groups. This impairment also appears to be relatively specific, since both subjects performed as well, or better, than the unilateral frontal lobe groups, both at longer delays (4 and 12 sec) and in the spatial recognition memory task. One possible interpretation of this finding, is that the relatively specific matching deficits in primates with orbitomedial prefrontal lesions, even at short delays [2], may be contingent upon bilateral frontal lobe damage in these animals.

In the present study, all three patient groups were impaired on a test of paired-associate pattern–location learning. Among control subjects, performance on this task correlated significantly with performance on the tests of pattern *and* spatial recognition memory, confirming that both visual pattern and visuo-spatial memory are required in this more complex, learning task. This pattern of association has, in fact, been confirmed in a much larger ($N > 800$) group of healthy control subjects [64]. However, in the combined amygdalo-hippocampectomy/temporal lobe group, all aspects of performance (i.e. memory and learning) on the paired-associate learning task correlated much more strongly with the pattern recognition memory score than with the spatial recognition memory score. This finding suggests that in these patients, impaired performance on the paired-associate learning task is more likely the result of a more fundamental deficit in pattern recognition memory, rather than spatial recognition memory, a conclusion which is of course, consistent with the pattern of deficits observed in these tasks.

Like control subjects, the frontal lobe group's performance on the paired-associate learning task, correlated more generally with both pattern and spatial recognition memory a finding consistent with the hypothesis of Eacott and Gaffan [7]. However, the learning aspect of this task also has a conditional element, since subjects were required to remember

and then learn associations between up to eight different visual stimuli and particular locations on the screen. Tests of conditional associative learning for stimulus–stimulus relationships are known to be impaired in monkeys [49, 51] and in patients [50, 53] with frontal lobe damage but not in temporal lobe patients unless there is also extensive damage to the hippocampal system. The results of the present study therefore, extend these previous investigations to show that tests which require the formation of associations between visual stimuli and spatial locations are also sensitive to frontal lobe damage. However, there are important procedural differences between the task used in the present study and that developed previously by Petrides [50, 53], which may make the tests differentially sensitive to frontal or temporal lobe damage. For example, the task used by Petrides [50], was self-ordered, in that subjects were required to establish the relationships between stimuli from their own responses, whilst in the present study, the stimulus–location associations were made explicit to the subject from the outset.

The results of the present study also suggest that both the frontal lobe and the medial temporal lobe structures play important roles in spatial *working* memory. In general, spatial working memory deficits are associated, in primates at least, with bilateral damage to the area surrounding the sulcus principalis (e.g. [11, 48]). Importantly, however, it is well established that damage to the hippocampus and related structures 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 [1, 40, 41, 60, 61, 71]. In the present study, the increase in errors among frontal lobe patients was related to the inefficient use of a searching strategy known to improve performance on this task, suggesting deficient organization or "executive" input in this patient group. In contrast, the temporal lobe and amygdalo-hippocampectomy groups showed normal, systematic searching patterns and in the latter group, errors were only made at the most challenging level of task difficulty, possibly suggesting a more fundamental disruption of mnemonic processing in these groups. 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 [15, 57].

In the present study, no consistent relationship was found between the pattern of cognitive deficits and laterality of excisions in any of the patient groups although, in certain tasks, 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. These results concur in a general sense, with recent PET studies by Petrides *et al.* [55, 56]. In those investigations, significant increases in regional cerebral blood flow were observed bilaterally using both visual and verbal memory tasks. With respect to the more posterior lesion groups, the present results suggest that deficits in tests of short-term visuo-spatial recognition memory and learning may not be as closely associated with damage to one or other hemisphere as other, more traditional, tests of mnemonic function [19, 30, 31]. Alternatively, it is important to emphasize that patients with temporal lobe epilepsy often have tissue removed which may have been dysfunctional presurgically. Thus, in these subjects, the contralateral hemisphere may have come to subserve functions normally mediated by the damaged hemisphere in the normal brain. Accordingly, unilateral resection for epilepsy, as was the case for all subjects in the temporal lobe and amygdalo-hippocampectomy groups, may fail to produce asymmetric memory failures because these patients have come to develop unilateral memory systems in the intact hemisphere which are bilaterally distributed in healthy subjects. In future, this question may be resolved, at least in part, by further functional imaging studies which

utilize techniques such as PET and functional magnetic resonance imaging (fMRI) to identify specific patterns of increased blood flow which are associated with particular cognitive functions in normal control subjects.

