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Some cognitive effects of frontal-lobe lesions in man

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The study of patients undergoing unilateral frontal-lobe excisions for the relief of focal epilepsy has revealed specific cognitive disorders that appear against a background of normal functioning on many intellectual, perceptual and memory tasks. Lesions that invade the frontal eye field cause subtle impairments of voluntary oculomotor control, which reveal themselves as an inability to suppress an initial glance at a potentially distracting stimulus. After frontal lobectomy in either hemisphere, deficits are found quite consistently on motor-differentiation tasks (Konorski 1972) in which the subject must learn to produce different responses to different, randomly presented, environmental signals. More directly related to the concept of planning are those sequential tasks in which the subject is free to choose his own order of responding, but must not make the same response twice. Here the left frontal lobe plays the major role, a finding consistent with the notion of left-hemisphere dominance for the programming of voluntary actions. In contrast, the right frontal lobe appears to be more critically involved in monitoring the temporal sequence of externally ordered events, although the verbal or non-verbal nature of the stimuli remains a relevant factor.

1. Introduction

The findings reported here derive from the study of young adult patients at the Montreal Neurological Hospital who had undergone unilateral frontal-lobe excisions of varying locus and extent for the relief of focal epilepsy. All patients were left-hemisphere dominant for speech, although not all were right-handed. Figure 1 shows the estimated lateral extent of removal in some representative cases; it will be noted that some removals (J.Mo., E.Yo.) were limited to the posterior dorsolateral frontal cortex, whereas others (T.Ca., A.Dr.) were close to being complete frontal lobectomies. Because the removals from the left hemisphere always spared the speech area of Broca, these removals tended to be slightly smaller than those from the right but there was considerable overlap between the groups in this respect.

For each experiment to be reported, the performance of patients with frontal-lobe lesions was compared with that of patients with lesions of similar aetiology who had undergone a left or right anterior temporal lobectomy, as well as with that of an appropriately matched normal control group. Since the experiments spanned a number of years, the precise make-up of the frontal-lobe groups varied somewhat from task to task, but there were no instances of removals limited to the orbital surface.

The cortical excisions depicted in figure 1 have little effect on intelligence as measured by standard tests (Hebb 1945; Milner 1964, 1975; Teuber 1964; Zangwill 1966); nor do they often cause perceptual and memory deficits of the kind seen in our patients with temporal-lobe lesions (Milner 1968, 1975, 1980). Nevertheless, over the years we have observed losses on a number of tasks (Milner 1964; Jones-Gotman & Milner 1977; Kolb & Milner 1981; Guitton et al. 1982; Petrides & Milner 1982), some of which appear pertinent to the topic of this session.

I shall begin by discussing the effects of unilateral frontal eye-field lesions on the voluntary control of saccadic eye movements and then go on to describe recent work by Petrides dealing with the regulation of responses by environmental cues. The final section discusses disturbances in the temporal organization of behaviour.

2. VOLUNTARY CONTROL OF SACCADIC EYE MOVEMENTS AFTER UNILATERAL FRONTAL-LOBE EXCISIONS

It has been known for over a century that the primate frontal cortex contains an area, the frontal eye field, where electrical stimulation elicits conjugate eye movements directed towards the contralateral visual field (see, for example, Ferrier 1874; Robinson & Fuchs 1969), and

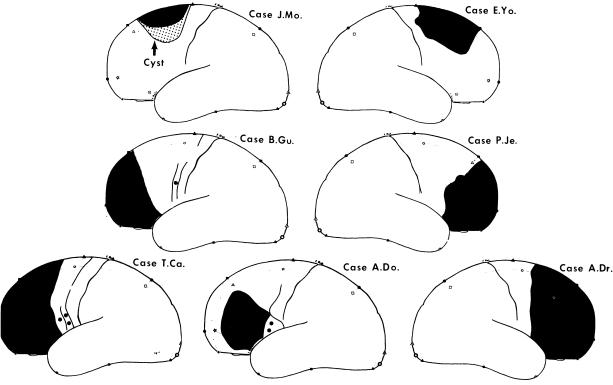


FIGURE 1. Diagrams, based on the surgeon's drawings at the time of operation, showing the estimated lateral extent of cortical excision in seven representative cases of unilateral frontal lobectomy. Dots indicate points at which electrical stimulation of the exposed cortex interfered with speech.

where ablation provokes a transient contralateral neglect associated with ipsilateral deviation of the eyes and head (see, for example, Bianchi 1895; Kennard & Ectors 1938; Welch & Stuteville 1958; Brucher 1966; Latto & Cowey 1971 a; Crowne et al. 1981). In man, this area, as mapped out by cortical stimulation in waking patients (Foerster 1931; Rasmussen & Penfield 1948), appears to lie just rostral to the motor cortex, at the junction of the representation of face and hand; in the monkey, it is found in the prearcuate region, corresponding to Brodmann's area 8 (see Barbas & Mesulam (1981) for a more detailed review).

