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THE FRONTAL LOBE SYSTEM: CORTICAL–SUBCORTICAL INTERRELATIONSHIPS

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Abstract. The prefrontal cortex in the monkey is related structurally and functionally to several subcortical structures in such a way as to suggest that they constitute a neural system. Both anatomical and behavioral evidence justify implicating in such a system the prefrontal cortex itself, the head of the caudate nucleus, the globus pallidus, the substantia nigra, the subthalamic nucleus, the septal nuclei, the hippocampus, the centromedian nucleus, and the hypothalamus. There is, furthermore, an indication that this system is organized into at least two well-defined subsystems: a "dorsal" system originating in the dorsolateral prefrontal cortex involving the anterodorsal sector of the caudate, the lateral pallidum, the subthalamic nucleus, and the hippocampus; an "orbital" system originating in the orbital prefrontal cortex and involving the ventrolateral sector of the caudate nucleus, the medial pallidum, the centromedian nucleus, the hypothalamus and the septal nuclei. While the anatomical and behavioral dissociation between these two systems is emphasized, attention is also drawn to the many possibilities for the two systems to converge upon one another.

At the Symposium on the "Frontal granular cortex and behavior" held at the Pennsylvania State University in 1962 we (Rosvold and Szwarcbart 1964) proposed that the intimacy of the relationship between certain subcortical structures and the prefrontal cortex justified considering that together they might constitute a neural system regulating functions involved in the performance of delayed-response type tasks. It seemed to us that the evidence, admittedly scant, was sufficiently compelling to warrant implicating in such a system the prefrontal cortex itself, the head of the caudate nucleus, the globus pallidus, the substantia nigra, the subthalamus and the hippocampus. To be sure, our notions with respect to the structures to be included in a cortical–subcortical

frontal-lobe system have changed over the years, nevertheless the general schema has proved a useful heuristic device. Many studies relating to prefrontal cortical–subcortical mechanisms have been done in other laboratories and we are to hear some of them described at this Symposium by other participants. My purpose is to review principally our own studies and to bring up to date the evidence for and against the systems concept.

Cortex

The point of departure for the present analysis is the prefrontal cortex itself for it is in relation to the deficits produced by ablations of this cortex that the question of subcortical mechanisms arises. In assessing cortical–subcortical systems, it is important to recognize that the prefrontal cortex is not a unitary substrate singularly concerned with a unitary function, but rather that this expanse of cortical tissue can be subdivided into at least two major behaviorally meaningful subdivisions — one located mainly on the ventral or orbital surface and the other occupying a dorsolateral position on the convexity. Mishkin (1964) in his paper at the 1962 Symposium reviewed the series of studies showing how the classical delayed-response type task contained at least two factors and how lesions in the different subdivisions of the prefrontal cortex could contribute to impairment on this task by selectively affecting vulnerability to one or the other of these factors. Briefly, the deficits on this task exhibited by monkeys with orbital frontal lesions appeared to be due to the necessity of reversing dominant response tendencies on successive trials while that of the animals with lateral frontal lesions seemed to be related to the spatial factors in the test. This dissociation of effects was clearly evident in two of our early studies. The first, with Brutkowski (Brutkowski, Mishkin and Rosvold 1963), demonstrated that the abnormal tendency of monkeys with orbital frontal lesions to respond on negative trials of a differentiation problem clearly distinguished them from monkeys with lateral frontal removals. The second was an unpublished study cited by Mishkin (1964) in which the requirement of reversing responses on a place discrimination task posed more of a problem for monkeys with lateral removals than for those with orbital lesions. In the nearly ten years that have elapsed since the Pennsylvania State Symposium, the dissociability of the functions of the orbital and dorsolateral prefrontal subdivisions, evident in these early studies, has been amply confirmed (Butter et al. 1963, Ławicka et al. 1966, Mishkin et al. 1969, Goldman et al. 1970, Pohl 1970, Goldman 1971) and the cortical localization of these functions have been more exact definition (Mishkin et al. 1969).

In more recent years, attention has been given less to dissociating between the functions of the two major subdivisions of the prefrontal cortex and more to localization of function within each division. With respect to the orbital cortex, Iversen and Mishkin (1970) have shown that lesions in the inferior convexity of the frontal lobe resulted in greater impairments on delayed alternation than did lesions in the medial orbital cortex. Object reversal, on the other hand, was more affected by medial orbital lesions than by removal of the inferior convexity. Butter (1968) in his own laboratory, has gone further with localization of function within the orbital cortex and his results indicate that the posteromedial cortex on the ventral surface is a focal area for performance on bar-press extinction.