In summary, this study has demonstrated that the performance of patients with frontal lobe damage and patients with excisions of the temporal lobe/medial temporal lobe structures may be clearly dissociated on a novel battery of tests of spatial working memory, visual–spatial recognition memory and learning. These tests are based directly on a number of existing neuropsychological paradigms commonly used to assess cognitive dysfunction in non-human primates (e.g. [2, 13, 35, 48]) with selective neurochemical or neuroanatomical lesions and the results are broadly consistent with the findings from those experimental studies. Among the frontal lobe patients, deficits were most profound in those tests which required the active manipulation of information within memory or the formation and recall of associations between spatial and visual representations, a pattern consistent with previous studies of identical or similar groups of patients (e.g. [57], see also [42, 44, 46, 47]). It is also important to consider the deficits observed in the temporal lobe and amygdalo-hippocampectomy groups in this study, in terms of their performance on other tasks which do not require recognition memory and learning. For example, the same two groups of patients included in the present investigation, perform at least as well as controls on a test of attentional set-shifting which is extremely sensitive to deficit in the frontal lobe group [44]. Similarly, the same patients have been assessed on a computerized version of the Tower of London test of planning [42, 69]. Unlike the frontal lobe group who show deficits in both accuracy and latency of planning, the temporal lobe and amygdalo-hippocampectomy patients are completely unimpaired (see results section). The requirements of the Tower of London task are considerably more complex than either of the tests of pattern recognition memory used in the present study. This dissociation clearly demonstrates then, that the deficits observed among temporal lobe and amygdalo-hippocampectomy patients on test of visual pattern recognition memory, delayed matching to sample and paired-associate learning have a considerable degree of psychological specificity.

The results of this study are also particularly relevant to recent work on the progression of cognitive deficits in patients with PD [45, 45] and DAT [65, 67]. For example, in medicated and non-medicated patients in the early stages of PD, performance on the same tests of pattern and spatial recognition memory employed in the present study, is unaffected, whilst impairments are observed in patients with more severe clinical symptoms [45; see also 23, 65]. Similarly, whilst all three patient groups performed well in a separate test of simultaneous visual matching to sample, medicated patients with severe clinical symptoms were significantly impaired when a 0–12 sec delay was introduced. In contrast, in the test of spatial *working* memory, significant impairments were found in both groups of medicated PD patients and a non-significant trend toward impairment was also observed in the non-medicated group. The results of the present study therefore suggest, that the late emergence of deficits in delayed matching to sample and pattern recognition memory in PD, may reflect a relative sparing of functions associated with temporal lobe structures, early in the course of the disease. This sparing contrasts markedly with the susceptibility of these same PD patients to tasks sensitive to frontal, but not temporal, lobe damage [43, 47].

Patients with both mild [65, 67] and moderate [67] DAT have also been tested on this same battery of tests of visuo-spatial recognition memory and learning. Unlike the patients with PD, profound deficits in recognition memory functions were observed, even in the earliest stages of the disease. In stark contrast, these same patients with mild DAT are

unimpaired on the frontal lobe test of attentional set-shifting [66] which has proved to be so sensitive to early PD [6, 43, 46)]. The present findings allow us therefore, to interpret previously reported deficits in patients with PD and DAT more precisely, in terms of characteristic patterns of neuropsychological degeneration. Thus, in PD, the relative sparing of pattern recognition compared to spatial recognition suggests that in these patients, cognitive deficits emerge and subsequently progress according to a defined sequence, beginning with "frontal" type deficits and only later including more posterior cortical functions [43, 45]. Moreover, the marked susceptibility of patients with DAT to delayed matching to sample deficits is clearly consistent with the typical progression of regional neuropathological signs in the cortex of these patients [17, 73].

Acknowledgements—This research was supported by a Programme Grant from the Wellcome Trust to T. W. Robbins, B. J. Everitt and B. J. Sahakian. We thank Prof. P. Rabbitt for allowing us access to control subjects drawn from the North East Age Research panel at Newcastle University and Ms. J. Iddon for her invaluable assistance with data extraction. Drs J. Doyon, V. Sziklas and M. Petrides are also thanked for critically appraising earlier versions of this manuscript.