There is now good evidence that the frontal eye fields of the monkey are normally involved in the coordination of vision and eye movement and in the generation of saccades, although the

area can be removed bilaterally with only mild residual oculomotor deficits (Latto & Cowey 1971 a, b). Schiller et al. (1980) have shown that monkeys with combined destruction of the frontal eye fields and the superior colliculus of the midbrain no longer make visually guided saccades outside a limited central range, the effect of the combined lesions being far more serious than that produced by either lesion alone. The experiments described below were designed to explore further the role of the frontal eye field in man.

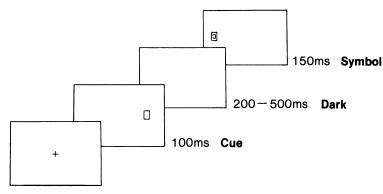


FIGURE 2. Diagrammatic representation of the anti-saccade task (Guitton et al. 1982). The subject faces a cathoderay oscilloscope on which there is a central fixation point (f.p.). After a short random time, the f.p. is extinguished and a stimulus cue appears for 100 ms randomly either 12° to the left or 12° to the right. The subject must not look in the direction of the cue but in the opposite direction, an equal distance from f.p., where a symbol (a square with a gap in it) will shortly appear. His task is to indicate with his thumb the direction of the gap. Task difficulty is increased by decreasing the interval between cue and symbol, from 500 ms down to 200 ms. Eye movements are monitored throughout by electro-oculography.

Guitton et al. (1982) have recently examined the ability of patients with unilateral frontal-lobe or temporal-lobe lesions to make voluntary saccadic eye movements towards or away from briefly appearing targets presented at random to right or left of fixation. In their procedure (Hallett 1978; Hallett & Adams 1980), the subject sits facing a cathode-ray oscilloscope on which a central fixation point is displayed; after a variable time interval, the fixation point is extinguished and a stimulus cue is exposed for 100 ms at 12° to the right or left of it. In the standard saccade task, the subject merely has to look towards the location of the cue. Under these conditions, both groups of patients, when tested as early as 14 days post-operatively, responded with normal accuracy and latency even to cues appearing in the field contralateral to the lesion. This is consistent with the observations of Latto & Cowey (1971a) for frontal eye-field lesions in the monkey.

The anti-saccade task, which was more demanding, is illustrated in figure 2. In this case, the subject is instructed to look away from the cue towards the corresponding position in the opposite visual field, so as to be able to report the position of a gap in a small square that will appear there briefly some 200 ms later. On this task, patients with frontal-lobe lesions had more difficulty than normal subjects in inhibiting a short-latency initial response towards the cue. This tendency was particularly marked in those patients whose excisions appeared to encroach upon the frontal eye field, and in these cases the loss of inhibition was equally apparent in both visual fields. Frontal-lobe removals that appeared to spare the eye-field region produced milder deficits; in general, such patients had difficulty in suppressing a reflex-like saccade to the cue when that cue appeared in the visual field contralateral to their lesion, and this difficulty could

be overcome by increasing the intra-trial interval from 200 to 500 ms (which was not true for the patients with eye-field lesions).

On the anti-saccade task, normal subjects (and patients with temporal-lobe lesions) failed to inhibit a short-latency response towards the cue in about 20 % of the trials; this initial saccade would then be followed by a large corrective saccade towards the location at which the target symbol was to appear. In contrast, patients with frontal eye-field lesions had difficulty in executing corrective responses generated by the damaged hemisphere (i.e. following an initial saccade to a cue in the field ipsilateral to the lesion). When the initial saccade was made towards a stimulus in the contralateral field, the corrective saccade was executed normally.

The difficulty experienced by patients with frontal eye-field lesions in suppressing an initial saccade to the cue, as well as their difficulty in generating corrective movements from the damaged hemisphere, point to the importance of this cortical region for certain aspects of oculomotor control (cf. Holmes 1938). This result could not have been predicted from earlier neurophysiological studies in the monkey (Bizzi 1968; Bizzi & Schiller 1970), which revealed cells in the frontal eye field that discharged during and after the performance of spontaneous saccades but not before a movement was made. The present findings are, however, concordant with the results of more recent unit-recording experiments in behaving animals that demonstrate the presence of visually triggered neurons whose firing is enhanced before the onset of a saccade (Wurtz & Mohler 1976; Goldberg & Bushnell 1981), and particularly with the further suggestion that the critical signal from the frontal eye fields is not the retinal location of a target but rather the movement that the target will evoke (Goldberg & Bruce 1981).

