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A SEARCH FOR THE SPATIAL ENGRAM WITHIN THE FRONTAL LOBES OF MONKEYS

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Abstract. Four investigations were conducted concerning the relationship between sulcus principalis and the monkey's spatial capacities. The results of the first two studies indicated that lesions limited to the middle third of sulcus principalis but including both the superior and inferior banks resulted in severe deficits on spatial delayed-alternation and place reversal learning. Lesions of the anterior or posterior sectors of principalis or of the periarcuate region produced only mild, if any, impairments on the same spatial tasks. The third study demonstrated that the midprincipalis sector could be differentiated from the anterior and posterior sectors of principalis on anatomical as well as functional bases. The midprincipalis sector had heavy projections to the cingulate and retrosplenial regions while the posterior third had many efferent connections with the parietal lobe. The anterior third had limited projections to the cingulate region and none to the parietal lobe. The fourth investigation demonstrated that intact neural structures could assume some spatial functions after sequential destruction of sulcus principalis. Monkeys with serial, in comparison to one-stage, bilateral ablations of sulcus principalis demonstrated normal performance on a delayed-response task and on some place reversals, and partial recovery of delayed-alternation.

Since Jacobsen's (1935) early reports of large cognitive-learning deficits following ablation of the monkey's prefrontal association cortex a number of investigations (Mishkin 1964, Butter 1969, Mishkin et al. 1969, Iversen and Mishkin 1970) have demonstrated that the dorsolateral and orbital sectors of the prefrontal cortex subserve different functions, with the dorsolateral more involved in spatial tasks and the orbital more in the inhibition or control of dominant response tendencies. Within the dorsolateral sector, both Mishkin (1957) and Gross (1963) have reported that sulcus principalis represents a focal region for spatial tasks such as delayed-alternation and delayed-response. Monkeys with dorsolateral lesions ventral and/or dorsal to the principal sulcus were less impaired on these spatial tests than were monkeys with bilateral lesions limited to the banks and depths of the sulcus.

While these earlier attempts at localization of function analyzed the prefrontal cortex along the dorsal-ventral dimension, only recently have some investigators (Stamm 1969, Goldman and Rosvold 1970) examined the anterior-posterior axis to further define the minimal lesion both necessary and sufficient for a severe spatial deficit. Goldman and Rosvold (1970) have demonstrated that ablation of sulcus principalis and of the periarcuate region (including both banks of the arcuate sulcus) result in different types of spatial impairments (delay vs. non-delay spatial tasks), and Stamm (1969), using stimulation rather than ablation techniques, han shown that the posterior and middle thirds of sulcus principalis are the most crucial for delayed-response performance.

Given then the importance of sulcus principalis for the monkey's spatial capacities and the possibility that these abilities depend upon a specific anterior-posterior sector of principalis, we initiated a series of investigations designed to assess three questions concerning structure (sulcus principalis) and function (spatial abilities): (i) Is there a "spatial" focus within sulcus principalis? While Stamm's (1969) stimulation results suggest that the spatial deficits reported after total principalis lesions (Mishkin 1957, Gross 1963) may stem from a small area of tissue in the middle and/or posterior regions of the sulcus, there have been no lesion studies that systematically compared the behavioral functions of different sectors of sulcus principalis. (ii) If such a focus exists, can it be differentiated from other sectors of principalis on the basis of anatomical connections as well as behavioral functions? Since previous neuroanatomical studies (Nauta 1964, Johnson et al. 1968) have shown that sectors of the prefrontal cortex (dorsolateral vs. orbital) which differ in their behavioral functions also have different cortical and subcortical projections, it was anticipated that any "new" spatial focus within principalis might also have its own unique anatomical characteristics. (iii) Under what conditions can the structure–function relationship between sulcus principalis and its spatial capacities be altered so that other cortical or subcortical structures can assume principalis' behavioral functions? While it is now apparent that some recovery or compensation of spatial functions occurs after ablation of the dorsolateral prefrontal cortex during infancy (Harlow et al. 1964, Kling and Tucker 1968, Goldman et al. 1970). there has been no assessment whether such recovery is possible in the adult monkey.

Effect of selective lesions of sulcus principalis on retention of delayed-alternation

Twelve rhesus monkeys (*Macaca mulatta*) weighing between 3 and 4 kg were the subjects for this experiment. All monkeys learned preoperatively 5-sec spatial delayed-alternation (DA) in a modified Wisconsin General Test Apparatus (WGTA) with black wooden plaques covering the two foodwells on the tray. This test, of course, required the animal to alternate his responses to the right and left plaques on succeeding trials in order to receive a reward. If the monkey made an error on a given trial (that is, failed to alternate), the reward remained on the same side until the monkey responded to the correct plaque on some succeeding trial. A 5-sec interval between trials was employed. The monkeys were given 30 trials, including correction trials, each day to a criterion of 90 correct responses in 100 consecutive trials (including the correction trials).

After reaching learning criterion, 9 of the 12 animals received bilateral cortical lesions by subpial aspiration under aseptic conditions, and the remaining three monkeys served as unoperated controls (UC). Three monkeys received lesions of the periarcuate region (PA) including both banks and limbs of the arcuate sulcus but sparing the most superior 5 mm of the superior limb and the most inferior 8 mm of the inferior limb. Care was taken not to involve the posterior sector of sulcus principalis although the tissue surrounding the sulcus was included in this lesion.

For three animals cortical removal was limited to the middle third (9 mm) of sulcus principalis (MP). Both the superior inferior banks were removed; care was taken to spare the anterior and posterior thirds of the sulcus.

Three monkeys had bilateral removal of the inferior parietal lobe (IP). This lesion included the caudal third of the lower bank of the intraparietal sulcus and the adjacent part of the inferior parietal lobule, and it extended ventrally to the caudal tip of the Sylvian fissure and the dorsal bank of the superior temporal sulcus.

All monkeys were tested for retention of DA 10–14 days after surgery. Again, they received 30 trials a day until they reached a criterion of 90 correct responses in 100 consecutive trials. If an animal failed to relearn within 1000 trials, testing was terminated at this point. The results of this and all following tests of DA retention were analyzed by the Kruskall–Wallis and Mann–Whitney *U* non-parametric statistical tests.

The results for this first DA retention are shown in Table I. The three MP monkeys failed to relearn DA while all PA, IP, and UC did so. The difference in trials and errors between MP and the other groups is statistically significant ($p = 0.05$).

TABLE I

Mean number of trials and errors to relearn 5-sec spatial delayed-alternation

Group	Trials	Errors
Operation (retention) I		
MP	1000	408
PA	343	61
IP	30	8
UC	83	16
Operation (retention) II		
PA	260	76
IP	227	45
UC	57	9
Operation (retention) III		
MP	1000	359
AP	243	44
PP	570	131

After this first retention test the 6 operated monkeys that had relearned DA received a second operation. Monkeys that had received periarcuate lesions in the first operation received bilateral inferior parietal lesions in the second (IP); monkeys that had had inferior parietal removals in the first operation now received periarcuate lesions (PA). A second test of DA retention was conducted with the 6 animals with new lesions and the 3 UC monkeys.