REFERENCES

1. Aggleton, J. P., Hunt, P. R. and Rawlins, J. N. P. The effects of hippocampal lesions upon spatial and non-spatial tests of working memory. *Behav. Brain Res.* **19,** 133–146, 1986.
2. Bachevalier, J. and Mishkin, M. Visual recognition impairment following ventromedial, but not dorsolateral, prefrontal lesions in monkeys. *Behav. Brain Res.* **20,** 249–261, 1986.
3. Corkin, S. Some relationships between global amnesias and the memory impairments in Alzheimer's disease. In *Alzheimer's Disease: A Report of Progress in Research*, Aging, Vol. 19, S. Corkin, K. L. Davis, J. H. Growdon, E. Usdin and R. J. Wurtman (Editors), pp. 149–164. Raven Press, New York, 1982.
4. Corkin, S., Growdon, J. H., Nissen, M. J., Huff, F. J., Freed, D. M. and Sagar, H. J. Recent advances in the neuropsychological study of Alzheimer's disease. In *Alzheimer's Disease: Advances in Basic Research and Therapies*, R. J. Wurtman, S. H. Corkin and J. H. Growdon (Editors), pp.75–93. Centre for Brain Sciences and Metabolism Charitable Trust, Cambridge, MA, 1984.
5. Cowey, A. and Gross, C. G. Effects of foveal prestriate and inferotemporal lesions on visual discrimination by rhesus monkeys. *Exp. Brain Res.* **11,** 128–144, 1970.
6. Downes, J. J., Roberts, A. C., Sahakian, B. J., Evenden, J. L., Morris, R. G. and Robbins, T. W. Impaired extra-dimensional shift performance in medicated and unmedicated Parkinson's disease: Evidence for a specific attentional dysfunction. *Neuropsychologia* **27,** 1329–1343, 1989.
7. Eacott, M. J. and Gaffan, D. Inferotemporal–frontal disconnection: The uncinate fascicle and visual associative learning in monkeys. *Eur. J. Neurosci.* **4,** 1320–1332, 1992.
8. Falconer, M. A. Anterior temporal lobectomy for epilepsy. In *Operative Surgery*, Vol. 14, Neurosurgery, V. Logue (Editor), pp. 142–149. Butterworths, London, 1971.
9. Flowers, K. A. Pearce, I. and Pearce, J. M. S. Recognition memory in Parkinson's disease. *J. Neurol. Neurosurg. Psychiat.* **47,** 1174–1181, 1984.
10. Freedman, M., Oscar-Berman, M. Selective delayed response deficit in Alzheimer's disease and Parkinson's disease. *Archs Neurol.* **43,** 886–890, 1986.
11. Funahashi, S., Bruce, C. J. and Goldman-Rakic, P. S. Mnemonic coding of visual space in the monkey's dorsolateral prefrontal cortex. *J. Neurophysiol.* **61,** 1–19, 1989.
12. Funahashi, S., Bruce, C. J. and Goldman-Rakic, P. S. Visuospatial coding of primate prefrontal neurons revealed by oculomotor paradigms. *J. Neurophysiol.* **63** (4), 814–831, 1990.
13. Gaffan, D. Recognition impaired and association intact in the memory of monkeys after transection of the fornix. *J. comp. Physiol. Psychol.* **86,** 1100–1109, 1974.
14. Garron, D. C., Klawans, H. L. and Narin, F. Intellectual functioning of persons with idiopathic Parkinsonism. *J. Nerve. Mental Dis.* **154,** 445–452, 1972.
15. Goldman-Rakic, P. S. Cellular and circuit basis of working memory in prefrontal cortex of nonhuman primates. In *Progress in Brain Research*, Vol. 85, H. B. M. Uylings, C. G. Van Eden, J. P. C. De Bruin, M. A. Corner and M. G. P. Feenstra (Editors), pp. 325–336. Elsevier Science Publishers B.V. (Biomedical Division), 1990.