With regard to the dorsolateral subdivision, we (Goldman, Rosvold, Vest and Galkin 1971) have recently completed a series of studies which indicate that this subdivision also can be further fractionated into behavioral subunits. We were able to demonstrate that the functions measured by two spatial tasks — delayed alternation and a conditional position response test — could be dissociated and were localized in different areas of the dorsolateral cortex. Figure 1 shows the lesions that were

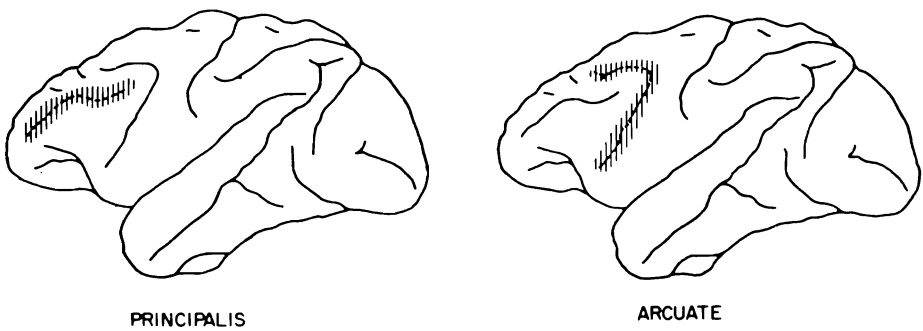

Fig. 1. Schematic representation of the lesions in the principal and arcuate sulci which resulted in the dissociation of functions illustrated in Fig. 2.

compared and Fig. 2 shows the results. It may be seen that the tasks which contain both spatial and delay factors are selectively impaired by lesions of the cortex in the principal sulcus while those involving a spatial factor and no delay or delay but no spatial factor are impaired by lesions in the arcuate cortex. While it is too early to be sure what the functions of the arcuate cortex might be, these results suggest that the principal sulcus may be uniquely concerned with proprioceptive memory.

These studies on the cortex form the background for the studies on subcortical structures now to be discussed.

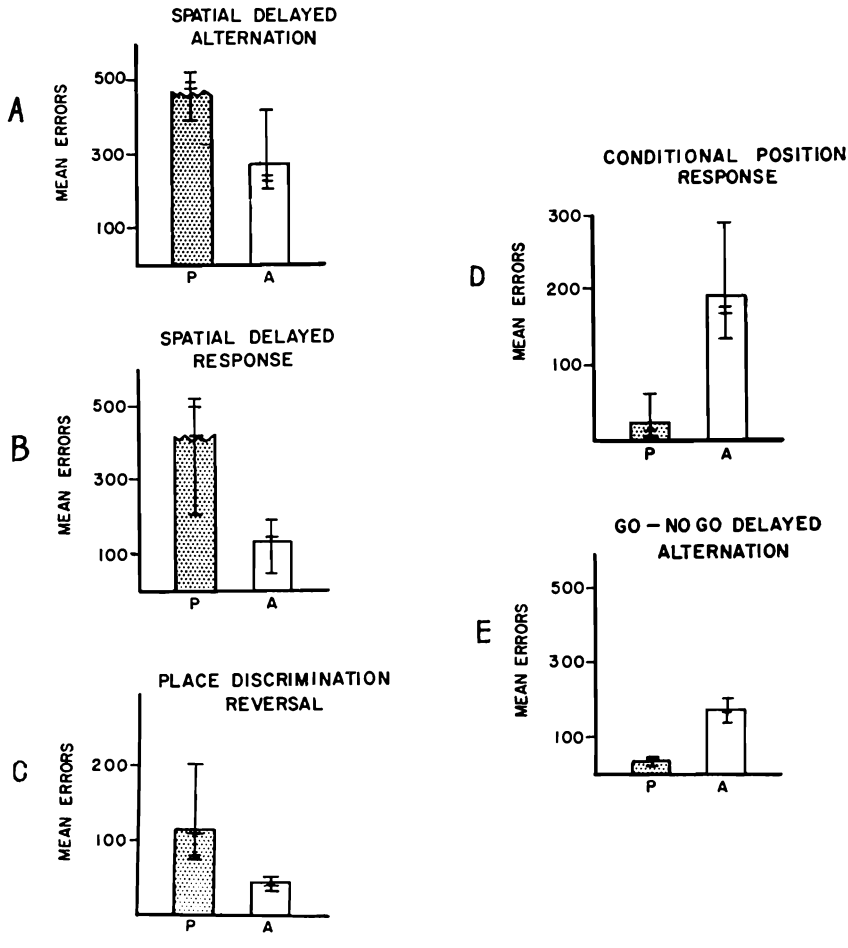

Fig. 2. Effect of principalis (P) and arcuate (A) lesions on *A*: spatial delayed alternation; *B*, spatial delayed response; *C*, place discrimination reversal; *D*, conditional position response; and *E*, go–no go alternation. (From Goldman et al. 1971.)