3. Performance on conditional associative-learning tasks after frontal lobectomy

Research on the effects of frontal-lobe lesions in animals has shown that the frontal cortex plays an important role in the control of a class of behaviour in which arbitrary stimuli become signals for the production of responses that bear no natural relation to those signals. Thus, there is by now considerable evidence from experiments both in dogs (Lawicka 1969; Dabrowska 1972) and monkeys (Gross & Weiskrantz 1962; Goldman & Rosvold 1970; Stamm 1973; Lawicka et al. 1975; Milner et al. 1978) that certain frontal-lobe lesions impair performance on conditional learning tasks (termed motor-act differentiation tasks by Konorski 1972) in which the animal is required to make response A to stimulus X and response B to stimulus Y. In the monkey the critical area appears to be the periarcuate region.

These tasks have frequently involved directional responses to spatial cues, as in Goldman & Rosvold's study in which monkeys had to learn to go to the left food-well in response to a sound from above and to the right food-well in response to a sound from below. In such cases the deficits have tended to be interpreted in terms of an underlying spatial disorder (Mishkin 1964; Goldman & Rosvold 1970); yet impairments have also been found on non-spatial conditional-learning tasks (Gross & Weiskrantz 1962; Dabrowska 1972), and it may be that we are dealing with a more general difficulty in response selection, although the critical cortical field could differ depending on the specific task (Konorski 1972).

There appears to be an interesting parallel between the behavioural deficits shown by animals on conditional learning tasks and the frequently reported failure of patients with massive frontal-lobe lesions to regulate their behaviour by external stimuli. In such cases, not only

social cues (which may be misinterpreted) but explicit signals and instructions may fail to guide the patient's responses, even though he can be shown to have registered them (Milner 1964; Luria 1969, 1973). Thus, Luria & Homskaya (1964) describe patients with massive frontal-lobe tumours who could not be trained to respond consistently with the left hand to a green light and the right hand to a red light, although they could repeat the instructions

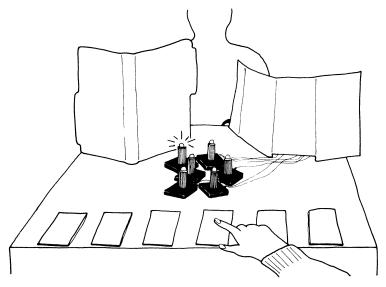


FIGURE 3. Sketch of apparatus used by Petrides to test spatial conditional associative-learning. The stimuli are presented by means of six identical blue lamps, randomly grouped together. When one of these lights up, the subject must respond by touching a particular one of the six identical response cards arranged horizontally in front of him.

correctly and knew which hand was which. Such observations have led Petrides to construct two new conditional associative learning tasks (one spatial, the other not) in order to look for possible deficits in patients who have undergone a frontal lobectomy. His findings are described below.

(a) Spatial conditional associative-learning

In this task (figure 3) the stimuli are presented by means of six identical small blue lamps grouped closely together in irregular array. Each of these lamps had been arbitrarily paired with one of six identical white cards arranged horizontally in front of the subject. At the beginning of each trial one of the lamps lights up and the subject must then touch one card after another, in any order, until he discovers the correct one. After each response he is told whether or not the response was correct and when he touches the correct card the light is extinguished. A different lamp then lights up to initiate the next trial. Testing is continued until the subject achieves a criterion of 18 consecutive correct responses or until 180 trials have been completed. The order of presentation of the stimuli is randomized within each set of six trials.

Figure 4 shows the mean error scores for normal control subjects and for patients grouped according to side and site of cortical excision. Here and in subsequent figures, the left and right temporal-lobe groups have been further subdivided according to whether or not the hippocampus or the parahippocampal gyrus, or both, had been radically excised in the temporal lobectomy. It can be seen that both frontal-lobe groups were impaired and there was no

significant difference between them in terms of error score. The results for the temporal-lobe groups were quite striking: whereas the two left temporal-lobe groups and the right temporal-lobe group with small hippocampal excisions performed as well as normal subjects, the right temporal-lobe group with extensive removal of the hippocampus was as severely impaired as the frontal-lobe groups. The latter finding is consistent with many previous studies demonstrating the importance of the right hippocampal region for spatial learning and spatial memory (Corkin 1965; Milner 1965; Corsi 1972; Smith & Milner 1981).