All monkeys relearned DA within 1,000 trials (Table I) although the PA monkeys required significantly ($p = 0.05$) more trials and errors than did the UC group.

To ascertain whether the midprincipalis area represented a focal point for DA deficits, 5 of the 6 monkeys (one died after the second DA retention) with periarcuate and parietal lesions received a third operation. For 2 monkeys, the middle third of sulcus principalis was removed (MP); for three others, the lesion was confined to the anterior third of principalis (AP). The 3 controls underwent their first operation receiving lesions in the most posterior third of principalis (PP). 10–14 days following surgery the monkeys were administered another (third) est of DA retention.

As indicated by the results of the first operation, the 2 monkeys with midprincipalis lesions failed to relearn DA within 1,000 trials (Table I). However, the 6 monkeys with anterior or posterior principalis lesions all relearned. Despite the large discrepancy between the means of the anterior and posterior groups, the differences are not significant ($p > 0.05$) largely because of the poor retention of one AP monkey (114 errors, 590 trials).

Following completion of the third DA retention, all monkeys were sacrificed and their brains prepared for histological examination. The extent of the lesion on each coronal section was measured with calipers and transferred to a diagrammatic model of the principal sulcus. This model included not only the anterior-posterior extent of the sulcus but also the surface-depth dimension along the entire AP extent. A polar planimeter was used to compute the total area of the sulcus and of the tissue destroyed. With these measurements it was possible to estimate percentage of damage to the total sulcus.

Figure 1 shows the reconstructions of three brains with AP, MP, or PP lesions. For two of the brains the dorsolateral extent of periarcuate and inferior parietal damage is also presented. The various principalis lesions involved from 30 to 42% of the total sulcus with only slight differences among the three principalis groups. In Fig. 1 the AP lesion in

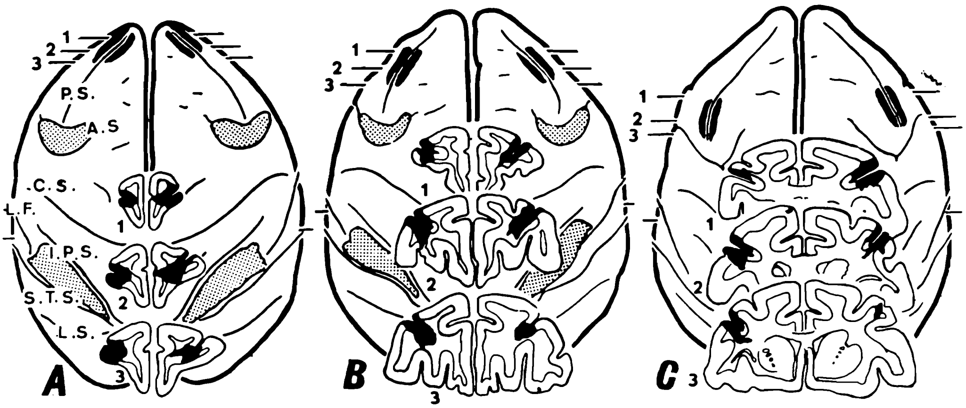

Fig. 1. Reconstructions of three brains with anterior (*A*), mid- (*B*), or posterior (*C*) principalis lesions. Three cross sections through different levels of the lesions are shown for each brain. Area in black represents dorsolateral extent of principalis damage; stippled area in brains (*A*) and (*B*) indicates periarcuate and inferior parietal lesions made in the first two operations. A.S., arcuate sulcus; C.S., central sulcus; I.P.S., intraparietal sulcus; L.F., lateral fissure; L.S., lunate sulcus; P.S., principalis sulcus; S.T.S., superior temporal sulcus.

brain *A* involves 35% of the sulcus, the MP lesion in brain *B* 39%, and the PP lesion in brain *C* 32%. In the area of the lesions the gray matter was almost completely ablated with only slight involvement of underlying white matter. No damage to the caudate nucleus or other subcortical structures was noted after any of the lesions.

As in previous reports (Mishkin 1957, Goldman and Rosvold 1970), this study demonstrates the importance of sulcus principalis for DA performance but, unlike the earlier studies, suggests that this sulcus is not homogeneous with regard to DA. Lesions 9 mm in extent and limited to the middle third of sulcus principalis resulted in DA deficits at least as large as those reported after total ablation of the sulcus, while lesions in other sectors of principalis or in the periarcuate frontal region had only mild-to-moderate behavioral effects. The finding that all 5 monkeys with midprincipalis lesions failed to relearn, whereas all 6 with anterior or posterior principalis lesions did so, suggests that these differences are highly reliable.

These findings are consistent with those of other studies employing unit recording (Kubota and Niki 1971) and stimulation (Stamm 1969) techniques. Kubota and Niki (1971) found that the unit activity of two types of prefrontal cells correlated with delayed-alternation performance and that both cell types were limited to the midprincipalis area. Stamm (1969) has reported that electrical stimulation of the midprincipalis, but not anterior principalis, region significantly impaired delayed-response performance. However, Stamm also found that stimulation of the posterior principalis region resulted in severe delayed-response deficits while in the present study ablation of the posterior principalis region was followed by only transient DA impairments. It seems possible that spread of current from the posterior to the middle sector of principalis may account for the more severe spatial deficit in Stamm's study.

Spatial deficits in monkeys after selective lesions within the middle third of sulcus principalis

The results of the first investigation demonstrated that the midprincipalis region serves as a focus for DA performance, but the possibility of further localization of spatial abilities within the 9 mm midprincipalis region still remained. Since Sanides' (1969) report that the superior (upper) and inferior (lower) banks of sulcus principalis are architectonically distinct suggested that the two banks (within the midrincipalis area) might be subserving different behavioral functions, we examined the spatial capacities (DA and place reversal) of monkeys with lesions confined to the superior and/or inferior banks of the midprincipalis region.

In addition to the question of localization, this investigation also assessed whether the midprincipalis region represents a focal region for a general spatial deficit or whether its involvement is limited to DA. Although Mishkin (1964) noted that DA, place reversal (PR), and other tasks requiring spatial discriminations are impaired after total dorsolateral prefrontal ablations, the recent finding (Goldman and Rosvold 1970) that DA and a conditional position response task depend upon different sectors of the dorsolateral cortex raises the possibility that DA and PR may also be mediated by different cortical foci and that their correlation after large prefrontal lesions is artifactual. If, however, performance on DA and PR are correlated after small 9 mm lesions within the midprincipalis region, then it seems likely that the two tests do depend upon the same neural structures and involve a common spatial factor. Our second investigation examined these possibilities.

Thirteen naive rhesus monkeys ranging in weight from 3 to 4 kg served as subjects. Again, all testing was performed in a modified WGTA. Pre-operatively, all animals learned DA with the same methods and to the same criterion employed in the previous study.