Hippocampus

At the previous Symposium we reviewed the behavioral, anatomical, and electrophysiological evidence supporting the inclusion of the hippocampus in the frontal-lobe system. We also presented new behavioral data confirming that hippocampal lesions impair the monkey's performance on spatial delayed alternation and indicating further that the severity of this impairment depends on the size of the lesion. However, hardly had this material been published when Dorff (1964), working in our own laboratory, found that hippocampal lesions did not necessarily

result in impairment on delayed-alternation performance. But because his lesions proved to be relatively small, and interanimal variability great, we tended to discount his negative findings and argued that if the lesions had been large enough, the variability would have been overcome and reliable deficits would have emerged. To test this, we (Waxler and Rosvold 1970) made much larger lesions by electrocautery, resection, or

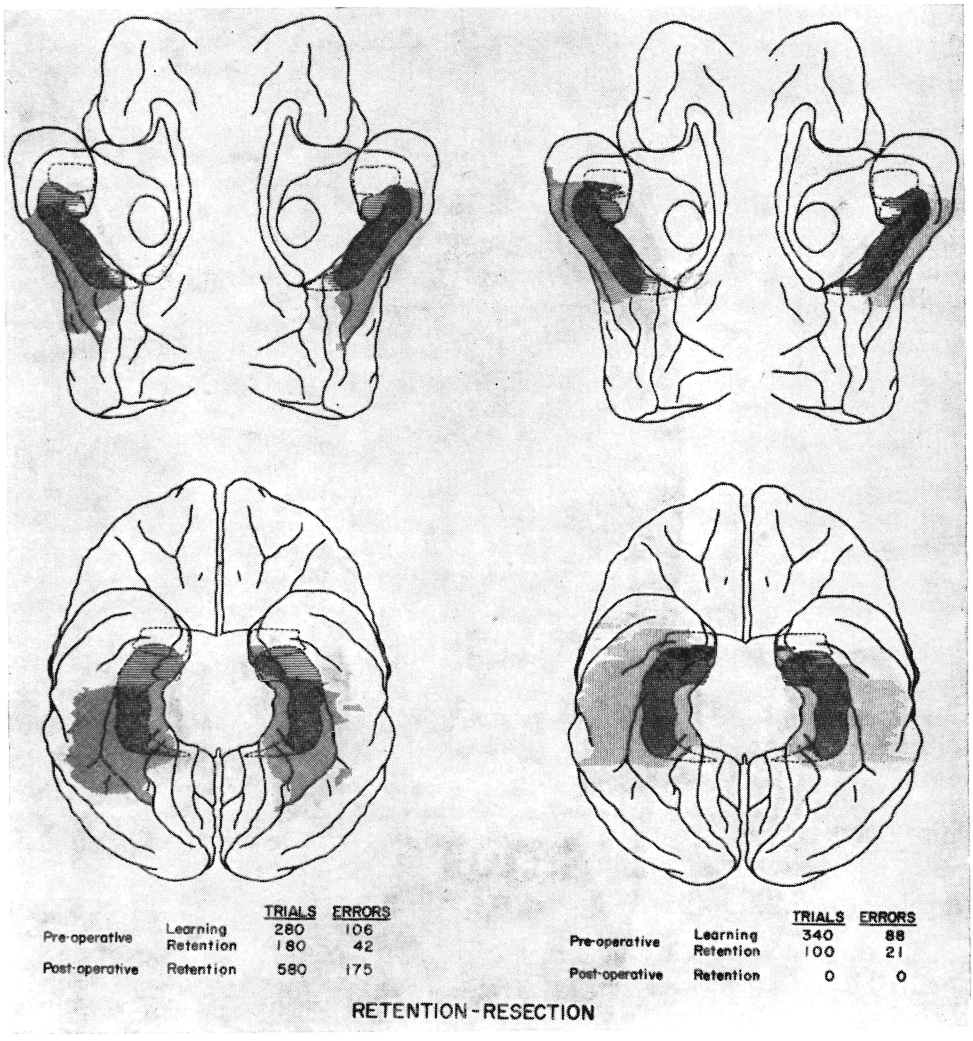

Fig. 3. Reconstructions of the lesions of two of the subjects who were tested for retention of delayed alternation after resection of the hippocampus. Dashes outline the hippocampus and the amygdala. Horizontal striations, hippocampal damage; dots, cortical damage; random stipple, amygdala damage. (From Waxler and Rosvold 1970.)