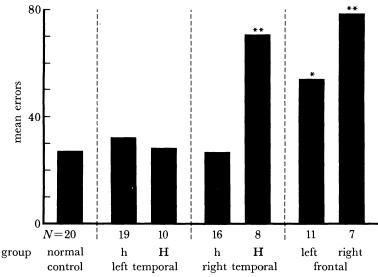


FIGURE 4. Spatial associative learning task: histograms showing mean error scores for normal control group and for patients grouped according to side and site of lesion (h, small hippocampal removal; H, large hippocampal removal). The right temporal-lobe group with extensive hippocampal excision and both frontal-lobe groups were significantly impaired: *, p < 0.025; **, p < 0.001.

(b) Non-spatial conditional associative-learning

In this task, the subject is first taught to reproduce from memory a set of six different hand postures (hand flat, palm down; hand flat, palm up; hand flat, palm vertical, facing inwards; fist perpendicular to table; fist with palm upwards; first with index finger extended and palm downwards). Every subject tested has been able to do this reliably within a few trials, after which he is shown six differently coloured light-caps and told that each one is associated with one particular hand-posture, the task being to learn which response to make to each colour. The six caps remain in view throughout, and at the beginning of each trial one of them is pushed forward and the subject must discover by trial-and-error which hand-posture to produce. The testing procedure and criterion of learning are the same as those used on the spatial task.

Figure 5 shows the mean error scores for the normal control group and the various patient groups. Again we find a marked impairment in both frontal-lobe groups but no significant difference between them. The results for the temporal-lobe groups differ from those obtained on the spatial task, since this time it was the group with extensive left hippocampal removals that was impaired, not the group with right. This finding probably reflects a strong verbal-memory component in the task (Corsi 1972; Milner 1974; Read 1981), since most subjects

tended to verbalize the associations between colours and hand postures, whereas such a tactic was rarely used on the spatial task. The further possibility that the deficit seen after left hippocampal lesions reflects the dominance of the left posterior cortex for the control of hand postures cannot, however, be ruled out (Liepmann 1908; Kimura & Archibald 1974; Seltzer & Van Hoesen 1979).

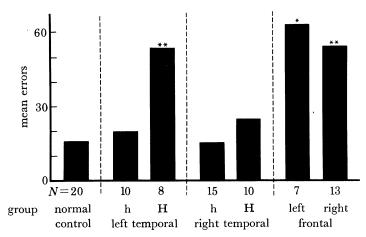


FIGURE 5. Non-spatial conditional associative-learning task (colours to hand-postures): histograms showing mean error scores for normal control subjects and for the various groups of patients. The left temporal-lobe group with extensive hippocampal excision was impaired as well as the two frontal-lobe groups: *, p < 0.01; **, p < 0.001.

The deficits shown by patients with frontal-lobe lesions on both the spatial and nonspatial conditional learning tasks argue against Luria's notion of a selective impairment in the verbal regulation of behaviour and in favour of a more general deficit in the utilization of external cues to guide responses (Milner 1964; Drewe 1975). They also provide yet another example of convergent findings for monkey and man.

4. FRONTAL LOBES AND THE TEMPORAL ORGANIZATION OF BEHAVIOUR

Disturbances in the selection and execution of cognitive plans have frequently been cited as being among the most characteristic manifestations of frontal-lobe disease (see, for example, Luria 1969, 1973; Shallice & Evans 1978; Fuster 1980). In such cases, the ability to perform the individual actions that make up the sequence is usually preserved but the overall temporal organization is lost, with the result that some actions may be performed in the wrong order, or even omitted altogether. Thus in the well known case of right frontal-lobe tumour described by Penfield & Evans (1935), the patient, an experienced housewife, became unable to plan and prepare a simple meal for her family, although she had not forgotten how to cook any of the individual dishes. Similar disturbances in the temporal organization of behaviour have been observed after frontal-lobe lesions in chimpanzees (Jacobsen et al. 1935) and monkeys (Deuel 1977).

The examples cited above deal with the temporal ordering of skilled actions to obtain a goal. Other experiments have focussed on the narrower but perhaps more interesting question of how well animals with frontal-lobe lesions can initiate and keep track of their own movements

(Pinto-Hamuy & Linck 1965; Pribram & Tubbs 1967; Brody et al. 1977; Brody & Pribram 1978; Passingham 1978).