After learning DA all monkeys received a bilateral midprincipalis lesion. For 5 of the monkeys, the lesion involved the superior bank of the middle 9 mm of sulcus principalis (SB); for 4 monkeys, the lesion involved the inferior bank of the midprincipalis region (IB); for 4 monkeys, the lesion involved both banks in the midprincipalis region (CB). For the SB and IB lesions all gray matter in the depths of the bank was ablated without damaging any appreciable amount of cortex on the adjoining bank. Two of the CB monkeys had superficial damage of both the inferior and superior banks of the principal sulcus; the two remaining CB monkeys had damage which included both the superficial region and depths of the superior and inferior banks in the midprincipalis region.

Figure 2 shows the reconstructions of representative IB (Monkey 43) SB (Monkey 53), and CB (Monkeys 57 and 31) lesions. One CB reconstruction (Monkey 57) had only superficial damage to both banks while the other CB (Monkey 31) reconstruction had extensive damage to the superficial aspects and depths of the superior bank and to the depths of the inferior bank. Table II shows for each monkey the percentage of the total sulcus destroyed, as well as percentage of damage to the superior and to the inferior banks of the sulcus. While the CB group had somewhat greater total damage than did the IB and SB groups, statistical analyses (Mann–Whitney *U*) did not show any of the group comparisons (CB vs. IB; CB vs. SB; IB vs. SB) to be significant.

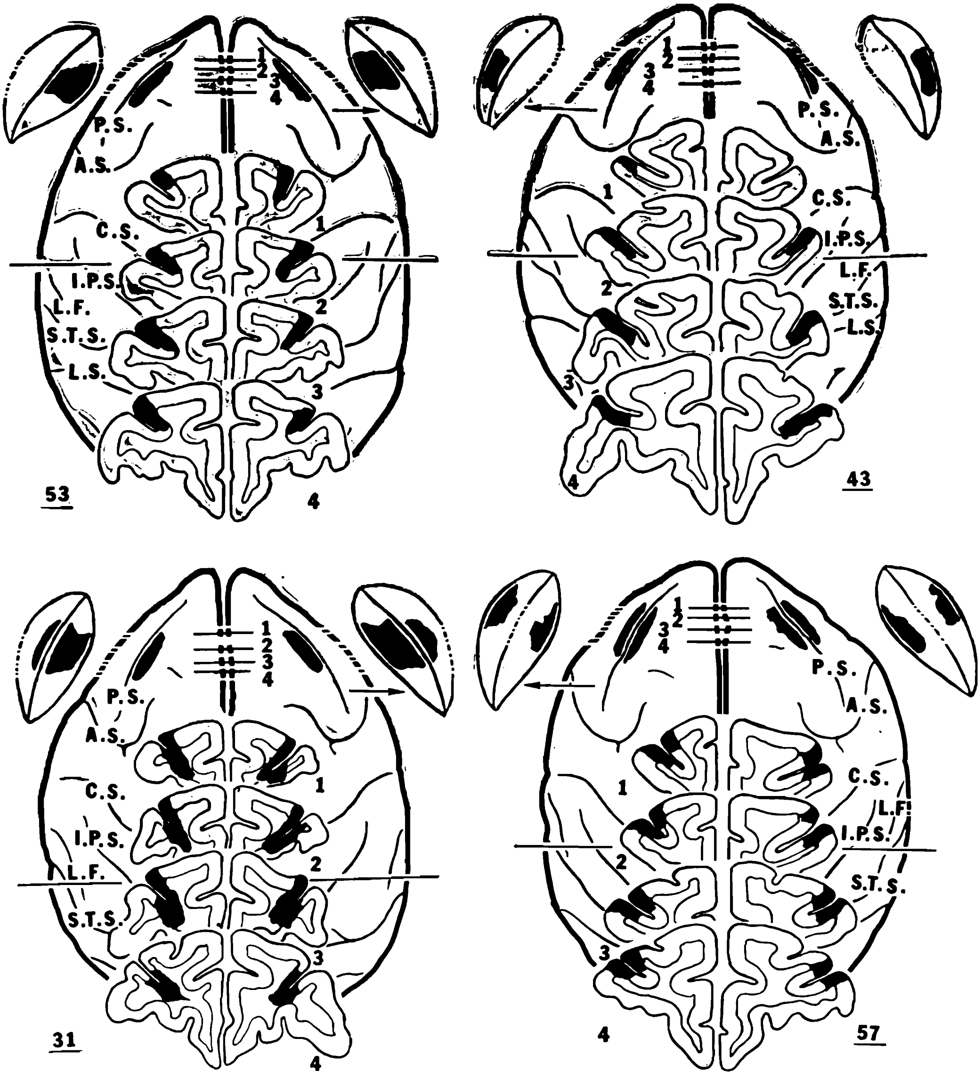

Fig. 2. Reconstructions of one SB (Monkey 53), one IB (Monkey 43), and two CB (Monkeys 31 and 57) lesions. Dorsal view with coronal sections are presented. To the right and left of each dorsal reconstruction is an open diagrammatic model of sulcus principalis showing the entire sulcus including the depths and the lesioned area (in black). P.S., principal sulcus; A.S., arcuate sulcus; I.P.S., intraparietal sulcus; L.F., lateral fissure; S.T.S., superior temporal sulcus.

10–14 days following surgery all monkeys were retrained on DA. If a monkey failed to reach criterion within 1000 trials, DA testing was terminated.

Following the attainment of criterion or failure on DA, all monkeys

TABLE II

Anatomical and behavioral results: percentage of total damage to principal sulcus, to superior bank, to inferior bank, errors on DA retention, savings (errors) on DA retention, total errors on PR learning

S	Lesion group	Percentage of total sulcus	Percentage of superior bank	Percentage of inferior bank	DA Retention	DA Savings	PR Learning
35	SB	18	36	2	140	41	37
48	SB	16	30	2	0	100	61
51	SB	16	33	2	29	73	16
53	SB	17	33	1	51	57	5
60	SB	22	36	6	0	100	16
$\bar{X}$	SB	18	34	2.6	44	74	27
34	IB	17	0	33	17	88	66
37	IB	14	0	28	152	8	36
43	IB	16	0	31	8	91	37
54	IB	12	0	26	13	92	35
$\bar{X}$	IB	15	0	30	48	70	44
31	CB	32	41	23	287*	—196	85
32	CB	26	36	16	478*	—265	76
65	CB	30	30	30	115	—4	15
57	CB	15	14	16	275*	—511	197
$\bar{X}$	CB	26	30	21	289	—244	93

* Failed to relearn in 1 000 trials.

commenced PR testing. The animals were initially trained to discriminate between the left and right foodwells (now covered by identical red wooden plaques). Thirty trials were administered daily until the monkey reached a criterion of at least 27 correct responses (90% or better) in a single testing session. On the day after criterion had been achieved, the location of the reward was shifted to the previously unreinforced position. This shift of reward constituted the first of the three place reversals which comprised this task. Again, the monkeys were given 30 trials per day until they reached the criterion of at least 27 correct responses on any one day. The second and third reversals were administered in an identical manner.

