Chapter 3

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A PROGRESS REPORT
ON THE NEUROLOGICAL PROCESSES
DISTURBED BY FRONTAL LESIONS
IN PRIMATES

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> The experiments in this monograph aim at an analysis of typical mammalian behavior under conditions where the determining stimulus is absent at the moment of response. . . . Our investigation thus forces us to the consideration of the functional presence of a representative factor in the behavior of animals and children. Not only this, but the problem of the nature of this representative factor confronts us. . . . (Hunter, 1913, by permission.)

THE EXPERIMENTAL ANALYSIS OF THE EFFECTS OF FRONTAL ABLATIONS IN subhuman primates has proceeded to the point where specific hypotheses can be fruitfully forwarded, tested, and appropriately modified because of the rich background of data available. A brief résumé of the American efforts, mainly those initiated in the Yale and Wisconsin laboratories, will introduce the experiments reported at this time; a more comprehensive review of these data as they relate to the work of others is in preparation.

INTRODUCTION

Immediate Memory

Jacobsen (1936), taking off from clinical reports of the effects of frontal lobe injury, sought a behavioral index of "higher mental functions."

28

He found such an index in Hunter's (1913–1915) delayed-reaction task, a problem originally devised to test whether animals (and infants) had some simple form of "ideas" that could bridge the temporal gap between a stimulus situation and a subsequent opportunity for response. In Jacobsen's hands, this delayed-response task proved to be a selective index of primate frontal lobe injury—a result which has been repeatedly and extensively confirmed (Pribram et al., 1952).

Jacobsen next asked what might underlie the deficient performance of the delayed-reaction task. He suggested that an impairment of recall, manifest as a defect in an "immediate memory" process, could account for the deficit. He had some reservations as to this suggestion: He was not sure that hypothesis of an overly rapid decay of a memory trace would fully account for the performance defect in delayed reaction; other factors affecting recall might well be influenced by the frontal resection.

Hyperreactivity

These reservations received support from subsequent work performed by Jacobsen's collaborators. Malmo (1942), Finan (1942), and Nissen et al. (1938) found experimentally that aspects other than the trace of memory were involved by the frontal procedure: action at the time of stimulus presentation and *distractibility* were shown to be important. These results were interpreted to indicate that the delayed-response task tested for one trial learning and retroactive inhibition rather than for memory-trace decay.

At this point in the history of the problem a somewhat different yet related proposal was forwarded: the impaired delayed-reaction performance is only secondary to another effect of frontal surgery in the monkey, *locomotor hyperactivity* (Richter & Hines, 1934; Kennard et al., 1941; Pribram et al., 1952; French, 1959a). Hyperactivity can be described as repetitive and continuous quadrupedal pacing beginning immediately after surgery, qualitatively similar but with greater intensity and persistence than the pacing of caged animals in a zoo.

Richter & Hines (1934) described the hyperactivity as a "perseverative tendency" in that movements, once begun, persisted, but they abandoned the idea for lack of evidence. This idea has recently been revived by French (1959c). He states that the "sequence of locomotion" competes with other activities. French noted the lessened frequency and duration of bar-pressing responses in frontals and attributed this to the hyperactivity, stating that "responses inconsistent with continuous locomotion are curtailed." Expressing this another way, Orbach (1959) has suggested that the motility interferes

with the adoption of mnemonic devices such as positioning and the use of spatial cues. He suggests that the hypermotility is related to the presence of peripheral vasodilation, since muscular activity warms the animal.

Wade (1947) had earlier espoused the proposal that the delayed-response deficit is based on locomotor hyperactivity, and had shown that barbiturate medication, which reduces hyperactivity, also results in a re-establishment of adequate delayed-reaction performance in the frontally lesioned primate. However, the same author (Wade, 1952), reported that lobotomized monkeys showed *hypoactivity* in contrast to the hyperactivity of frontal lobectomized monkeys. Yet these lobotomized subjects were also impaired in their delayed-response behavior. In this instance the author attributed the defect to "loss of interest," not to hypomotility.

This change in interpretation was necessitated since, in the meanwhile, a simple explanation in terms of hyperactivity had become untenable. Physical and pharmacological manipulations other than barbiturate medication were found to be effective antidotes to the frontal injury—despite the fact that some of these agents did not alter locomotor activity. After starvation, insulin administration, and temporary exposure to cold, frontally lesioned monkeys performed well the delayed-reaction task (Pribram, 1950). The results were interpreted to indicate that all the effective agents increased "appetite"; in consequence the monkeys "attended" better the baiting (pre-delay) stimulus (a peanut). These results and their interpretation were thus in accord with those of Finan, Malmo, and Nissen, who had taken the position that frontal lobectomy influenced the monkey's responsivity to the stimulus aspects of the situation.

Mettler (1944) had come to a similar conclusion when he noted that a bilaterally frontally ablated monkey "was inherently *over-reactive* as well as *over-active.*" *Hyperreactivity* was deemed more central than hypermotility, hyperkinesia, or hyperactivity, for it describes a state or disposition to react rather than any particular activity per se.

Task Novelty and Reliability

A specific inquiry into the stimulus conditions under which this dispositional defect appears was undertaken meanwhile. Monkeys were trained on *variations* of the delayed-reaction task (Mishkin & Pribram, 1956). Ordinarily, the identical-appearing food cups are positioned in the right and left foreground of the monkey and are baited in view of the animal. Response is to be made to the baited cup. The first variation of the task was to place a single cup in the center foreground. When this cup was baited within view of the subject, response was to be made after the delay period;

when a bare hand was held above the cup, the monkey was subsequently to withhold response. Interestingly, frontally lesioned monkeys performed well this "go–no go" type of task. The question arose whether this improved performance was to be attributed to the go–no go aspect of the test or to the concomitant change in the stimulus situation which had been made: the cue was no longer "peanut-here" or "peanut-there" as in the classical situation, but was now "peanut" versus "bare hand." The results of further variations in the procedure showed that this change to peanut versus bare hand was crucial, for when peanut-here and peanut-there were used as cues in a go–no go variation of the task, the frontally injured monkeys failed. Conversely, when peanut versus bare hand signaled go-here or go-there, the lobectomized animals performed almost as well as did their controls.

These experiments, taken together with the earlier ones, support the hypothesis that the subject's response to the stimulus on the occasion of the predelay portion of the task is crucial to understanding the defect that follows frontal injury in primates; the notions based *solely* on memory-trace decay, i.e., the classical "immediate memory" hypothesis, were untenable.

Is this all-important stimulus aspect of the task modality-specific? The suggestion had been made that visual performances are especially affected by frontal lesions (Denny-Brown, 1951). Others had countered that kinesthesis is crucial since the classical delayed-reaction task is predominantly spatial. These proposals were disconfirmed by a series of experiments. Place as a crucial cue was ruled out by showing that frontally lesioned monkeys have considerable difficulty in performing a nonspatial task, object alternation (Pribram & Mishkin, 1956; Pribram, 1961). In fact, their difficulty in performing spatial and object alternation was comparable. And spatial alternation, a relative of the delayed-reaction task, had been found to be as good an index of frontal lobe injury as is delayed reaction itself (Jacobsen & Nissen, 1937).