(a) Performance on subject-ordered pointing tasks

In a task designed to explore this question at the human level (Petrides & Milner 1982), subjects were presented with stacks of cards (8 in \times 10 in; ca. 20 cm \times 25 cm) on each of which a set of 6, 8, 10 or 12 stimuli was displayed in a regular array. For any given stack, the size of the set and the items composing it remained constant, as did the form of the array, but the relative positions of the items varied at random from card to card. The subject's task was to go through the stack, touching one and only one item on each card and taking care not to touch the same item twice. Thus the subject himself initiated the programme and determined the order of responding. The only restrictions were that he was not to point repeatedly to the same location, nor (for verbal items) to point to the stimuli in an alphabetical order, because either of these approaches would have oversimplified the task. Three trials were given for each set of stimuli, beginning with the 6-item set and increasing the size of set progressively up to 12 items, no item appearing in more than one set.

Four versions of the pointing task were constructed, differing only in the nature of the stimulus material: (a) concrete, high-imagery words (e.g. lemon, hammer); (b) abstract, low-imagery words (e.g. attitude, situation); (c) representational drawings (illustrated in figure 6); (d) abstract designs (illustrated in figure 7). The words used in the two verbal tasks were of relatively high frequency in the language, although differing between tasks in their image-evoking properties (Paivio et al. 1968); the abstract designs were easy to distinguish from one another but difficult to code verbally. All four tasks were given to all subjects, the abstract designs being given first (followed by the representational drawings) to render less likely the use of verbal strategies on the non-verbal versions of the task.

We predicted that patients with frontal-lobe lesions would find these tasks difficult and that there might be differential effects related to the side of the lesion (Milner 1971, 1974). Patients with left frontal-lobe lesions were expected to show their greatest deficits on the verbal tasks and patients with right frontal-lobe lesions on the non-verbal ones, particularly the abstract designs. As will be seen below (figures 8–11), we found the left frontal-lobe group to be impaired on all tasks, and the right frontal-lobe group on the non-verbal tasks only.

Figures 8 and 9 show the mean number of errors made on the high-imagery and low-imagery words, respectively, by the normal control group and by patients grouped according to side and site of brain lesion. On the high-imagery words, which was the easier task, only the group with left frontal-lobe lesions was impaired, whereas on the low-imagery words both this group and the left temporal-lobe group with large hippocampal removals had significant deficits.

The representational drawings proved to be the easiest task of all; nevertheless, both frontal-lobe groups were impaired on it, as was the right temporal-lobe group with extensive encroachment upon the hippocampal region. On this task, we also obtained a significant Group-Set-Size interaction, the left frontal-lobe group showing an impairment even on the 8-item set, whereas the deficit of the right temporal-lobe group with large hippocampal lesions did not become apparent until the 10-item set and that of the right frontal-lobe group was only found on the most difficult, 12-item set. These relations between set size and performance are displayed in figure 10 for the three impaired groups and the normal control group only.

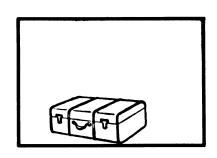
The results for the abstract designs were congruent with those for the representational

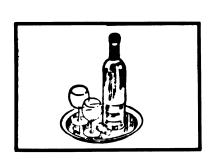


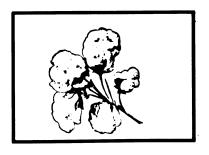






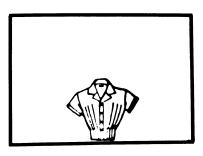


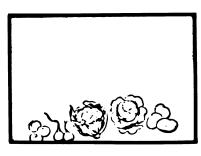












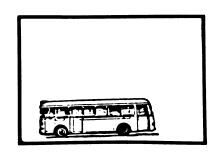


FIGURE 6. Self-ordered pointing task: stimuli used in the 12-item set of representational drawings. (From Petrides & Milner (1982), as are also figures 7-11.)

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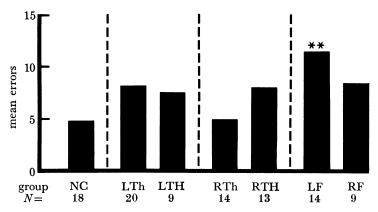


FIGURE 8. Self-ordered task: high-imagery words. Mean total error scores for normal control subjects and for patients grouped according to side and site of brain excision. NC, normal control group; LTh, left temporal-lobe group with little hippocampal involvement; LTH, left temporal-lobe group with extensive hippocampal involvement; RTh, right temporal-lobe group with little hippocampal involvement; RTH, right temporal-lobe group with extensive hippocampal involvement; LF, left frontal-lobe group; RF, right frontal-lobe group. The same abbreviations are used in figures 9, 10 and 11. **, p < 0.01.