Table II shows the number of errors made by each operated monkey in relearning DA. The CB group made significantly (Mann–Whitney U, $p > 0.05$) more errors than did the SB or IB groups while the difference between the SB and IB group did not approach significance. Analysis of the savings scores (in percentage) for DA retention (Table II) revealed that all the CB monkeys had negative savings scores while all the SB and IB animals had positive scores. The differences between the CB and IB groups and between the CB and SB groups were significant ($p > 0.025$, $p < 0.01$, respectively). Again the difference between the IB and SB groups did not approach significance.

To assess whether size of lesion, as well as locus, was an important factor in DA performance a Spearman Rank Order Correlation was performed. The results of this analysis did not indicate a significant correlation (*rho* = 0.30, $p > 0.05$) between total lesion size and DA retention errors, a finding which suggests that locus of lesion and not size of lesion is the more critical factor in DA deficits.

TABLE III

Mean errors on three place reversals by SB, IB, and CB groups

Group	Reversal 1	Reversal 2	Reversal 3
SB	17.8	6.6	2.6
IB	21.8	13.5	8.3
CB	48.8	33.5	11.0

Table III shows the mean errors compiled by the three groups on the three place reversals. While the mean errors for the three groups suggest that the CB group is impaired in comparison to the SB and IB groups, only one group comparison (Reversal 2, CB vs. SB) proved significant (Mann–Whitney *U*, $p < 0.05$). To further assess whether DA and PR performances were related within our population, a rank order correlation was performed on DA and total PR error scores (Table II). The results of this analysis yielded an insignificant correlation (*rho* = 0.41, $p > 0.05$).

While the results of the group comparisons on PR and of the correlation between DA and PR suggest that these two tasks are not closely related, one further factor may have masked a significant relationship between DA and PR. Of the 13 monkeys, only 3 failed to relearn DA before commencing PR learning. Thus, if an animal regains the ability to alternate or spatially reverse his responses from trial-to-trial (i.e., retention of DA), there may be no reason to expect it to encounter difficulty on a second PR task. If, on the other hand, a monkey fails to regain his pre-operative spatial alternation performance, it may also evidence difficulties on a second PR task. To assess whether failure to relearn DA is a good predictor of PR performance, the PR performance (total errors) of the three monkeys that failed DA retention was compared with the

PR performance of the 10 monkeys that relearned DA within 1000 trials (Table II). The monkeys that failed (mean: 119) made significantly (Mann–Whitney U, $p < 0.01$) more errors on the three place reversals than did those that relearned (mean: 32).

The results of this investigation have relevance for four issues pertaining to the function of sulcus principalis.

1. As demonstrated in the previous investigation, bilateral lesions limited to the middle third of sulcus principalis do result in moderate-to-serve deficits in DA retention. Unlike the prévious investigation, however, the impaired monkeys (i.e., the CB group) in the present study had lesions which involved less than one-third of the total sulcus. In fact, 2 of the 3 monkeys that failed DA (Monkeys 32 and 57) had only 26 and 15% of their sulci destroyed. It appears then that a bilateral principalis lesion involving less than 30% of the total sulcus but located within the middle third (i.e., middle 9 mm) of the sulcus results in severe DA retention deficits.

2. Despite cytoarchitectonic differences between the superior and inferior banks (Sanides 1969), neither of these cortical regions within the midprincipalis sector appear to serve in isolation as a focal region for DA performance. Rather, some damage to both banks is necessary to produce a severe impairment in the retention of DA. While it is possible that increased size and not involvement of both banks is the critical factor for DA performance, other findings make this “mass action” interpretation dubious. The correlation between lesion size and DA deficit was low and insignificant, and the CB group did not differ significantly from the IB or SB groups with regard to total lesion size. In addition, Monkey 57 who had a superficial lesion of both banks and failed to relearn DA had a smaller lesion (15% of total sulcus) than seven of the nine monkeys with damage confined to either the superior or inferior bank. It seems then that involvement of both banks, not lesion size, is the more critical factor for DA performance.

3. The present findings also suggest that the cortical tissue in the depths and in the more superficial regions of the sulcus are both involved in DA performance. Monkeys 57 and 65 had lesions limited to the superficial regions of both banks and were impaired on DA. Monkeys 31 and 32 had lesions which destroyed the depths of both banks, and these animals were also severely impaired on the DA task. This evidence for equality of depth and superficial tissue must be tempered, however, by the fact that the monkeys with depth lesions also had damage to the superficial regions of the superior bank.

4. The behavioral results indicate that DA and PR learning share a common spatial factor (Mishkin 1964) which is mediated in part by

cortical tissue in the midprincipalis region. Monkeys that fail to relearn DA make significantly more errors on PR than do monkeys that relearn DA. If an animal fails to reverse his spatial responses on successive trials (DA), then he also evidences difficulty in the reversal of a learned position habit (PR). In contrast, animals that retain or relearn the ability to reverse spatial responses from trial-to-trial later reverse acquired spatial habits without difficulty. Because of this dichotomy in PR performance between monkeys that relearn and monkeys that fail to relearn DA, the overall correlation between DA and PR was low and insignificant. Several monkeys that were impaired on DA (i.e., made more than 100 errors and had near zero or even negative savings scores) but relearned the task within 1,000 trials were unimpaired on PR. Thus, the lack of significant differences between the CB and the other lesioned groups on PR can be attributed to the PR performance of one CB animal (Monkey 65) who made 115 errors (i.e., a moderate deficit) in relearning DA and then only 15 total errors on PR.

Efferent cortical projections of the anterior, middle, and posterior sectors of sulcus principalis

Given these functional differences between the middle and other sectors of principalis, it seemed pertinent to determine whether the various sectors could be differentiated anatomically as well as behaviorally. While a number of investigations (Nauta 1964, Akert 1964, Johnson et al. 1968, Pandya and Kuypers 1969) have established that sulcus principalis, the surrounding dorsolateral prefrontal cortex, and the orbital prefrontal cortex have distinctive cortico-cortical and cortico-subcortical projections, little is known concerning the anatomical connections of the various sectors of sulcus principalis. Thus, in our initial anatomical investigation, we examined the efferent cortico-cortical projections of the anterior, middle, and posterior sectors of sulcus principalis.

Nine rhesus monkeys received unilateral ablations (subpial aspiration) of various parts of the upper and lower banks of sulcus principalis. After a survival time of 7 days the animals were sacrificed and their brains prepared for histological examination. The cut brain sections were stained by the modified Nauta and Fink–Heimer methods. The degenerating elements were noted and charted by means of a X-Y recorder, and the patterns of cortical degeneration and the extent of the individual lesions were then mapped on tracings of the lateral, medial, and basal views of each brain.

Figure 3 shows the anatomical results for monkeys with lesions of the superior bank of sulcus principalis. In case 1, the lesion involved the rostral third of the sulcus; in case 2, the middle third; and in case 3, the posterior third. These three sectors of principalis can be differentiated by treir efferent connections with the cingulate, parietal, and temporal regions. The lesion in the middle sector of principalis resulted in heavy fiber degeneration along the entire cingulate gyrus, in the retrosplenial area, and along the medial portion of the parahippocampal gyrus. In comparison, the brain with a lesion in the posterior principalis sector (case 3) displayed little, if any, degeneration in the cingulate region while the brain with an anterior principalis lesion (case 1) showed limited (i.e., less than in case 2) degeneration along the cingulate gyrus and neighboring retrosplenial area.