16. Gross, C. G. and Weiskrantz. Evidence for dissociation of impairment on auditory discrimination and delayed response following lateral frontal lesions in monkeys. *Exp. Neurol.* **5,** 453–476, 1962.
17. Haxby, J. V., Grady, C. L., Koss, E., Horwitz, B., Schapiro, M., Friedland, R. P. and Rapoport, S. I. Heterogenous anterior–posterior metabolic patterns in dementia of the Alzheimer type. *J. clin. exp. Neuropsychol.* **10,** 576—596, 1988.
18. Jacobsen, C. F. Studies of cerebral function in primates. I. The functions of the frontal association areas in monkeys. *Comp. Psychol. Monog.* **13,** 1–60, 1936.
19. Jones-Gotman, M., Smith, M. L. and Zatorre, R. J. Neuropsychological testing for localizing and lateralizing the epileptogenic region. In *Surgical Treatment of the Epilepsies*, J. Engel, Jr, (Editor), pp. 245–261. Raven Press, New York, 1993.
20. Jonides, J., Smith, E. E., Koeppe, R. A., Awh, E., Minoshima, S., Mintun, M. A. Spatial working memory in humans as revealed by PET. *Science* **363,** 623–625, 1993.
21. Kowalska, D. M., Bachevalier, J. and Mishkin, M. The role of the inferior prefrontal convexity in performance of delayed nonmatching-to-sample. *Neuropsychologia* **29,** 583–600, 1991.
22. Kimura, D. Right temporal-lobe damage. *Arch. Neurol.* **8,** 264–271, 1963.
23. Lange, K. W., Robbins, T. W., Marsden, C. D., James, M., Owen, A. M. and Paul, G. M. L-Dopa withdrawal in Parkinson's disease selectively impairs cognitive performance in tests sensitive to frontal lobe dysfunction. *Psychopharmacology* **107,** 394–404, 1992.
24. Lees, A. J. and Smith, E. Cognitive deficits in the early stages of Parkinson's disease. *Brain* **106,** 257–270, 1983.
25. Loranger, A. W., Goodell, H., McDowell, F. H., Lee, J. E. and Sweet, R. D. Intellectual impairment in Parkinson's syndrome. *Brain* **95,** 405–412, 1972.
26. McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D. and Satdlan, E. M. Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. *Neurology, Cleveland,* **34,** 939–944, 1984.
27. Meyer, V. and Yates, H. J. Intellectual changes following temporal lobectomy for psychomotor epilepsy. *J. Neurol. Neurosurg. Psychiat.* **18,** 44–52, 1955.
28. Milner, B. Psychological defects produced by temporal-lobe excision. *Res. Publ. Ass. Res. Nerv. Ment. Dis.* **36,** 244–257, 1958.
29. Milner, B. Visual recognition and recall after right temporal-excision in man. *Neuropsychologia* **6,** 191–209, 1968.
30. Milner, B. Interhemispheric differences and psychological processes. *Br. Med. Bull.* **27,** 272–277, 1971.