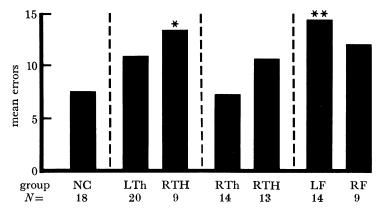


Figure 9. Self-ordered task: low-imagery words. Mean total scores for normal control group and for the various patient groups. *, p < 0.05; **, p < 0.01.

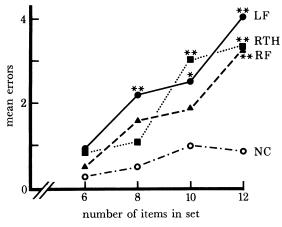


FIGURE 10. Self-ordered task: representational drawings. Graphs showing mean error score as a function of set size for the NC, RTH, LF and RF groups, respectively. Note that the LF group was already impaired with a set size of 8 items, whereas the RF group was impaired only on the 12-item set. *, p < 0.05; **, p < 0.01.

drawings, although in this case the Group-Set-Size interaction just missed significance. The mean error scores for the various groups are displayed in figure 11.

The differential effects of left and right hippocampal lesions on the performance of the verbal and non-verbal versions of the pointing task are consistent with our earlier findings for serial order tasks (Corsi 1972). They are also consistent with animal studies that point to deficits on

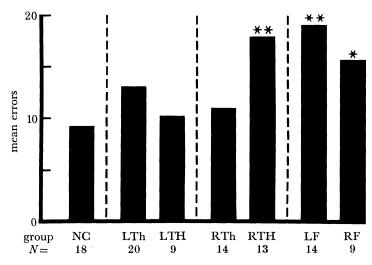


FIGURE 11. Self-ordered task: abstract designs. Mean total error scores for the normal control group and for the various patient groups. Here, as in figures 8 and 9, errors are summed across all four sets. *, p < 0.05; **, p < 0.01.

sequential tasks after hippocampal lesions (Kimble & Pribram 1963) but not after lesions of the temporal neocortex (Pinto-Hamuy & Linck 1965). These deficits emphasize the memory demands of the tasks; no patient in any group had difficulty with the 6-item sets but the larger sets clearly make demands on an active working memory.

The deficits found in the frontal-lobe groups confirm that patients with these lesions are less able than normal subjects to keep track of their own responses. For the longer sequences, normal subjects tried to group the items together in a meaningful way (such as always touching the suitcase after the train). Such organization was less evident in the behaviour of the frontal-lobe groups (cf. Meyer & Settlage (1958) for an animal parallel).

(b) Recency discrimination

The major contribution of the left frontal lobe to performance on the subject-ordered tasks is in marked contrast to our previous findings for tasks using similar material (high-imagery words, representational drawings and abstract paintings) but requiring the temporal ordering of two recent events (Milner 1971, 1974). On these recency-discrimination tasks, which are described below, deficits were found after frontal lobectomy, but with a suggestion of a greater contribution from the right frontal lobe than the left.

In the verbal form of the recency task, the subject is given a pack of 184 cards, on each of which two spondaic words are inscribed (e.g. cowboy, railroad). He must read the words aloud and then turn to the next card. From time to time a test card appears bearing two words with a question-mark between them and the subject must then say which of the two words he read



FIGURE 12. Recency-discrimination task: representational drawings. Sample test card.

The subject must point to the item he saw more recently.

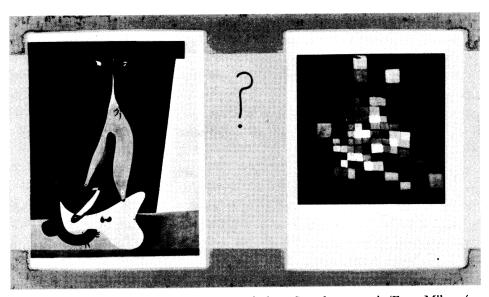


FIGURE 13. Recency-discrimination task: abstract paintings. Sample test card. (From Milner (1974).)

...ore recently. Usually both words on the test card will have appeared before (say, 8 cards ago compared with 16) but in the limiting condition one of them will be new, at which point the task becomes a simple test of recognition, with the subject indicating which word he has seen before.

The material used in the representational-drawings and the abstract-paintings forms of the

recency test is illustrated in figures 9 and 10, respectively. On each task, the subject was allowed only a few seconds to inspect each card before being told to turn to the next and whenever a test card appeared he pointed to the item he thought he had seen more recently.