Parietal degeneration also varied with the placement of the principalis lesion. After ablation of the posterior sector of principalis (case 3) degenerating elements were noted on the lateral as well as medial portions of the parietal lobes. The degenerating terminals on the medial surface were confined to a sector behind the cingulate sulcus while on the lateral surface degeneration occurred in the caudal portion of the superior parietal lobule and in the corresponding banks of the intraparietal sulcus. Neither the anterior nor the midprincipalis lesions resulted in such parietal degeneration.

The temporal lobes also displayed fiber degeneration after superior bank lesions. This degeneration was marked in case 1 and 2 in which the terminations were found in the rostral half of the upper bank of the superior temporal sulcus and in the adjacent portion of the superior temporal gyrus. Case 3 contained only occasional degenerated fibres in the temporal region.

In general, lesions of the inferior bank of sulcus principalis (six monkeys) led to degeneration patterns similar to those found after superior bank lesions (Fig. 4). The midprincipalis lesions (case 8) resulted in heavy cingulate and retrosplenial degeneration while the anterior lesions (case 5) were followed by limited cingulate degeneration and the posterior lesions (case 10) by none. In contrast, only the posterior principalis lesions displayed degenerating elements in the parietal region although in these instances the degeneration was limited to the lateral surface of the parietal region. For the temporal lobes, the degeneration pattern was again topographic: the anterior and midprincipalis brains showed degeneration in the rostral superior temporal region while the posterior principalis brains displayed degeneration in the posterior superior temporal region.

The inferior bank lesions did differ, however, in one important respect from the upper bank lesions — i.e., the lower, but not the upper, bank had connections with the orbital prefrontal cortex. Lesions of the inferior bank resulted in fiber degeneration along both the lateral and

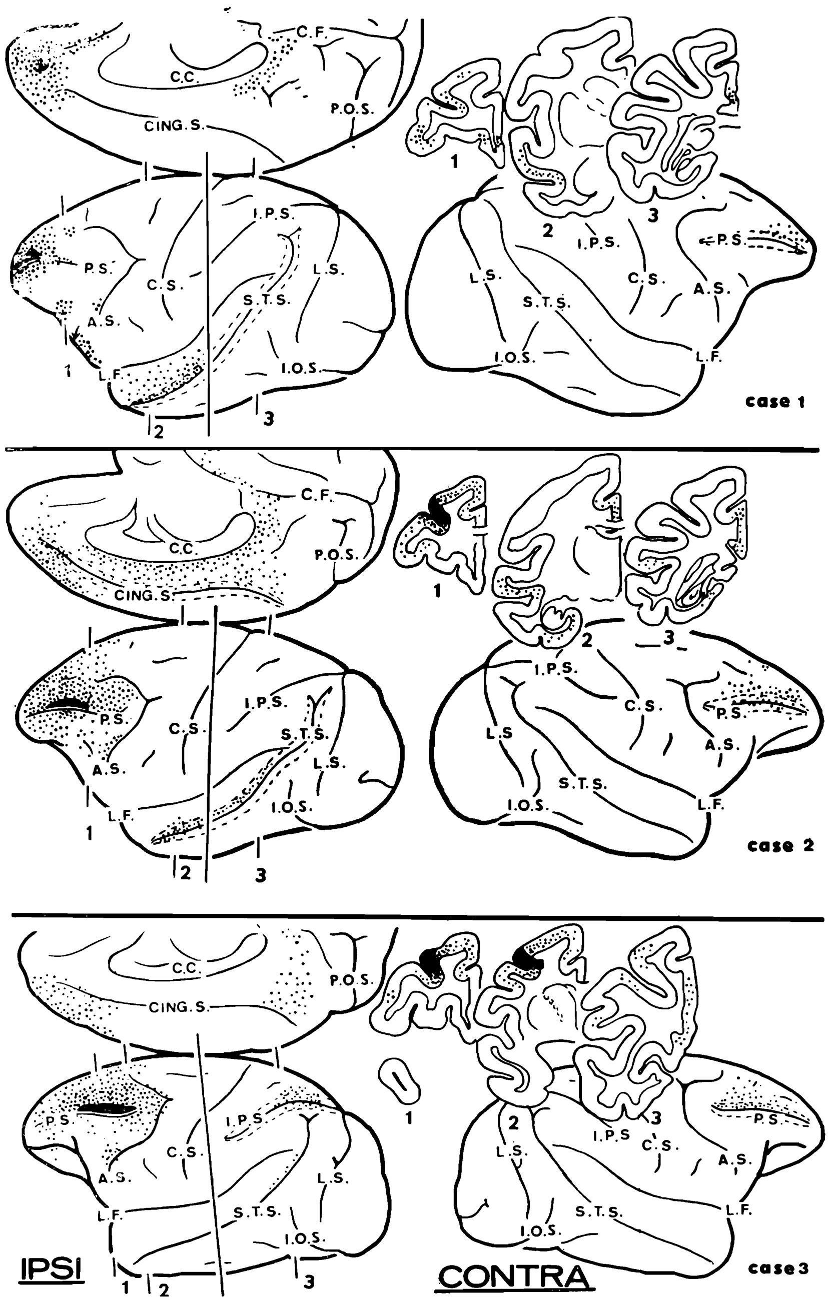

Fig. 3. Diagrammatic representation of the three lesions (jet black) of the upper bank of the principal sulcus and resulting fiber degeneration (dots) in ipsi- (on left) and contra- (on right) lateral hemispheres. Representative transverse sections from the ipsilateral hemispheres are shown in the upper right hand corners. A.S., arcuate sulcus; C.C., corpus callosum; C.F., calcarine fissure; C. S., central sulcus; Cing. S., cingulate sulcus; I.O.S., inferior occipital sulcus; I.P.S., intraparietal sulcus; L.F., lateral fissure; L.O.S., lateral orbital sulcus; L.S., lunate sulcus; M.O.S., medial orbital sulcus; P.O.S., parieto-occipital sulcus; P.S., principal sulcus; S.T.S., superior temporal sulcus.