To rule out vision, one experiment was done in which the frontal eye fields were selectively removed. No severe impairment of delayed reaction ensued (Pribram, 1955b). In another experiment, frontally lesioned monkeys were given an operant conditioning problem in which two schedules of reinforcement (fixed interval and fixed ratio) were alternated. The schedule in force was initially indicated by a colored light (green for interval and red for ratio). During the test procedure, these lights were turned off so that only the cadence of alternation signified the schedules. Frontally lesioned monkeys failed the test procedure—they had been guided by the visual cue during the initial part of the task (Pribram, 1961).

So it appears that the frontal deficit cannot be attributed to a selective

change in either the kinesthetic or the visual mode. Indeed, modality specificity is unlikely to be a factor in determining the defective performance.

Yet the deficit is a specific one. As an alternative to modality specificity the idea was proposed that the reinforcing properties of stimuli, i.e., the outcome or consequences of behavior, are selectively affected by frontal ablations. Reinforcement can be conceived in several different fashions; for example, one set of experiments tested whether the effects of frontal lesions were similar to those of food deprivation or satiation. A clear-cut answer in the negative was obtained: the effects of varying food intake and the frontal lesion were easily distinguished.

Another experiment, however, gave a promising lead. Operant performance during the condition of extinction (as if the apparatus had run out of peanuts) showed a marked persistence of bar pressing on the part of the frontally injured monkeys when their performance was compared with that of control subjects.

This lead was followed in subsequent experiments and, in essence, led to those reported here. An attempt was made to relate quantitatively the amount of change in behavior after frontal resection to the complexity of the task. When task complexity was varied by increasing the number of alternative choices in the problem, no relation between deficit and complexity was obtained. In fact, whenever a *novel* cue was presented the frontally lesioned monkeys chose this cue *more promptly* than did the controls, irrespective of the number of alternatives among which the choice had to be made (Pribram, 1961). This finding confirmed earlier observations reported from the Yale and Wisconsin laboratories. The increased pacing of the frontally lesioned primate will stop in the absence of light or vision (Kennard et al., 1941; Davis, 1951) and for short intervals otherwise. Over a period of several months postoperatively the increased locomotion diminishes to the preoperative level, but returns when the animal is placed in a new environment or situation (French, 1959a). These investigators therefore concluded that the *novelty* of the stimulus conditions and environment is a more important factor in the control of motor activity of frontally lesioned monkeys than it is in normal subjects.

On the other hand, when the reliability of outcome was manipulated in a discrimination reversal task (by making changes in the criterion to be reached before reversal was begun), frontally lesioned monkeys showed a progressively greater defect the more *unreliable* the task (Pribram, 1961). This defect showed up as a *lag* in reversing choices when the reinforcement was switched to the previously nonreinforced cue.

Again, these observations were in consonance with those obtained in

other laboratories. The experimental results obtained by Harlow & Settlage (1948) had shown that operated rhesus monkeys "tended to persist in choice-response patterns which, currently inadequate for the solutions of a problem, had previously served to yield the food reward." Such persistence of erroneous response patterns, such *perseveration of set*, was found when position-discrimination and object-discrimination tests were alternated from day to day. The previously acquired position habit tended to persist on the days when an object-discrimination test was being given, and vice versa.

Brush et al. (1961) and Mishkin et al. (1962) have recently made much of this concept of perseveration and used it to explain the frontal animals' persistent responses to an incorrect, novel cue in an object discrimination task. Citing the tendency of all monkeys to choose a novel cue, they suggest that frontal lesions produce abnormal difficulty in suppressing whatever response normally prevails in a given situation.

They take this idea one step further. A "normal" response can be either learned or innate. In the Harlow & Settlage experiment (1948), there is no difference in the stimulus situation between the position-discrimination and the object-discrimination test. Thus, the previous *learned* response is normal in this situation; perseveration to an object or to a position occurs. In their own experiments, however, the perseveration to the novel cue is accounted for as due to perseveration of the normal *innate* response tendency.

In summary, whatever the experimental approach to the frontal defect, two specific observations repeatedly emerge: (1) an increased tendency to shift response, especially when novelty is introduced; (2) the frontally lesioned primate shows an increased perseveration of response in the face of a change in the problem. These observations appear to be at odds. Brush, Mishkin, Rosvold, and Prockop resolved the discrepancy to their satisfaction on the basis of whether innate versus learned sets were called for by the situation. The present experimental analyses were also undertaken in an attempt to resolve the issue. In addition, however, resolution aimed at some understanding of the mechanism made defective by the frontal lesion.

EXPERIMENTAL ANALYSES

Perseveration of Set and Tendency to Shift

The Multiple-choice Experiment: Experiment 1. Our first endeavor turned around a reanalysis of the data obtained in the multiple-choice experiment already reported (Pribram, 1960a). There was no question that during criterion performance in this experiment the frontally lesioned monkeys

shifted their responses away from the reinforced cue, i.e., made more errors than their controls did. Figure 3.1 reviews these results.
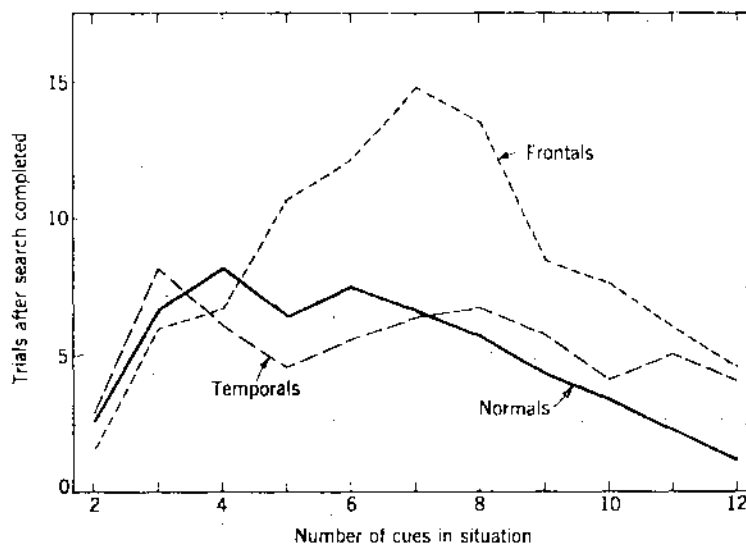

Figure 3.1. Graph of the average of the number of trials to criterion taken in the multiple-object experiment by each of the groups in each of the situations after search was completed, i.e., after the first correct response. Note the difference between the curves for the controls and for the frontally operated group, a difference which is significant at the 0.05 level by an analysis of variance ($F = 8.19$ for 2 and 6 df) according to McNemar's procedure performed on normalized (by square root transformation) raw scores.

Several questions remained, however. One of them is taken up below under the section on tendency to shift. Here the evidence is presented in support of the perseveration of set observations. The hope is that by so doing, the conditions in which perseveration is observed can be further specified and distinguished from those in which the tendency to shift occurs.

A brief review of the experimental situation and procedure used in the multiple-choice task follows:

Twelve sophisticated subjects were used. Four had been given inferotemporal, four had had anterofrontal ablations some two years before. Only the results of the frontal and unoperated control groups' performances are to be presented here.