Of these tests, patients with left frontal-lobe lesions showed a moderately severe deficit when the stimuli were verbal (high-imagery words) but were unimpaired when the recency judgements involved representational drawings or abstract paintings. In contrast, patients with

Table 1. Deficits on serial-ordering tasks after left (L) or right (R) frontal-lobe excision, as related to type of task and stimulus material

task	high-imagery	low-imagery	representational	abstract
	words	words	drawings	designs
self-ordered pointing recency discrimination	L L > R	L not tested	L > R	L = R

right frontal-lobe lesions were severely impaired on the abstract paintings (performing at, or near, chance level), as well as being significantly impaired on the representational drawings. Further, on the high-imagery words, their performance was only slightly better than that of the left frontal-lobe group. Thus, although it is true that these results point to strong material-specific effects related to the side of the frontal-lobe lesion (Milner 1971, 1974), the effects of right frontal-lobe lesions are clearly more striking than the effects of left.

Table 1 shows in schematic form the differing pattern of results obtained on the self-pointing and the recency-discrimination tasks, despite the similarity of the stimulus material. If one considers more closely the requirements of the two tasks, it is possible to offer a tentative explanation of these findings. In the recency task, the subject is required to monitor a sequence of externally ordered events that succeed one another quite rapidly. If indeed, as Geschwind (1977) has argued, the right hemisphere is dominant for visually guided attention, one might expect the right frontal lobe to be more critically involved than the left in the performance of such a task. In contrast, the major role played by the left frontal lobe in the subject-ordered pointing task, requiring active planning as well as monitoring of self-initiated responses, is consistent with the notion of left-hemisphere dominance for the programming of voluntary actions.