31. Milner, B. Hemispheric specialization: Scope and limits. In *The Neurosciences: Third Study Program*, F. O. Schmitt and F. G. Worden (Editors), pp. 75–89. MIT Press, Cambridge, MA, 1974.
32. Mishkin, M. Visual discrimination performance following partial ablations of the temporal lobe: II. Ventral surface versus hippocampus. *J. comp. Physiol. Psychol.* **47,** 187–193, 1954.
33. Mishkin, M. Effects of small frontal lesions on delayed alternation in monkeys. *J. Neurophysiol.* **20,** 615–622, 1957.
34. Mishkin, M. Memory in monkeys severely impaired by combined but not by separate removals of amygdala and hippocampus. *Nature (Lond.)* **273,** 297–298, 1978.
35. Mishkin, M. A memory system in the monkey. *Phil. Trans. R. Soc. Lond. B,* **298,** 85–95, 1982.
36. Mishkin, M. and Pribram, K. H. Visual discrimination performance following partial ablations of the temporal lobe: I. Ventral versus lateral. *J. comp. Physiol. Psychol.* **47,** 14–20, 1954.
37. Morris, R. G. and Kopelman, M. D. The memory deficits in Alzheimer-type dementia: A review. *Q. J. exp. Psychol.* **38a,** 575–602, 1986.
38. Mortimer, J. A., Pirozzolo, F. J., Hansch, E. C., Webster, D. D. Relationship of motor symptoms to intellectual deficits in Parkinson's disease. *Neurology* **32,** 133–137, 1982.
39. Nelson, H. E. *National Adult Reading Test (NART) Test Manual.* NFER-Nelson, Windsor, 1982.
40. Olton, D. S. and Papas, B. C. Spatial memory and hippocampal function. *Neuropsychologia* **17,** 669–682, 1979.
41. Olton, D. S., Walker, J. A. and Gage, F. H. Hippocampal connections and spatial discrimination. *Brain Res.* **139,** 295–308, 1978.
42. Owen, A. M., Downes, J. D., Sahakian, B. J., Polkey, C. E. and Robbins, T. W. Planning and spatial working memory following frontal lobe lesions in man. *Neuropsychologia* **28,** 1021–1034, 1990.
43. Owen, A. M., James, M., Leigh, P. N., Summers, B. A., Marsden, C. D., Quinn, N. P., Lange, K. W. and Robbins, T. W. Progression of fronto-striatal cognitive deficits in Parkinson's disease. *Brain* **115,** 1727–1751, 1992.
44. Owen, A. M., Roberts, A. C., Polkey, C. E., Sahakian, B. J. and Robbins, T. W. Extra-dimensional versus intra-dimensional set shifting performance following frontal lobe excisions, temporal lobe excisions or amygdalo-hippocampectomy in man. *Neuropsychologia* **29,** 993–1006, 1991.
45. Owen, A. M., Beksinska, M., James, M., Leigh, P. N., Summers, B. A., Marsden, C. D., Quinn, N. P., Sahakian, B. J. and Robbins, T. W. Visuo-spatial memory deficits at different stages of Parkinson's disease. *Neuropsychologia* **31,** 627–644, 1993a.
46. Owen, A. M., Roberts, A. C., Hodges, J. R., Summers, B. A., Polkey, C. E. and Robbins, T. W. Contrasting