A modified Wisconsin General Testing Apparatus was used. The monkeys were divided into an operated and an unoperated control group. Each group consisted of four animals. The operated Ss had undergone bilateral cortical resections of the frontal intrinsic cortex some 18 months prior to the

onset of the experiment. In the testing situation these animals were confronted initially with two "junk" objects placed over two holes (on a board containing 12 holes in all), and a peanut was placed under one of the objects. An opaque screen was lowered between the monkey and the objects as soon as the monkey had displaced one of the objects from its hole. When the screen was lowered, separating the monkey from the 12-hole board, the objects were moved randomly to two different holes on the board. The peanut remained under a particular object until the S had reached a criterion performance of five consecutive correct responses. After the monkey reached criterion performance, a third object was added. Each of the three objects in turn becomes the positive cue. Testing then proceeded as before, and continued until the animal reached criterion performance with each of the positive objects. A fourth object was then added and the entire procedure repeated. As the animal progressed, the number of objects was increased serially through a total of 12. After the addition of each new object, each of the remaining objects became positive in a regular order. The testing procedure was the same for all animals throughout the experiment. The order of introduction of the objects was balanced so that the order was the same for only one monkey in each group.

Analysis of the problem posed by this experiment had indicated that solution is facilitated when a monkey attains two strategies: (a) during search—moving, on successive trials, each of the objects until the peanut is found; (b) after search—selecting on successive trials the object under which the peanut had been found on the preceding trial. These strategies should be regularly alternated, *ababab* etc., for the most effective problem solution.

The frontal animals tended to persist in their previous strategy after new conditions requiring the alternate strategy had been signaled. After once finding the peanut, the frontals had difficulty in attaining the strategy of returning on successive trials to the object under which they had found the peanut. As seen in Figure 3.2, their probability of response to the positive cue after one rewarded trial was significantly less than that of the controls. Although their performance in comparison with that of the controls improved after several rewarded trials in a row, the frontals' performance was still more variable; they were less likely to return to the positive cue.

As described above, when a monkey chooses the positive cue five times in a row, he attains criterion. The situation then changes so that the initial strategy is in order—that of moving on successive trials each of the objects until the peanut is found. This change is signaled by the fact that a response
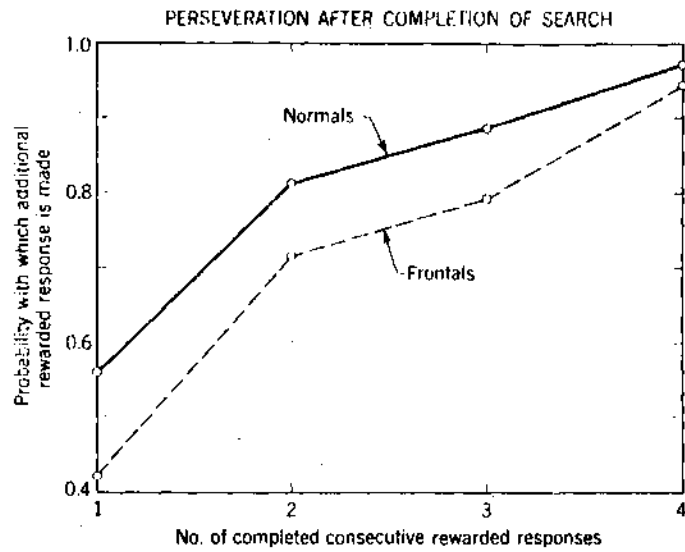
PERSEVERATION AFTER COMPLETION OF SEARCH

No. of completed consecutive rewarded responses

Figure 3.2. Graph of the average probability of response to the correct cue according to the number of consecutive correct responses already made. The differences between the frontal and the normal groups are significant at the 0.05 level (according to a two-tailed Fisher t-test).
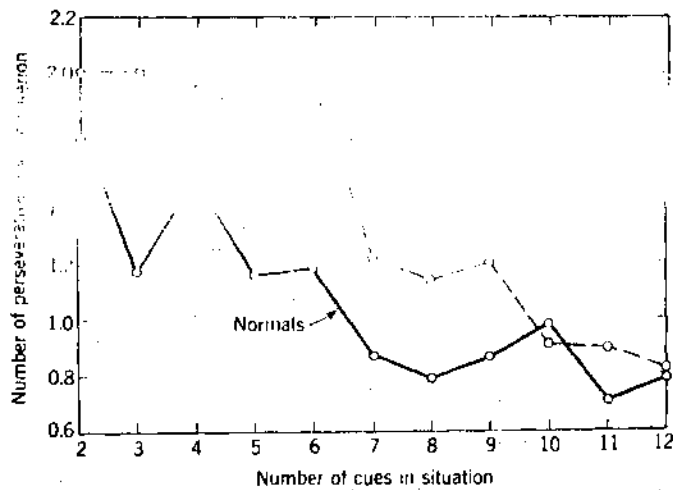

Number of cues in situation

Figure 3.3. Graph of the average number of perseverative responses to the previously positive cue. The differences between the frontal and the normal groups are significant at the 0.05 level (according to a two-tailed Fisher t-test).

to the previously rewarded cue is no longer the occasion for a reward. Having gone to the positive cue five times in a row, frontal animals had difficulty in switching back to the strategy of search. Figure 3.3 shows that the frontal animals continued going back to the previous positive cue significantly longer than the controls do.

Yet, in one situation, the frontally lesioned group of monkeys did *not* continue to respond to the previously positive cue longer than their controls did. When a *novel* cue was presented, the frontals actually chose it in fewer trials than the controls did, though the differences in performance did not reach significance (see Figure 3.4).
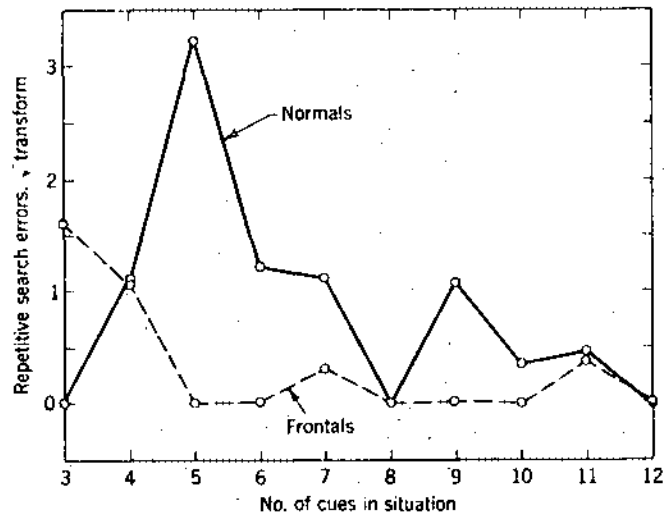

Figure 3.4. Graph of the average number of repetitive errors made in the multiple-object experiment during those search trials in each situation when the additional; i.e., the novel, cue is first added. A repetitive error is made by a monkey when he moves more than once, during a succession of trials, an object other than the one under which the peanut is placed.

The Effects of Lobotomy in Man: Experiment 2. The success of fine-grained analysis of performance in a previously reported discrimination reversal problem (Pribram, 1961), in showing difference between the behavior of frontally lesioned monkeys and their controls when gross analysis failed to do so, led us to undertake a very simple experiment with lobotomized patients. This study suffers from many of the defects that so often plague experiments performed on clinical subjects. Nonetheless, the results were clear-cut and in accord with those obtained in monkeys despite the fact that the data were gathered before we made any of the above analyses.

We were somewhat pleasantly surprised. As lobotomized subjects are be-
coming rare, we thus want to include our findings here.

The subjects were ten male patients, five lobotomized and five unop-
erated ward-mate controls, from the Veterans Administration Hospital in
Menlo Park, California. All subjects were diagnosed as schizophrenic. There
was no essential difference between groups as to further diagnosis; most of
the patients were classified as both reactive and severe. The lobotomies
were performed bilaterally between 1947 and 1954 by the standard Freeman
& Watts technique (1944). Three of the five lobotomized subjects (F2, F3,
F5) had suffered from occasional postoperative seizures which were readily
controlled by dilantin or mesantoin medication.