lobectomy to assure removal of the entire hippocampus in every way that had been tried and tested the effects of such lesions on both initial learning and post-operative retention of spatial delayed alternation. As may be seen in Fig. 3 and 4, no matter which method of making the lesions was used, no matter whether the monkeys were tested in retention or initial learning, the effects on delayed alternation were the same: some animals were severely impaired, others not at all. Figure 5 illus-

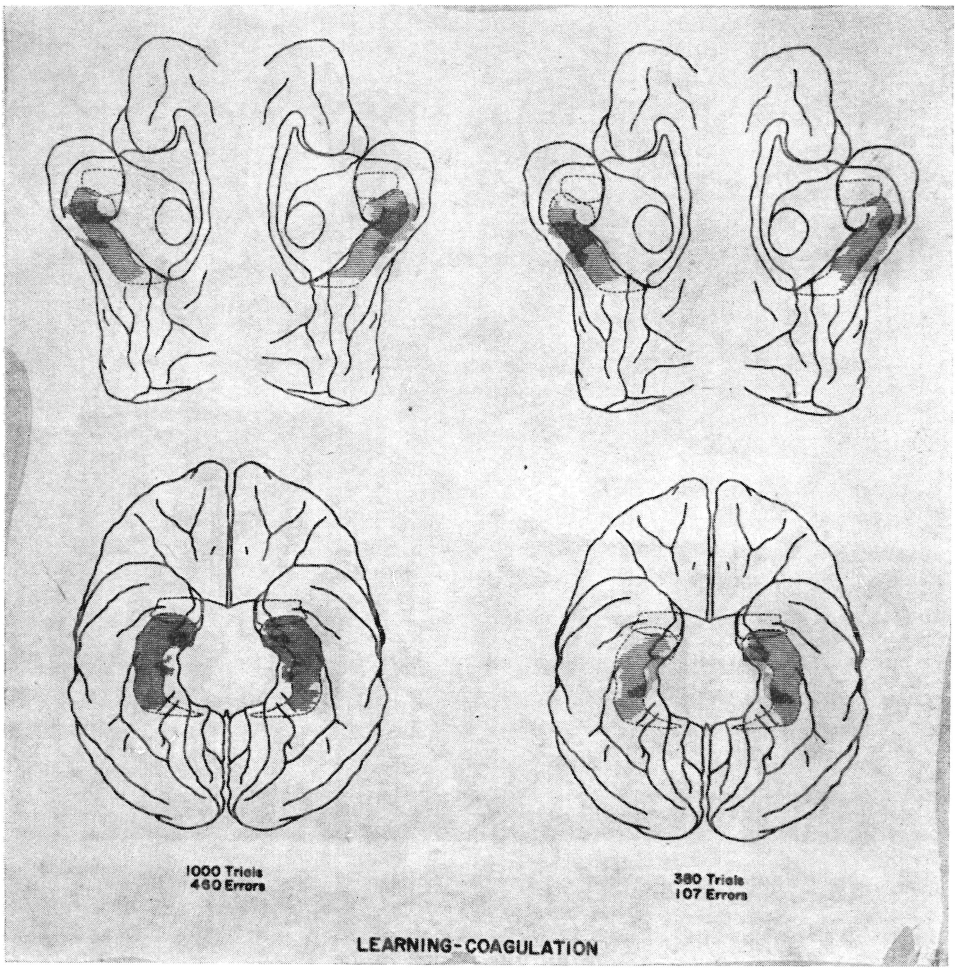

Fig. 4. Reconstructions of the lesions of two of the subjects who were tested for learning of delayed alternation after electrocoagulation of the hippocampus. Dashes outline the hippocampus and the amygdala. Horizontal striations, hippocampal damage; dots, cortical damage; random stipple, amygdala damage. (From Waxler and Rosvold 1970.)

trates that the distribution of scores was essentially bimodal; about half were within the normal range while the other half were outside the normal distribution altogether. It must be admitted, then, that including the hippocampus in the frontal-lobe system is not, on the basis of effects of lesions on delayed-alternation performance, unquestionably justified. Still further difficulties for doing so are raised by the findings, most