mechanisms of impaired attentional set-shifting in patients with frontal lobe damage or Parkinson's disease. *Brain* **116,** 1159–1179, 1993b.

47. Owen, A. M., Morris, R. G., Sahakian, B. J., Polkey, C. E. and Robbins, T. W. Double dissociations of memory and executive functions in working memory tasks following frontal lobe excisions, temporal lobe excisions or amygdalo-hippocampectomy in man. Submitted for publication.
48. Passingham, R. E. Memory of monkeys (*Macaca mulatta*) with lesions in prefrontal cortex. *Behav. Neurosci.* **99,** 3–21, 1985.
49. Petrides, M. Motor conditional associative learning after selective prefrontal lesions in the monkey. *Behav. Brain Res.* **5,** 407–413, 1982.
50. Petrides, M. Deficits on conditional associative-learning tasks after frontal and temporal-lobe lesions in man. *Neuropsychologia* **23,** 601–614, 1985a.
51. Petrides, M. Deficits in non-spatial conditional associative learning after periarcuate lesions in the monkey. *Behav. Brain Res.* **16,** 95–101, 1985b.
52. Petrides, M. Frontal lobes and memory. In *Handbook of Neuropsychology*, Vol. 3, F. Boller and J. Grafman (Editors), pp. 75–90, 1989.
53. Petrides, M. Nonspatial conditional learning impaired in patients with unilateral frontal but not unilateral temporal lobe excisions. *Neuropsychologia* **28,** 137–149, 1990.
54. Petrides, M. Monitoring of selections of visual stimuli and the primate frontal cortex. *Proc. R. Soc. Lond. B* **246,** 293–298, 1991.
55. Petrides, M., Alivisatos, B., Evans, A. C. and Meyer, E. Dissociation of human mid-dorsolateral from posterior dorsolateral frontal cortex in memory processing. *Proc. natl Acad. Sci. U.S.A.* **90,** 873–877, 1993a.
56. Petrides, M., Alivisatos, B., Evans, A. C. and Meyer, E. Functional activation of the human frontal cortex during the performance of verbal working memory tasks. *Proc. natl Acad. Sci. U.S.A.* **90,** 878–882, 1993b.
57. Petrides, M., and Milner, B. Deficits on subject-ordered tasks after frontal- and temporal-lobe lesions in man. *Neuropsychologia* **20,** 249–262, 1982.
58. Piggott, S. and Milner, B. Memory for different aspects of visual scenes after unilateral temporal- or frontal-lobe resection. *Neuropsychologia* **31,** 1–15, 1993.
59. Pirozzolo, F. J., Hansch, E. C., Mortimer, J. A., Webster, D. D. and Kuskowski, M. A. Dementia in Parkinson's disease. A neuropsychological analysis. *Brain Cognit.* **1,** 71–83, 1982.
60. Rawlins, J. N. P. and Olton, D. S. The septo-hippocampal system and cognitive mapping. *Behav. Brain Res.* **5,** 331–358, 1982.
61. Rawlins, J. N. P. and Tsaltas, E. The hippocampus, time and working memory. *Behav. Brain Res.* **10,** 233–262, 1983.
62. Reitan, R. M. and Boll, T. J. Intellectual and cognitive functions in Parkinson's disease. *J. consult. clin. Psychol.* **37,** 364–369, 1971.
63. Riklan, M., Whelihan, W. and Cullinan, T. Levodopa and psychometric test performance in Parkinsonism—Five years later. *Neurology* **26,** 173–179, 1976.
64. Robbins, T. W., James, M., Owen, A. M., Sahakian, B. J., McInnes, L. and Rabbitt, P. M. Cambridge Neuropsychological Test Automated Battery (CANTAB): A factor analytic study of a large sample of normal elderly volunteers. *Dementia*, in press.
65. Sahakian, B. J., Morris, R. G., Evenden, J. L., Heald, A., Levy, R., Philpot, M. P. and Robbins, T. W. A comparative study of visuospatial memory and learning in Alzheimer-type dementia and Parkinson's disease. *Brain* **111,** 695–718, 1988.
66. Sahakian, B. J., Downes, J. J., Eagger, S., Evenden, J. L., Levy, R., Philpot, M. P., Roberts, A. C. and Robbins, T. W. Sparing of attentional relative to mnemonic function in a subgroup of patients with dementia of the Alzheimer type. *Neuropsychologia* **28,** 1197–1213, 1990.
67. Sahgal, A., Sahakian, B. J., Robbins, T. W., Wray, C. J., Lloyd, S., Cook, J. H., McKeith, I. G., Disley, J. C. A., Eagger, S., Boddington, S. and Edwardson, J. A. Detection of visual memory and learning deficits in Alzheimer's disease using the Cambridge Neuropsychological Test Automated Battery. *Dementia* **2,** 150–158, 1991.
68. Sahgal, A. and Iversen, S. D. Categorisation and retrieval after selective inferotemporal lesions in monkeys. *Brain Res. Amsterdam,* **146,** 341–350, 1978.
69. Shallice, T. Specific impairments of planning. *Phil. Trans. R. Soc. Lond. B.* **298,** 199–209, 1982.
70. Squire, L. R. and Zola-Morgan, S. The medial temporal lobe memory system. *Science* **253** (5026), 1380–1386, 1991.
71. Sziklas, V. and Petrides, M. Memory impairments following lesions to the mamillary region of the rat. *Eur. J. Neurosci.* **5,** 525–540, 1993.
72. Taylor, A. E., Saint-Cyr, J. A. and Lang, A. E. Memory and learning in early Parkinson's disease: "Evidence for a frontal lobe syndrome". *Brain Cognit.* **13,** 211–232, 1990.
73. Tomlinson, B. E. The pathology of Alzheimer's disease and senile dementia of Alzheimer type. In *Handbook of*

Studies on Psychiatry and Old Age, D. W. K. Kay and G. Burrows (Editors), pp. 89–117. Elsevier, Amsterdam, 1984.

74. Yasargil, M. G., Teddy, P. J. and Roth, P. Selective Amygdalo-hippocampectomy. Operative anatomy and surgical technique. In *Advances and Technical Standards in Neurosurgery*, L. Symon (Editor). Vol. 12, pp. 553–572. Springer, Vienna, 1985.