The mean age of both groups was 41. The IQ was determined by a
shortened form of the Wechsler Adult Intelligence Scale. The mean IQ
for the lobotomized group was 87.4, while that of the control group was
90.2. The mean years of education of the lobotomized group was 13.4; that
of the control group was 11.3. The lobotomized patients had been hos-
pitalized for a mean total length of 13.2 years with a range from 8 to 20
years. The control patients averaged 8.7 years of hospitalization, with a
range from 2.3 to 17 years. All patients had received electroconvulsive
shock therapy and were matched in this regard as well.

The apparatus was a board on which was mounted a lever which was
to be pushed to the right or left and then brought back to the central position
to complete a trial. The subject received a poker chip after each correct
lever deflection; at the end of five consecutive errorless alternations a light
went on and the subject was rewarded with a dime. The patient was then
advanced to the next problem. No verbal instructions were given, but the
signals indicating correct response (poker chip and light-dime combination)
were given in such a fashion that correct performance could be gauged from
the sequence of their appearance. The problems, in order given, were: al-
ternation, double alternation, triple alternation, etc., ending with quintuple
alternation.

Frontally lesioned patients had more difficulty in solving the series of
problems than the control group did. Three of the control patients, but only
one frontal, achieved the quintuple alternation. The other frontal subjects
and one of the controls could not solve the double alternation after 300 trials.

In both the single- and double-alternation problems, frontal subjects
made more perseverative errors than the controls did, a perseverative error
being defined as continued response to one particular side after the absence
of a poker chip has indicated that such behavior is incorrect and will not

lead to a reward. The difference between frontals and controls was significant at the 0.05 level.

TABLE 3.1

	Frontal subjects						Control subjects						P*
	F1	F2	F3	F4	F5	Mean	C1	C2	C3	C4	C5	Mean	
Perseverative errors (errors after receiving a signal to go to the other side)	4	31	0	36	13	16.8	0	1	1	0	3	1	0.05
No. of trials continuing single alternation pattern into double alternation	4	28	0	37	6	13.5	5	1	4	3	2	3	0.02

* The significance of the difference between the means for the normal and frontal groups was established by Mann-Whitney U tests.

Further analysis of the data showed that the frontal subjects tended to continue their previously rewarded response pattern, even while receiving information (i.e., no poker chip) that this behavior would not lead to further rewards. Thus, after frontal subjects received a dime following five errorless single alternations, their pattern of single alternation continued into the double-alternation problem longer than did that of the control subjects. Within the frontal group these scores were variable, but the difference between frontals and controls in this performance was significant at better than the 0.02 level.

A Multiple-reward Game: Experiment 3. As a test of the conditions under which the tendency to shift is observed in frontally lesioned monkeys, the following experiment was run. The experiment originated in the observation that the results obtained with the frontally lesioned group in the multiple-choice experiment could be understood if one made the simple hypothesis that frontally lesioned monkeys tend, more than their controls, to shift responses among alternatives. According to this hypothesis, search would remain essentially unimpaired but performance in a criterion run would suffer—and these were the actually observed results. According to this view, alternate explanations made in terms of a changed value of the reinforcement for the frontally lesioned subject would become unnecessary.

The present experiment was designed, therefore, to test whether shift among alternatives occurs when the reinforcing conditions are considerably different from those in the earlier study. The experiment was designed so that a subject failed to receive a reward only if he returned on a trial to the object he had chosen on the immediately preceding trial. Tendency to shift

on the part of frontally lesioned monkeys would result in a lower error score than that of controls; insensitivity to error or perseveration would produce a higher number of errors. Object or position preference could also be quantitatively gauged in this situation.

Twelve naive rhesus monkeys were used as subjects. Six monkeys received bilateral anterior frontal resections; the remaining six served as unoperated controls. Histological confirmation of the ablations is not yet available as the monkeys are still alive and working in other experiments.
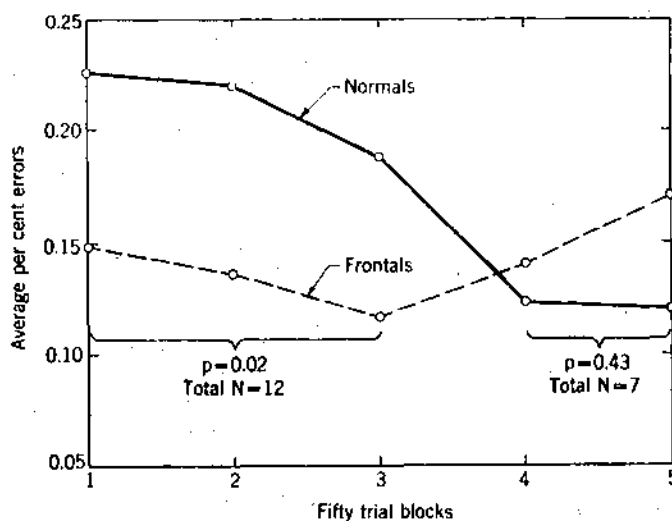

Figure 3.5. Graph of the average number of errors in the eight-choice game, where all objects were rewarded except the one selected on the previous trial. Six normal and six frontally lesioned monkeys were tested during the first 150 trials and three normal and four frontally lesioned monkeys during the final 100 trials. The other subjects succumbed to a gastrointestinal disturbance. Values are for the one-tailed Mann-Whitney U test applied to individual scores cumulated across the indicated blocks of trials. For this and the following three figures, similar graphs were plotted for the seven animals who completed the entire experiment. The same trends were shown but with more initial variability.

Each S was given 20 trials per day in a Wisconsin General Testing Apparatus. On each trial the monkey was presented with a row of eight "junk" objects, which covered food wells. He was allowed to displace one object and obtain the contents of its food well, then an opaque screen was interposed between S and the row of objects. The same eight objects were used throughout the experiment. On the first trial of each day, every object covered a raisin. On subsequent trials raisins were placed under all objects except the one which the animal had chosen on the preceding trial. Between

trials, each object was moved to a new position in a nonsystematic fashion. All 12 animals received 150 trials. Four frontals and three normals were run an additional 100 trials each.

The average percentage of errors by 50 trial blocks is shown in Figure 3.5. Cumulated over the first 150 trials, the normals made significantly *more* errors than did the frontals. After this, over the additional 100 trials, there was no difference in performance between the groups: the normals had improved to the level of the frontals.
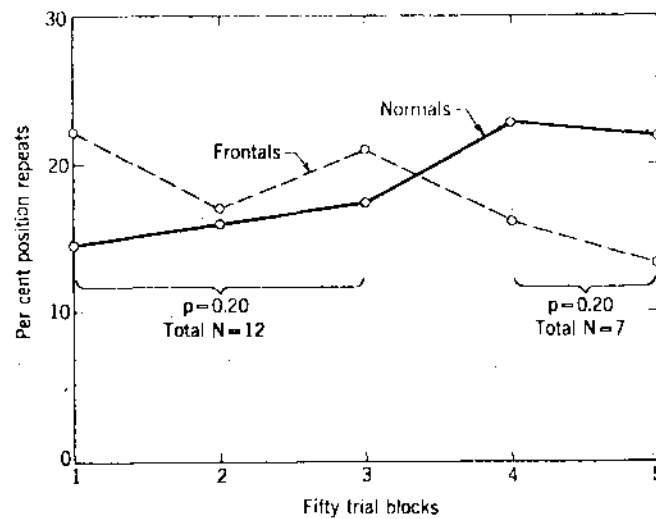

Figure 3.6. Graph of the average proportion of times animals chose the same position as on the previous trial in the eight-choice experiment. Subjects and statistical analysis as in Figure 3.5.