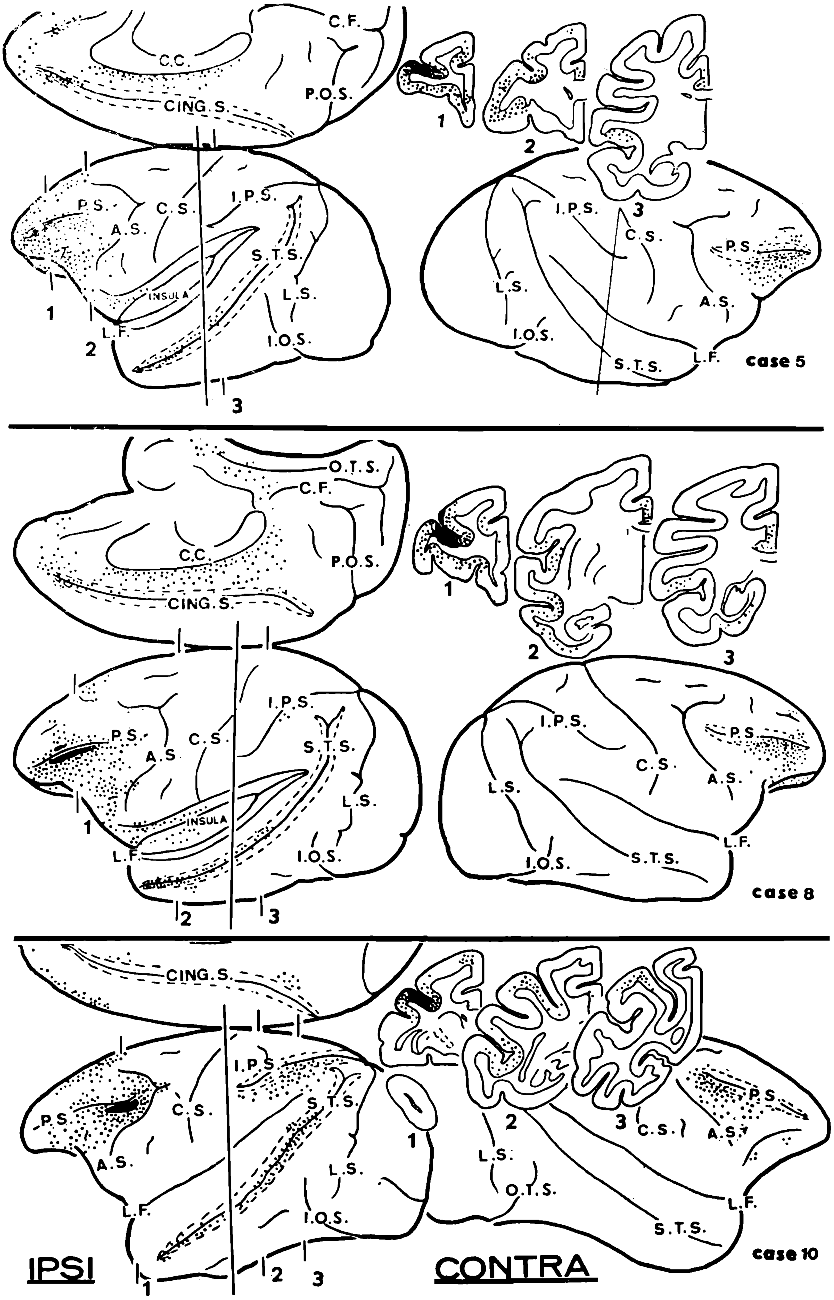

Fig. 4. Diagrammatic representation of the three lesions of the lower bank of the principal sulcus and resulting fiber degeneration in ipsi- (on left) and contra- (on right) lateral hemisperes. Representative transverse sections from the ipsilateral hemispheres are shown in the upper right hand corners. The same labeling key used in Fig. 3 is also employed in this Figure.

medial orbital sectors, but many more projections to the lateral than to the medial regions were noted.

These anatomical results indicate that various sectors of sulcus principalis may be differentiated not only on the basis of spatial function but also with respect to their efferent cortico-cortical connections. The middle third of the sulcus (both banks) has major connections with the cingulate gyrus and retrosplenial area while the caudal third of sulcus principalis, like its neighboring periarcuate region (Pandya and Kuypers 1969), has connections with the posterior parietal lobe. From these differential projection patterns it appears that the majority of prefronto-limbic projections arise from the cortex occupying the middle portion of sulcus principalis. The finding (Pribram et al. 1962) that cingulate lesions result in spatial deficits similar to those noted after midprincipalis lesions suggests that these two anatomically associated structures may constitute part of a neuroanatomical system concerned with a specific spatial function.

Although the caudal third of the principal sulcus is not involved in the prefonto-limbic system, it and the adjacent periarcuate region (Pandya and Kuypers 1969) send numerous projections to the parietal lobes. In addition, these adjoining prefrontal regions share a common pattern of inputs from other cortical areas. Pandya and Kuypers (1969) have reported that the periarcuate region (including both banks of the arcuate sulcus and the cortex in the concavity of the sulcus), the caudal sector of the principal sulcus, and the inferior parietal lobule receive afferent inputs from the visual, auditory, and somatosensory association areas and have suggested that these sensory convergence areas may be crucial for the integration of divergent sensory information. The recent behavioral evidence (Goldman and Rosvold 1970) that ablation of the periarcuate region is followed by deficits on a spatial task requiring the association of auditory, visual, and kinesthetic cues is consistent with this integration hypothesis. Similarly, N. Butters and D. N. Pandya (unpublished data) have found that ablation of both the periarcuate and inferior parietal convergence areas results in a severe deficit on a conditional multimodal task involving visual and auditory cues while intra-modal discriminations employing the same sensory cues remain unimpaired.

It appears then that the periarcuate-caudal principalis and the midprincipalis areas are involved in two distinct neuroanatomical systems concerned with different behavioral functions. The intact midprincipalis region (and cingulate cortex) may subserve delay-type spatial tasks (e.g., DA), and the periarcuate-caudal principalis (and inferior parietal lobule) may be involved in the mediation of multi-modal associations.

While the different sectors of principalis may be differentiated by their cingulate and parietal projections, these prefrontal regions share some common but topographic projections to the superior temporal lobe. The rostral portion of principalis projects to the rostral part of the superior temporal sulcus, the midprincipalis to the rostral and middle portions, and the caudal lower bank of the principal sulcus sends projections to the middle and caudal sectors. Unfortunately, in view of the current state of knowledge, it is difficult to attach any functional significance to these topographic prefronto-temporal connections.

Recovery of spatial functions after serial ablation of sulcus principalis

The three previous investigations are all exemplars of a traditional neuropsychological approach. An attempt was made to isolate the specific neural tissue (midprincipalis) involved with a behavioral function (spatial differentiations) and to describe some of the neuroanatomical characteristics (efferent cortico-cortical connections) of this tissue. Underlying this research strategy are some implicit assumptions concerning structure-function relationships in the adult brain. Although exceptions are made for the few "statictically variant" adults who quickly recover behavioral functions after extensive brain damage, it is generally assumed that structure–function relationships are fixed. More specifically, many investigators accept the notion that the brain is innately wired into fixed anatomical circuits consisting of cortical and subcortical structures that mediate specific behavioral functions and that once these circuits are damaged, no reorganization of neural circuits and behavioral functions is possible.

Despite the tenacity with which these notions are supported, a number of ingenious neuroanatomical and behavioral investigations concerned with recovery of function have cast serious doubts upon the assumptions of innate permanent circuits and fixed structure–function relationships. Raisman's (1969) demonstration of axonal migration from one neural locus to another after brain damage has questioned the permanency of neural connections and established the groundwork for a mechanism of neural reorganization. Many behavioral investigations (Harlow et al. 1964, Kling and Tucker 1968, Goldman et al. 1970) have reported that adolescent monkeys that had suffered extensive prefrontal ablations during infancy displayed almost normal performance on some spatial tasks (e.g., delayed-response), a finding which suggests that intact neural structures may assume the functions of tissue damaged early in life.