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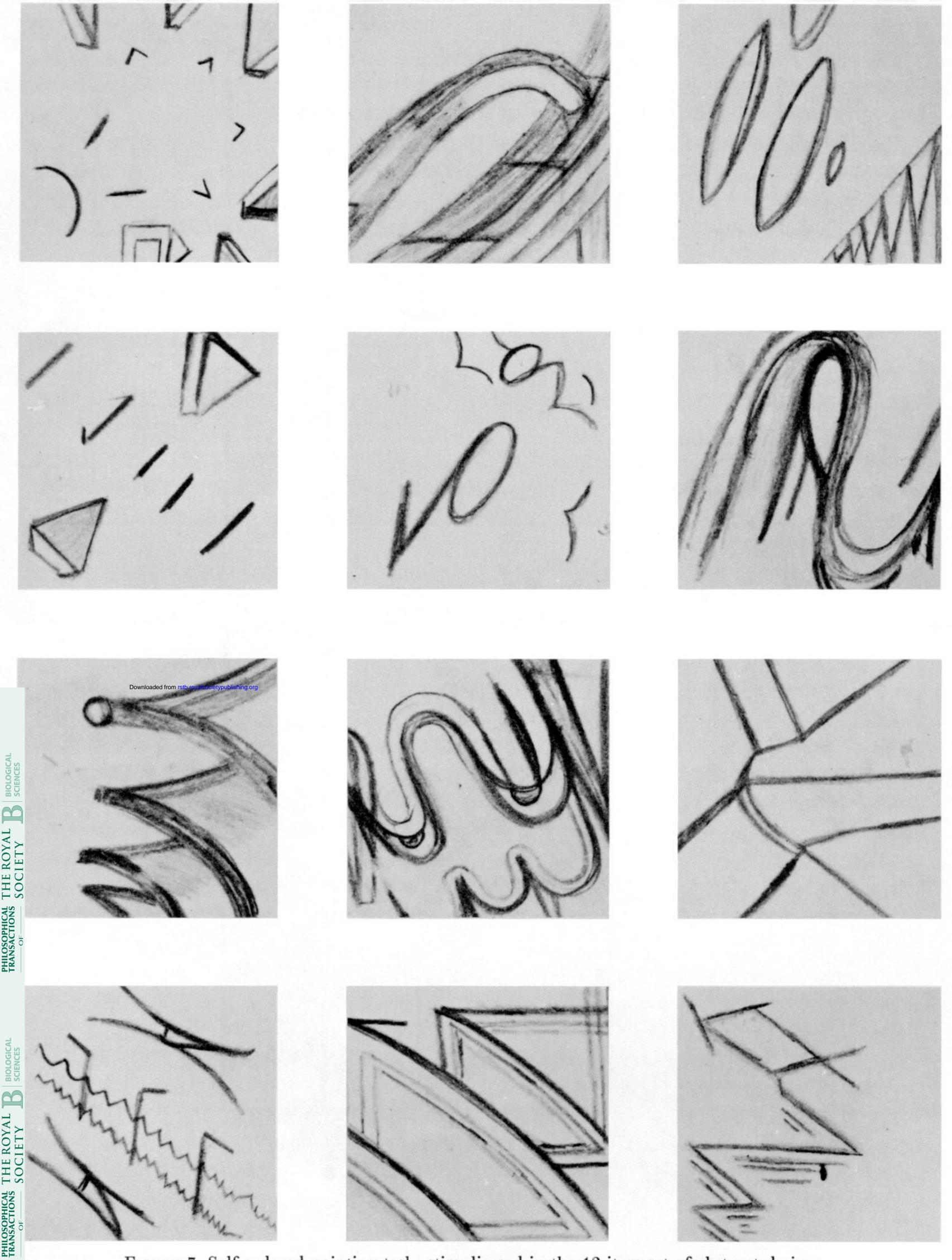
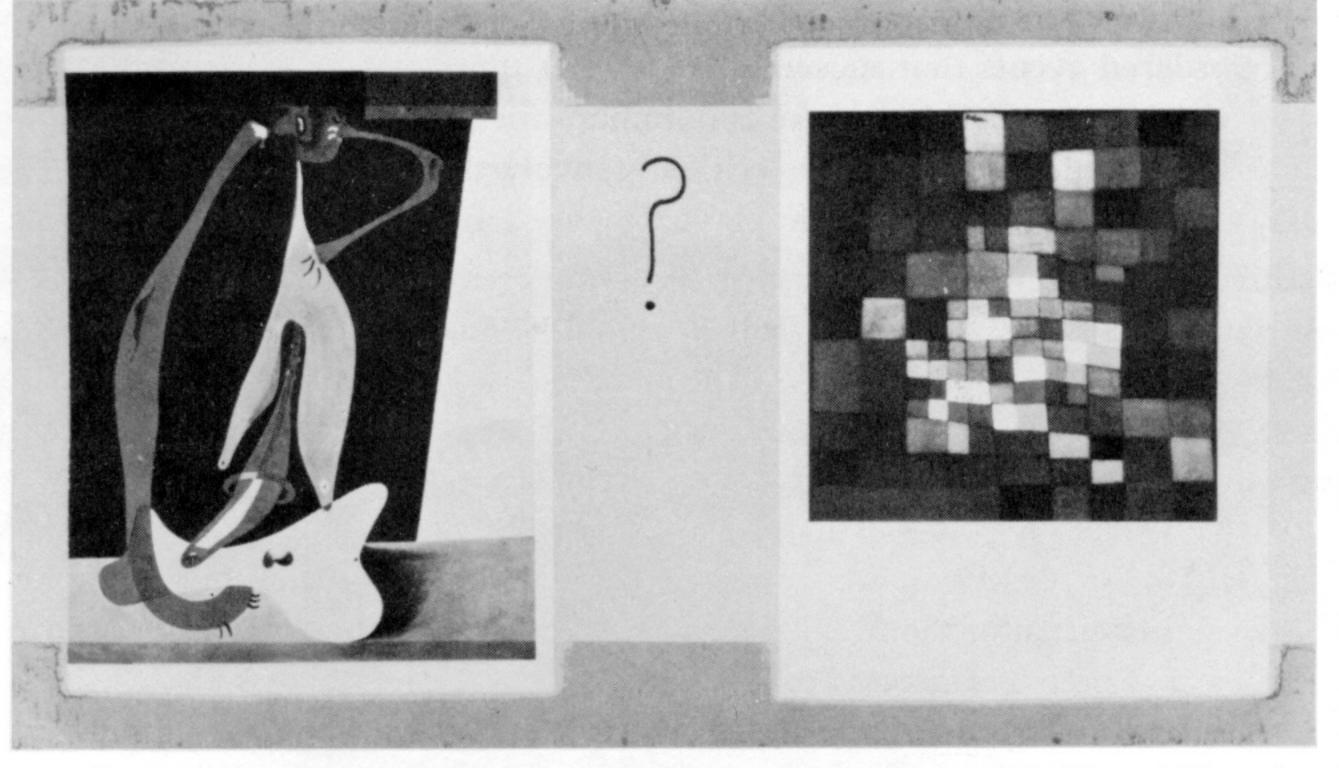


Figure 7. Self-ordered pointing-task: stimuli used in the 12-item set of abstract designs.



GURE 13. Recency-discrimination task: abstract paintings. Sample test card. (From Milner (1974).)