Nor was there a difference between groups in the number of times they chose the same position twice in a row. Figure 3.6 shows that neither the totals for the first 150 trials nor the totals for the additional 100 trials yielded significant differences.

The degree to which stable preferences developed over 50 trial blocks was measured by calculating for each animal the sum of the squares of the proportion of times each of the eight objects was sampled. This statistic inversely measures the average number of objects which the animal sampled during the 50-trial period. A comparison between groups of the average of this statistic for the first 150 trials showed that the normals chose significantly fewer objects than the frontals did, thereby showing *stronger* preferences. For the animals who ran the additional 100 trials, the result was ap-

parently the same except that significance was only borderline because of
the smaller size of the group. These data are presented in Figure 3.7.
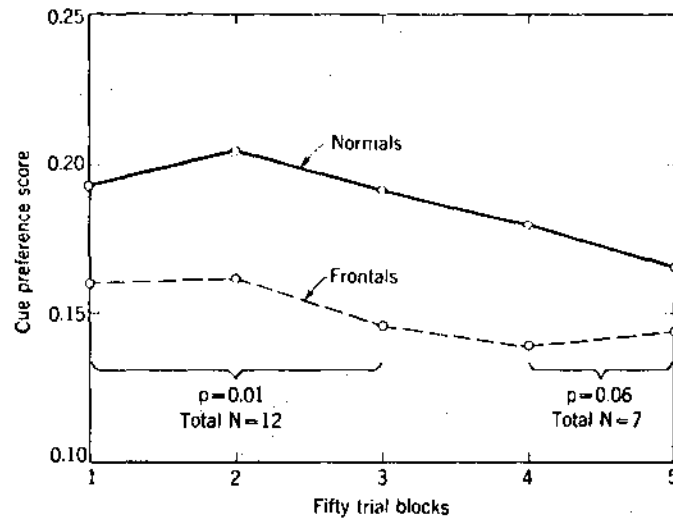

Figure 3.7. Graph of the average of object preference scores in the eight-choice game.
Score is the inverse of the average number of cues being sampled for an entire (50-
trial) block (see text), so that a high score indicates a restricted choice. Subjects and
statistical analysis as in Figure 3.5.

Finally, the error scores were corrected for the effects of preferences
and position habits so that the tendency to repeat object choices could be
measured relatively independently of other factors. The statistic computed
was the proportion of errors on trials where position changed, divided by
the preference score. If the animal chose randomly among the objects dur-
ing those 50 trials, the statistic would have an expected value of approxi-
mately 1. Averaged across the first 150 trials the scores were significantly
higher for the *normals*, indicating a stronger tendency to *repeat* object
choices. Although the normals averaged fewer corrected repeats than the
frontals did in the final 100 trials, because of large overlap, the difference
shown in Figure 3.8 was not significant.

In summary: (1) There was no significant difference between controls
and frontals in "position habits." (2) Controls show significantly greater
restriction of choice among alternative objects; i.e., frontals tend to choose
a greater variety. (3) Controls *initially* repeat their choices more often (cor-
rected for item 2 above) but learn not to do this as the experiment proceeds.

All these findings support the observations that frontally lesioned

monkeys shift their responses more readily than their controls in the multiple-choice situation.

Sampling and Search: Experiment 4. In view of this result, an additional analysis of the multiple-object experiment (experiment 1) was made to compare further the behavior during search of the normal and frontal monkeys. The question asked was whether the paradoxically better search
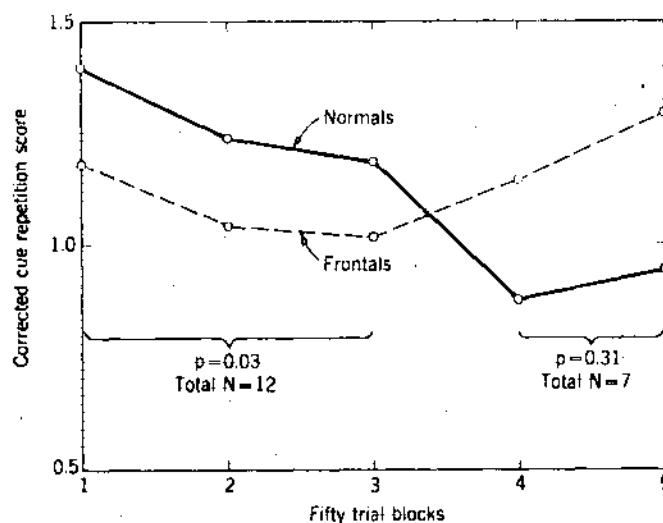

Figure 3.9. Graph of the object repeat score in the eight-choice game corrected for the effects of position habit (Figure 3.6) and of long-term (50-trial) preference (Figure 3.7). Scores greater than 1 indicate a tendency to repeat choice; scores less than 1 indicate alternation. Subjects and statistical analysis as in Figure 3.5.

performance of the frontally lesioned monkeys could be attributed to their increased tendency to shift.

In the multiple-object experiment, the cues are introduced in a regular order; the monkeys have the opportunity to learn which object follows which. If an animal acquires correct knowledge of the situation, learning the order of introduction of the objects, he can *sample* efficiently: the correct cue can be moved, and the peanut can be found early in the process of search. On the other hand, the monkey may sample randomly, finding that the correct cue occurs only by chance.

As is shown by Figure 3.9, the frontally operated monkeys sampled at about the chance level until the seven-cue situation. At this point, they improved markedly; the frontals chose the cues which were likely to be positive. In contrast, the control animals deviated from chance *sampling* sooner

than the frontals did. The behavior of the controls was *poorer* than chance from the four-cue to the eight-cue situation (significant at the 0.05 level for the seven-cue situation alone); the controls tended to move cues which had been positive for the last several successions of trials before picking the correct object. After the eight-cue situation, the control animals improved as
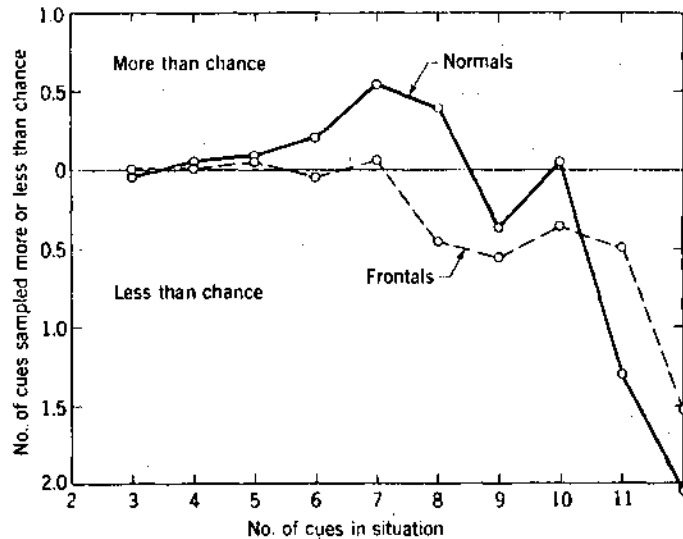

Figure 3.9. Graph for four normal and four frontally lesioned monkeys of the average number of different objects sampled in the multiple-choice experiment minus the score expected on the basis of random search among objects not yet sampled. The poor performance by the normal animals at and around the seven-cue situation indicates that the cues they investigated first during search were the cues which had been rewarded more recently.

rapidly as the frontals did until they were finding the correct object significantly *sooner* than chance.