In addition to these infant studies, other investigations have shown that such recovery of function is possible in mature organisms following sequential surgery. Rats with multiple-stage bilateral removals of cortical or subcortical structures are less impaired on several behavioral tasks than are animals with single-stage ablations of identical tissue (Stein et al. 1969). While these ameliorating effects of serial lesions have been demonstrated in cats (Chow and Randall 1964) and also in monkeys after ablation of primary sensory cortex (Stewart and Ades 1952), such recovery of function following serial damage to the prefrontal association cortices has not been reported on the primate level.

Given then the recovery of spatial functions after infant prefrontal lesions and the possibility that such neural plasticity can also occur in the mature organism after sequential surgery, we assessed in the present investigation whether serial ablation of sulcus principalis would result in a sparing of the spatial functions usually impaired after one-stage bilateral lesions. Monkeys with serial or one-stage bilateral ablations of sulcus principalis were tested on three spatial tasks: DA retention, 5-sec delayed-response (DR), and PR learning.

Ten naive adolescent rhesus monkeys ranging in weight from 3 to 4 kg served as subjects. Each of the monkeys was trained pre-operatively on 5-sec DA using the same apparatus (WGTA) and methods described in the previous investigations. Upon attaining criterion on DA, the animals were designated to receive either a single-stage (SS) or multiple-stage (MS) ablation of sulcus principalis.

All SS monkeys received bilateral lesions of principalis in one operation 10 weeks after reaching criterion on DA. In the MS group, sulcus principalis was removed in four operations spaced 3 weeks apart with the first operation occurring within 1 week of attaining criterion on DA. Each stage of MS surgery involved the removal of one bank of sulcus principalis (e.g., the first operation — left hemisphere, lower bank), and on each succeeding operation the hemisphere and bank were changed (e.g., the second operation — right hemisphere, upper bank). Two weeks after all surgery had been completed the monkeys commenced post-operative testing for retention of DA followed by training on a 5-sec DR task and then on PR learning. Following the completion of behavioral testing, the monkeys were sacrificed and their brains prepared for histological examination.

Like DA, DR and PR testing were conducted in a modified WGTA with raising serving as reinforcements. The monkeys were tested 5 days a week, 30 trials a day for all three tasks.

On the DR task, the monkeys were initially allowed to observe the investigator bait and cover one of the two foodwells and then to respond immediately (zero delay, no screen). Upon reaching criterion (at least 27 correct responses in 30 consecutive trials) at this non-delay interval, delay procedures were introduced by lowering an opaque screen between the monkeys and the manipulanda immediately after the baiting of a foodwell. At first the screen was lowered and raised as quickly as possible (zero delay, with screen). When the monkeys reached criterion at this 0-sec delay (with screen), the interval between the lowering and the raising of the screen was increased by 1-sec intervals each day until the monkeys demonstrated criterion performance with a 5-sec delay period. If at any given delay (e.g., 3-sec), the animals failed to obtain 27 correct responses in 30 trials, the interval was decreased by 1-sec on the following day (e.g., 2-sec). Testing was terminated if an animal failed to reach criterion at the 5-sec delay interval within 1000 trials.

PR training involved the same methods described in the second investigation except that four, instead of three, reversals were completed in this experiment.

Table IV shows the behavioral results for this experiment. All data were analyzed by the Fisher Randomization Test. To asses the monkeys' overall spatial performance, the total number of errors on all three spatial tasks was calculated for each animal. The MS made significantly ($p < 0.05$) fewer total errors than did the SS monkeys.

TABLE IV

Errors compiled by MS and SS monkeys on DA retention, DR acquisition, PR learning, and total errors

MS Monkeys	DA	DR	PR1	PR2	PR3	PR4	Total errors
36	5	107	59	16	14	11	212
52	384	68	20	16	17	6	511
46	345	34	19	15	7	3	423
39	308	86	17	8	5	3	427
62	330	20	25	11	6	2	394
$\bar{X}$	274	63	28	13	10	5	393
SS Monkeys							
41	76	123	17	13	7	6	242
42	542	31	11	11	89	33	717
38	479	245	68	101	41	30	964
58	360	178	22	27	28	10	625
59	445	97	36	13	11	6	608
$\bar{X}$	380	135	31	33	35	17	631

On DA retention, the MS monkeys made fewer errors than did the SS animals, but this difference does not approach statistical significance. However, in both surgical groups one monkey relearned DA within 1000 trials while the other four failed to do so. When the performance of monkeys who failed to relearn DA are compared, significant differences do appear. While the MS (mean: 193 errors) and SS (mean: 213 errors) monkeys perform almost identically for the first 500 retention trials, the MS (mean: 124) made significantly ($p < 0.05$) fewer errors than did the SS (mean: 191) monkeys during the last 500 retention trials. Thus, the MS monkeys show considerable improvement during the 1000 retention trials (78% correct responses during last 200 trials) while the SS monkeys reveal little improvement (60% correct during last 200 trials).

On DR, the MS monkeys made fewer errors than did the SS monkeys ($p < 0.07$). All 5 MS animals reached criterion within 1000 trials while 2 of the SS monkeys failed to do so.

The performances of the two groups on the first two spatial reversals were not significantly different, but on both the third and fourth reversals the MS made significantly ($p < 0.05$) fewer errors than did the SS monkeys. Again, like their performance on DA, the serial monkeys' PR performance improved with practice while the one-stage monkeys failed to demonstrate such gains.

The histological findings are graphically represented in Fig. 5. While all SS lesions were confined to the banks and depths of sulcus principalis MS ablations extended beyond principalis onto the surrounding lateral frontal cortex. This additional damage was unintended and appeared to be related to the multiple surgical entries into the same region. As a consequence of this additional damage, however, the MS monkeys had significantly larger total lesions ($p < 0.01$) than did the SS animals. The histology did not reveal a significant difference between the two groups in terms of the amount of damage to the banks and depths of sulcus principalis. There was no significant ($p > 0.10$) correlation between the extent of princnpalis damage and the post-operative perfomance of either the MS or SS monkeys (*rho*: +0.24, +0.21, respectively). Finally, the histological data did not provide an explanation for the atypical behavior of MS-36 or SS-41, the animals that relearned post-operative DA with considerable savings. Their lesions, both in terms of size and location, were indistinguishable from those of other members of their respective groups. Thus the performance of MS-36 and SS-41 was included in all post-operative analyses, with the exception of the comparison concerned with those animals that failed to attain criterial performance on DA retention.