If the monkey does not move the correct object (on his first trial) during search, it is possible for him to then commit a *search* error. A search error is made when a monkey moves any object more than once during the succession of trials before he finds the peanut. If the third cue moved by a monkey in the 12-object situation is correct, the animal will be sampling well. But if he has moved each of the two cues sampled several times, he will have made a number of search errors. Correspondingly, an animal can be sampling poorly; but, if he moves only those cues which have not already been picked up during the current succession of trials, he will make no search errors. Yet, poor sampling does tend to result in a large number of search trials. If an animal's sampling strategy is imperfect but he always

picks up a cue which has not previously been moved, additional trials offer the animal additional opportunities to err.

Moreover, if a high proportion of the cues are employed (poor sampling), search errors are more likely than if few cues are sampled. When only one cue has been sampled, the chances of the next responses being a search error are $1/x$, where x represents the number of objects in the situation; if seven objects are sampled, the chances of making a search error are $7/x$. It is possible to compute the chance number of search errors independently of the quality of sampling performance. For each trial, the probability of a search error is $\dfrac{\text{the number of cues sampled}}{\text{the number of cues in the situation}}$. For each succession of trials, the chance number of search errors can be computed by summing the probabilities of a search error on each trial. When the number of errors expected by chance is compared with the obtained number (Figure 3.10), some similarities with the sampling situation are seen. (The
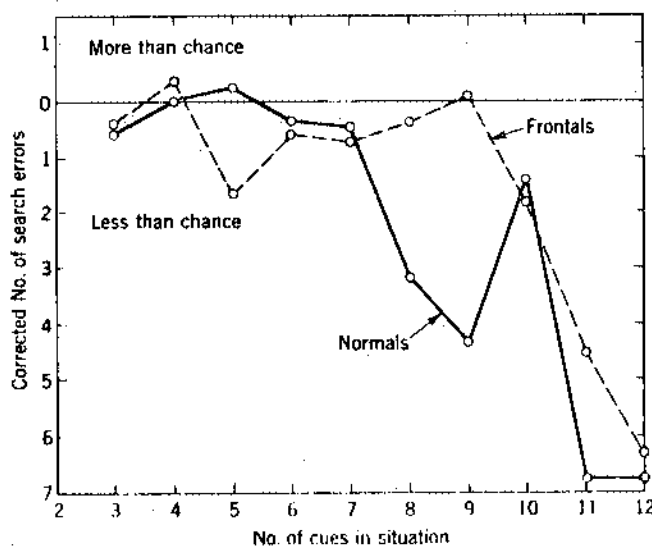

Figure 3.10. Graph for four normal and four frontally lesioned monkeys in the multiple-choice experiment. The average number of search errors minus errors expected on the basis of the number of cues already sampled is plotted. Scores indicate that both groups searched essentially randomly in the early part of the experiment, but that the normal animals started earlier to develop an efficient search strategy.

previously positive cue was eliminated from consideration in this measure of search errors because of the tendency of the frontal animals to perseverate to this cue.) As in the sampling analysis, both the frontal and the normal

group initially perform near chance, it is the controls who first begin to deviate markedly from chance search performance.

Random and Ordered Behavior

The results of these experiments tell once more the twice-told tale. Under the conditions provided and analyzed in experiments 1 and 2, frontal lesions produced perseveration of the set of responses that had proved useful to the subject in the immediately preceding circumstance. Under the conditions provided and analyzed in experiment 3 on the other hand, the frontally lesioned monkeys tended to shift their responses.

What features distinguish the conditions described in these experiments? In experiments 1 and 2 the reward situation is held constant for the duration of a problem, then changed. In experiment 3, the reward situation varies from trial to trial within the problem itself. Specifically, in those situations described under the section on perseveration of set and tendency to shift the cue-reinforcement configuration (i.e., the condition for reward) remains consistent during a period sufficient for the subject to develop an identifiable (adaptive) response pattern, perseveration occurs when the cue-reinforcement configuration is then changed to another but equally consistent cue-reinforcement configuration. The situation in experiment 3 is characterized by a varying cue-reinforcement configuration, and frontally lesioned monkeys react to this by an increased (compared with controls) variability in response pattern.

In general, therefore, these results can be summarized by stating that perseveration occurred with *inter*problem change and an increased tendency to shift with *intra*problem change of the cue-reinforcement configuration. An important exception must be noted, however. This exception arises whenever a *novel* cue is introduced into the situation. Frontally lesioned monkeys respond with alacrity to novelty. Brush, Mishkin, and Rosvold had also to deal with this unique impact of novelty, as Harlow and his associates did before them. This exception highlights the dilemma of interpretation.

It is also clear from the results of experiment 4 that the frontally lesioned monkeys perseverate their random search behavior longer than the controls do; this accounts both for the "better" and for "poorer" performance when compared to controls—and one could then apply this reasoning to those results in which the frontal groups are shown to shift their responses as in the multiple-reward experiment presented in experiment 3. One could further stretch the interpretation by declaring that random behavior can

become a perseverative tendency, much as Brush, Mishkin, Rosvold, and able, such clearly nonperseverative behavior as random response, response to novelty itself to be considered a manifestation of a set to respond randomly? Similarities could be drawn were one to evoke such concepts as, for instance, Hull's process of reactive inhibition.

The ideal interpretation would, of course, be in terms of some neurologically testable hypotheses based on such concepts. Unfortunately, the neurological data that are necessary are wanting. Until these data are available, such clearly nonperseverative behavior as random response, response to novelty, and the like, can, by stretching, always be attributed to some process "paradoxically perseverative," and there can be no direct test to dispute or to confirm the fit of the stretch.

COMMENTS

A temporary expedient in this situation is to describe a "model" of a process that would behave like the monkeys described above—a mechanism that allows a specific process to be selectively disrupted so as to simulate the performance and performance failures of the frontally lesioned primate (Pribram, 1960b).

Fortunately, this approach through simulation is fruitful today. Because simulation can be made precise with the use of computers, erroneous or vague models can be readily rejected. The experimentalist is therefore given a limited number of models, i.e., hypotheses about mechanism, that are found to fit the data. These he can then test against the real nervous system. By the use of this intervening step of model building, the neurological scientist can test notions about neural mechanism instead of notions directly derived from behavioral observation such as "perseveration of set," "tendency to shift," or even "immediate memory."

A model worth serious consideration derives from the work of Newell et al. (1958). These investigators have simulated the human cognitive, i.e., problem-solving, process by devising a hierarchically organized computer program composed of lists of items, each item capable of referring to another list. The structure of such programs can be variously represented as an English teacher's outline, a mathematician's branching set theoretical tree, or a systems engineer's flow diagram. Once such a computer program has been engaged it runs its problem-solving course relentlessly. Erroneous or nonsense solutions indicate errors in programs, errors that must be painstakingly sought out and corrected.

Instruction Programs

One of the most recent of these continually evolving problem-solving programs is EPAM II (Feigenbaum, 1959, 1961; Feigenbaum & Simon, 1961a, 1961b, 1961c; Newell, 1961). In this program, as in most others, a recurrent difficulty had to be met. Once the stored lists that compose a complex program reach a certain number, access to the list structure needs itself to be programmed to "get the show on the road," as it were. Three types of such instruction programs have to date been found useful.

The first type (type I) of instruction is contained in the problem itself; for instance, in its simplest form it will be an instruction that reads "find item X." This instruction both sets the problem and indicates that the computer's stored list structure is to be systematically searched until an item that matches X is found.

The second type (type II) of instruction program is closely related to the first, but is more complicated. This instruction reads that the first step in problem solving is to run the problem program through the computer's *permanently stored* list structure and to report the items on the problem list that match the items in the stored program. The residue, the items that fail to match, are also reported as such and stored in new locations in the permanently stored list structure.

The third, and for our purposes the most interesting, type of instruction program (type III) has an "iffy" nature. This type is a somewhat complex and hierarchically organized list structure independent of both the problem programs and the computer's stored list structures. The lists that comprise this program contain items such as "(1) take the problem program and search part A of the stored list structure for its match, (2) if no match is found, search part B; (3) and so on until a match is obtained." However, this routine is not fixed. Another set of items states: "Shuffle the *order* in which these items of instruction are to be tried in such a way that the instruction that has proved repeatedly successful is tried first, i.e., is placed first on the list." This is accomplished by temporarily storing the information about the outcome of prior searches (through A or B or . . .). This temporary storage must take place not in the computer's permanent memory where it would do little good, but in the instruction program itself. Needless to say, there is a limit to the complexity which such a flexible set of temporary instructions can attain if they are to remain an efficient tool for problem solving.

These temporary instruction programs are called noticing orders; those that shift the order of the items on their lists on the basis of the outcomes

of searches through their memories are known as flexible noticing orders. Noticing orders and the current problem program are kept separate from the computer's main storage facility in a "working" or temporary memory that is at all times immediately accessible to the programmer and computer.

To pursue the analogy: the primate brain must solve the same tasks that the computer has been programmed to solve. Since the computer processes were composed in order to simulate "primate" problem-solving processes, the processes are likely to be similar if not yet identical. However, this does not mean that the brain mechanism need mirror the computer mechanism that is set up to accomplish a particular process.

Noticing Order in a Working Memory

Noticing order is a process used by EPAM II and other problem-solving programs based on list structures. If noticing order is a process used by the primate brain when the subject is solving problems, several statements can be made about noticing order and the performance of frontally lesioned monkeys.

First, on problems where noticing order is unimportant, or where it is determined by the situation, frontally lesioned monkeys have no difficulty. This is especially apparent when the situation is novel; it is also shown by their unimpaired performance in the multiple-reward situation reported in experiment 3.

Second, on problems where noticing order is determined by running the problem through the subject's fixed store of representations of past experiences, the frontally lesioned monkeys also have no difficulty. Discrimination performances and discrimination learning have repeatedly been shown unaffected by frontal lesions. Matching from sample remains unimpaired. And, in the multiple-choice problem analysis presented in experiment 4, sampling and search, though different from controls because of irrelevant interproblem changes, are also essentially unimpaired.

When, however, problem solution demands a noticing order that is not contained in the problem itself nor in the permanently fixed store of representations of past experience of the subject, frontally lesioned primates have difficulty. Such problems have in common the factor of change, not in the stimuli per se, but in the way in which the already-experienced stimuli (e.g., cues and reinforcements) are compounded to form the new problem. The organism must react to these changes much as does the computer program: it must reshuffle the order in which the stimuli are processed. When change is occasional, i.e., when the change occurs between problems, the

frontal defect is minimal and shows up as perseveration of set since noticing order within each problem proceeds, once the frontally lesioned subject catches on that a change has taken place, according to the type I or type II process of noticing order. When, however, the change occurs within a problem; i.e., when the appropriate behavior sequence depends solely on the outcome of the immediately preceding application of the noticing order, the frontal defect shows up full-blown. As a rule, the monkey returns to random behavior since his apparatus for shifting noticing order is broken down with the result that the various behaviors tried all result in the same number of reinforcements. But perseveration may also be shown; when frontally lesioned monkeys are tested in the delayed-response or delayed-alternation situation; they frequently—more frequently than their controls —develop a position habit, since this behavior mode obtains as many reinforcements as random behavior does. The results of the experiment detailed in experiment 3 show that frontally lesioned monkeys are no more prone to position habits than unoperated monkeys are. Our view is that frontally lesioned monkeys, just as unoperated monkeys, take position habits whenever they cannot cope with a task, i.e., whenever the number of reinforcements they gain remains constant irrespective of their responses. Since frontal lesions impair delayed response and alternation learning, the operated subjects tend to take position habits—*but no more so than their controls would if they could not cope with the problem*. Support for this view comes from the observation that inferotemporally lesioned monkeys, when they have difficulty with visual discrimination problems, also slip easily into position stereotypes. At present, however, there is as yet no quantitative comparison of the relative proneness to stereotypy by frontally and inferotemporally lesioned monkeys in an insoluble problem.

In a sense, this explanation of the frontal defect in terms of impairment of a flexible noticing order is in partial agreement with the explanation made by Brush et al. (1961). They hypothesize that regression to a more primitive innate performance set occurs whenever the frontally lesioned primate cannot change this innate response tendency through learning. When, however, a task has already been learned, *this* performance is perseverated. As already noted, we could say the same, even for our tendency to shift results, were we to interpret the data in the multiple-reward experiments as perseveration of some initial "set to explore" or set to behave randomly, which is overcome by the controls as a result of reinforcing contingencies which do not effect the frontally lesioned group. As Wilson points out, however (1962), the notion of perseveration of set so conceived can be stretched over any data since all that need be done is to specify after the fact which

response tendencies are resistant to change. We here questioned whether the stretching does not go too far when it is made to cover random responses and response to novelty. Obviously, some responses are not resistant to interference by frontal lesions, e.g., alternation and delayed reaction. The explantation in terms of impairment of a flexible noticing order is considerably more predictive, yet captures the spirit of the intent of the perseveration of set hypothesis.

The suggestion is, therefore, that the frontally lesioned primate is defective in problem solving whenever a process that corresponds to a flexible noticing order is demanded. From the analysis made above, it follows that a disruption of the mechanism that allows stimuli to be temporarily compounded would impair this process. It follows also that this temporary flexible stimulus-compounding mechanism is separable from the process that allows more permanent storage of representations of experiences, (e.g., in a discrimination tree).

In another sense, this line of reasoning leads to a return to Jacobsen's initial idea of an "immediate memory" mechanism. The detour through the flexible noticing order spells out the emphasis that must be placed, because of repeated experimental findings, on the processing by a working memory of the stimulus aspects of the situation.

Stimulus Compounding and Dominant Foci

In addition, neurologically, the search is shifted. Earlier notions of the immediate memory process led to hypotheses about memory trace formation and decay, and to experiments aimed at uncovering reverberatory circuits in the brain. The concept of a flexible noticing order process within a working memory leads instead to tracking down the mechanism of temporary, flexible stimulus compounding, perhaps through the formation of readily shifted dominant neural foci (see review by E. R. John, 1961). Such dominant foci can be manipulated in a classical Pavlovian situation, for instance, by training a dog to raise his right hind leg to a signal. When the response had been well established, the dog's right motor cortex was exposed and a patty of strychnine sulfate-soaked filter paper was placed over the area that controls the left foreleg. While the strychnine was effective, the dog was placed in a conditioning situation. Now he raised his left foreleg instead of his right hind leg whenever the signal was given.