The present results indicate that partial recovery of spatial functions can occur not only after infant lesions but also following serial ablation of sulcus principalis in the mature monkey. Although the serial animals had larger prefrontal lesions than did the one-stage monkeys, the serial

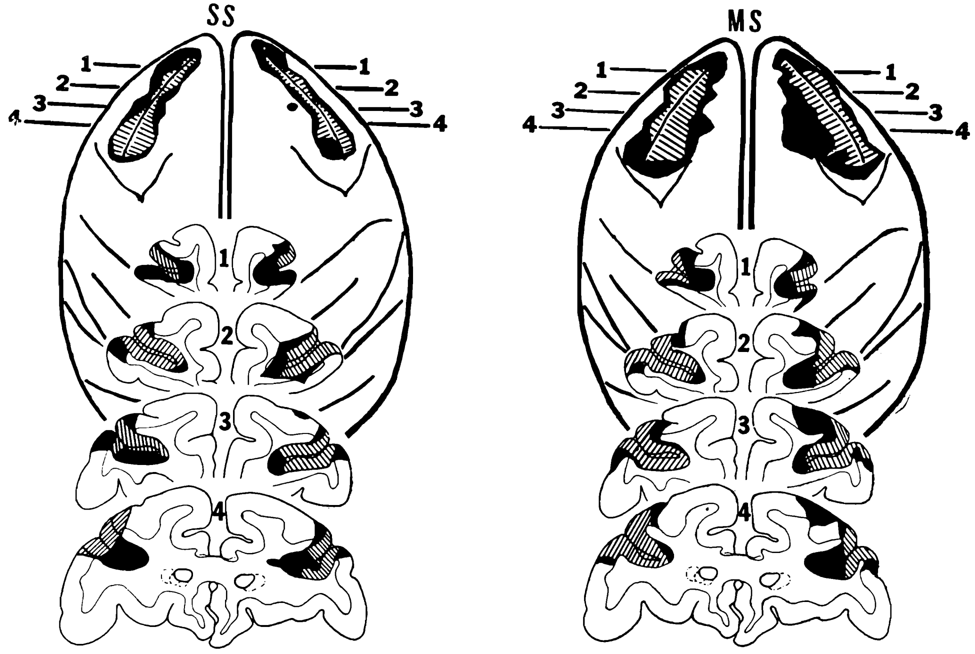

Fig. 5. Dorsal views and representative coronal sections of the maximum and minimum extent of frontal damage in the single- (SS) and multiple-stage (MS) surgical groups. The hatched areas represent the minimum insult observed, while the addition of the solid portions represent maximum damage.

monkeys made fewer total errors on the three spatial tasks, and on DR and the third and fourth place reversals their performance was unimpaired. In comparison to their scores on DR and PR, the MS monkeys' overall DA performance showed less recovery of function but the MS animals still made fewer total errors than did the SS monkeys on the second 500 DA retention trials. These DA and DR results closely parallel recent development findings (Goldman et al. 1970) which demonstrate that removal of prefrontal cortex within the first few months of life is followed by complete compensation of DR performance and partial recovery of DA. Goldman et al. (1970) found that relatively mature monkeys subjected to prefrontal lobectomies in infancy manifested only a minimal impairment on the acquisition of DR but were capable of achieving only an 80% level of correct responses on DA after 2000 training trials.

A number of possible explanations can account for this limited recovery of DA. First, DA may be a more difficult spatial task than either DR or PR. Thus, if recovery is only partial with the conditions employed in this study (i.e., four operations spaced 3 weeks apart), then the simpler spatial tasks should demonstrate more recovery than the more difficult tasks. Second, serial lesions may not spontaneously lead to a reorganization of structure and function, but rather may permit the more rapid reacquisition of spatial functions with extensive practice. The present findings that the MS monkeys approached normality on the second and third spatial tasks (DR and PR) and demonstrated significant improvement on the second 500 trials of the first task (DA) are consistent with this possibility.

A third, and perhaps the most intriguing possibility, involves the dissociation of DA and DR on the basis of underlying processes and/or compensatory structures. DA may involve other abilities besides spatial (e.g., sequential processing), and these capacities may not recover after serial removal of principalis due to the inadvertent ablation of the compensating structures as well as the intended principalis lesion. While there is now evidence (Kling and Tucker 1968) that recovery of DR depends upon the head of the caudate nucleus, DA, especially if it involves other processes besides spatial, may rely upon other compensatory structures. Given the demonstration that the midprincipalis sector normally serves as the focus for DA, it seems possible that the intact cortical tissue surrounding this central focus may be involved in the compensation of DA after serial or infant lesions. Damage to this surrounding tissue would, of course, greatly limit the amount of DA recovery but leave DR compensation unaffected. Doty's report (1961) that intact neural tissue immediately adjacent to a lesioned area may assume the functions of the damaged tissue lends support to this hypothesis.

Finally, the present findings underline the plasticity or malleability of structure–function relationships in mature organisms. With the appropriate surgical techniques (serial lesions) and post-operative experiences (Meyer 1958) intact neural structures may assume the behavioral functions of ablated tissue. This reorganization of structure–function characterizes not only sensory neural systems (Stewart and Ades 1952, Meyer 1958) but also association areas involved in higher learning-cognitive capacities (Stein et al. 1969, this study). It appears then that the demonstration of localization of function (as in the first two investigations of this chapter) does not also necessarily imply an innate and irreversible structure–function relationship.

SUMMARY

The present report has been concerned with three issues related to sulcus principalis (structure) and the monkey's spatial capacities (function): (i) the identification of a "spatial" focus within sulcus prin-

cipalis, (ii) a description of some of the anatomical characteristics of this focus, (iii) the possibility that intact neural structures can assume spatial functions when principalis is ablated in a mature monkey.

The findings indicate that the middle 9 mm of sulcus principalis serves as a spatial focus. Lesions limited to the midprincipalis region, but involving both the superior and inferior banks, resulted in severe deficits on 5-sec spatial delayed-alternation and place reversal learning while lesions confined to the anterior or posterior thirds of principalis or to the superior or inferior bank in the midprincipalis area were followed by only mild, if any, spatial impairments.

Besides this functional distinction, the midprincipalis region could also differentiated from the anterior and posterior sectors on the basis of its efferent cortico-cortical projections. The midprincipalis sector had heavy projections to the cingulate and retrosplenial regions; the anterior third of principalis had limited projections to this cortico-limbic area; and the posterior sector had none. In contrast, the posterior sector of principalis had many efferent connections with the medial and lateral parts of the parietal lobe while neither the anterior nor the midprincipalis sectors had such connections. These and previous anatomical and behavioral findings suggested that the mid- and posterior principalis sectors are involved in two distinct neural circuits concerned with different behavioral functions: the midprincipalis (and cingulate regions) with spatial functions, the posterior third of principalis (and the periarcuate prefrontal and the inferior parietal lobe region) with the mediation of multi-modal associations.

Despite this and previous demonstrations of a close association between sulcus principalis and spatial functions, the present findings indicate that this structure–function relationship is not necessarily fixed or permanent. Monkeys with serial bilateral ablations of sulcus principalis, in comparison to monkeys with single-stage removals of the same structure, showed either normal performance or an attenuated deficit on three spatial tasks. It appears then that recovery or compensation of function after frontal lesions is not limited to infancy but can occur in mature monkeys under certain methodological and environmental conditions.

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