The production and shift of dominant foci have recently been repeatedly studied (Morrell, 1961; Rusinov, 1956; Ukhtomski, 1927). Could frontal lesions be shown to alter the time course of the establishment or of

the shift of such dominant foci? If for no other reason than that the direction of experimentation has been altered, the experiments and analyses reported here may thus be shown by future events to have been worthwhile.

DISCUSSION

DR. HARLOW: I understand that on these problems you find differences between the frontal and normal animals. On search problems, perseveration may lead to high scores or low scores. You can't call strategy good or bad because it is perseverative or not perseverative. But this is a really beautiful technique, Karl, though it should be studied with older animals.

The reason I asked you about the age of your animals is that there is every reason to believe that an animal of this age makes the same kind of errors on the Hamilton search problems that are made by adults with bilateral frontal lesions.

We must specify the age of our animals; probably a lot of the confusion in the literature results from our not having this information. Actually, the older animal on the Hamilton perseveration test is consistent in his strategy. The young animal flits.

DR. PRIBRAM: I agree. However, there were differences in that study even between these 18-month-old animals, depending on whether they were normal or frontally lesioned. It was the normal animals who showed some tendency to pick up the same object more often, and they didn't shift as much. So, the results at least are there. They might have been much greater if we had used adult animals, of course. And other animals were tested on Hamilton's multiple-choice test about 2½ years after surgery, and surgery was performed about the 6 lb level, which, as you say, is probably a year or a year and a half.

DR. MEYER: The results of our research regarding search patterns in multiple-choice performance raise a question which is very important to any statement that you make about flexibility. It is a question of flexibility of what? Flexibility of response? Sets?

Paul Settlage and I (Meyer & Settlage, 1958) did the following experiment, much simpler than yours. There are four identical boxes. You put a peanut randomly in one of the four. Then you ask the monkeys simply to search through the boxes. Now, flexibility in that situation is the lack of predictability of any particular box opening, knowing that the monkey has opened one box, two boxes, three boxes, and so forth. On this test you have

most rigid animals, going one, two, three, four in the search patterns until they hit the peanut, and these are the normal monkeys.

The frontal animals go through the same routine, except they go one, four, three, two, and next time, one, three, two, four. They make exactly the same number of errors, they are just as good as the normal monkeys, but more flexible. You might say they are artists.

Now, is it flexibility that they lose?

DR. PRIBRAM: No, I wouldn't call that flexibility. That is where the analysis with respect to the nonordered patterns is important. In other words, they can perform but if you look for some order in their behavior there is none. By flexibility, I meant ordered flexibility. In other words, an instruction that they can follow which says "order your responses but differently each time."

DR. MEYER: If their behavior is not ordered, why are they as successful as normal animals?

DR. PRIBRAM: Probably on a statistical basis, I imagine. That is what we found in our four-choice situations also.

DR. MEYER: No, orderly behavior, it seems to me in this situation, is avoid the wrong alternative once the wrong alternative is discovered. They do that.

DR. HARLOW: You got differences between your normal and frontal groups in terms of search, not in terms of error. I didn't really trust this until we ran Hamilton perseveration as a maturation test. We had a 50-month-old group, a 30-month-old group, and a 12-month-old group. The 12-month group made more errors and showed more variation than the 30- and 50-month groups, which were very similar in total errors. In sequence changes, however, the 50-month group was far less variable than the two younger groups, which were closely similar in this respect. Because the Hamilton test looks so simple, you do not expect it to be so sensitive to maturational status.

DR. MEYER: The concept of order is still not resolved, it seems to me. The only disorderly behavior you can have in terms of success in a random search problem is that of making errors. If the animals are inherently disordered, they will repeat their past choices. That is one thing a frontal monkey does not do. They do not repeat their alternatives any more commonly than a normal does. A frontal monkey has to be very accurate to do this, because a normal monkey will settle down and start at one end and go through the list. Unless somebody coughs or slams a door, he never makes a mistake. If a frontal monkey is going to do well, without making the one, two, three,

four search pattern, he must have almost perfect retention of the alternatives he has used on this particular trial.

DR. PRIBRAM: That is what I thought at first. In our Hamilton situation, however, when we analyzed sampling and search patterns, we found that actually this kind of "randomization" can be obtained by doing just any old thing up to a point. Now, the frontally lesioned animal didn't maintain this, mind you, both in the sampling and search they learned; but they learned a little more slowly than did the controls. In other words, they came away from the chance pattern somewhat behind the controls. It wasn't very much, but certainly you can't say just because they avoid making errors in the search situation, which is what I had said previously too, that they are now using some kind of an order to control their behavior. There were ways of analyzing that data which cast some doubt on that notion.

DR. MEYER: But not orderly in terms of whether or not you can predict what they are going to do next, except that they will not repeat.

DR. GROSS: We did an analysis which I think is relevant to the discussion. We analyzed learning of the delayed-alternation test by frontals and normals by Frick-Miller method, but we did it in 100-trial blocks. We had analysis throughout the course of learning. In the beginning, the first 100 trials, say, we found frontals' behavior was less stereotyped than normal, and essentially you might say this was similar to your search situation, for the first 100 trials. But then as training went on, the frontals on this measure became more stereotyped in their behavior. They repeated the same response patterns more than the normals did. However, their performance in terms of percentage correct was poorer than that of the normals. So that they have stereotyped response patterns, but in this situation it was maladaptive. But then as training went on, and particularly after 1,000 trials, the frontal animals were still doing extremely poorly. At this point the response stereotypy was similar to that of the normals. So that if one selects 100-trial blocks in which the normals are doing as well as the frontals, if you take early blocks for the normals and very late blocks for the frontals, there is no difference on the Frick-Miller thing between the response pattern of the animals. This latter result might suggest that stereotypy of response would hardly be the sole principle reason why frontal animals fail in the alternation test.

DR. TEUBER: Since I have so often said publicly that delayed-response tests, or delayed-alternation tests, of the ordinary kind are *not* especially sensitive to frontal lobe damage in man, I want to take this back publicly on this occasion. Dr. Stephan Chorover in our laboratory has shown in an unpublished study with Malcolm Cole and George Ettlinger (unpublished observations, 1961) that severe and acute frontal damage *can* disrupt delayed

alternation. This work was begun at the Institute of Neurology (University of London, Queen Square), and has been continued in New York and now in Boston. The results are preliminary and tentative, but here are some examples: Of seven patients with severe frontal involvement (mostly by tumor), six failed a simple nonverbal delayed-alternation test. These results certainly fit those reported just now by Dr. Karl Pribram and, on other occasions, by Drs. Rosvold and Mishkin.

On the other hand, when we consider our cases of cerebral gunshot wounds, delayed-alternation defects of the kind observed by Chorover and his associates are rare, and not obligatory. Besides, in Chorover's own data there is a striking overlap. Although he found six failures on delayed alternation among seven cases of frontal lesion, he also found five such failures among eight nonfrontal lesions, i.e., cases of parietotemporal involvement. Thus, while a duly "monkified" (i.e., nonverbal) test of the delayed-alternation type may yield positive results after frontal lesions in man, the discriminating power of the test is none too great.

A further point: There are many indications from cases of gunshot wound of the frontal lobes that deficits in delayed alternation can be conspicuous in the acute phases after the injury, but are rapidly overcome. In this respect, one can probably say that these tasks are most persistently disrupted in the monkey, less in the chimpanzee, and least in man.