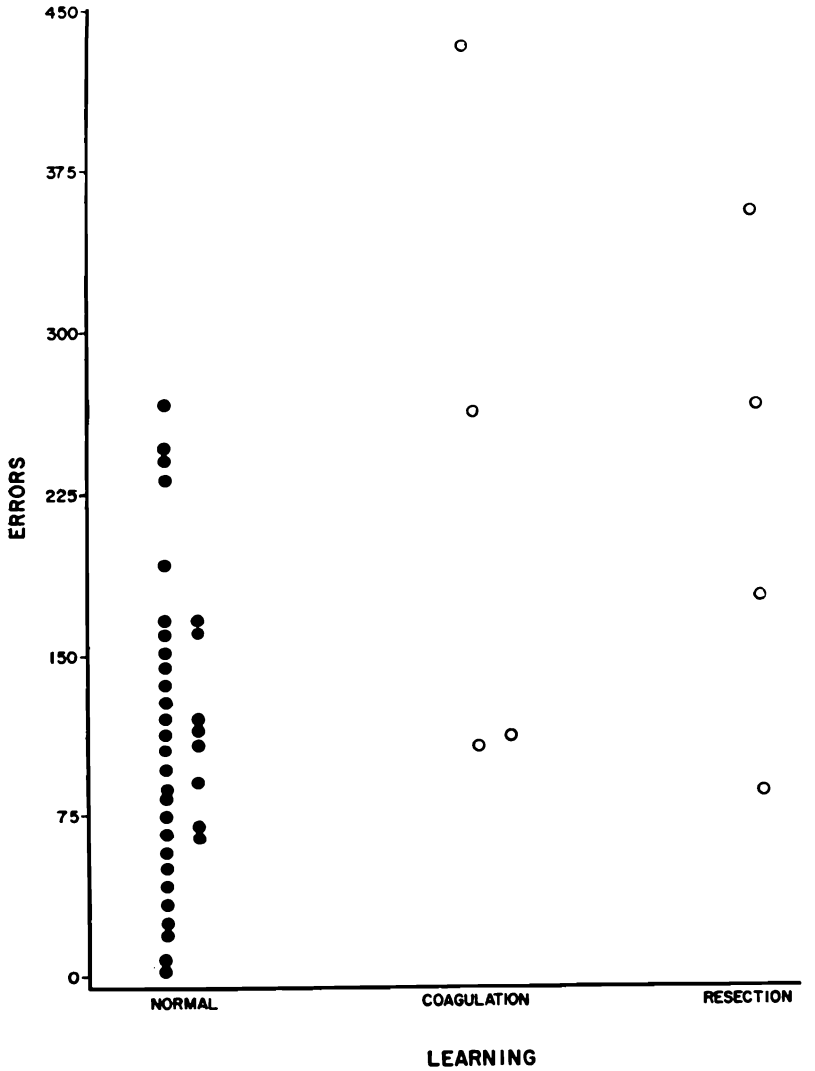

Fig. 5. Spatial delayed alternation learning error scores of 8 operated subjects compared with those of 36 normal subjects. Each circle represents the score of one subject. (From Waxler and Rosvold 1970.)

recently confirmed by Mahut (1971) of Northeastern University, that on another test of frontal-lobe function, spatial delayed response, monkeys with hippocampal lesions are not impaired.

These contradictory results are difficult for us to understand. Qualitative and quantitative differences between delayed response and delayed alternation are easy to point out, but that these differences are critical in determining the discrepancies in the effects of hippocampal lesions has not been demonstrated. With respect to the uncertain results on delayed alternation, the only interpretations we have been able to suggest, admittedly not very satisfying, are that some monkeys use a variety of strategies to perform delayed alternation and the utilization of some of these strategies requires an intact hippocampus while others do not, or alternatively, that in some monkeys other brain tissue compensates for the loss of the hippocampus.

The anomalous results notwithstanding, however, encouragement for relating the hippocampus to the frontal lobes continues to be provided. Mahut (1971) has very recently reported that, in her own laboratory at least, hippocampal damage invariably results in severe and long-lasting impairment on delayed-alternation performance. Furthermore, she has provided evidence, recently confirmed by Jones and Mishkin (unpublished data) in our own laboratory, that hippocampal animals are impaired on a spatial reversal test but not on an object reversal test, suggesting that the functions of the hippocampus, while resembling those of the frontal lobes, are principally related to those of the dorsolateral frontal cortex.

In the face of the equivocal behavioral evidence, the inclination is to deny that the hippocampus participates in the frontal-lobe system. However, the persistence of the positive evidence should not be ignored, and in view of the increasing anatomical and electrophysiological evidence supporting the view, I prefer, for the present, to think that it does play a role, particularly in the sphere of dorsolateral frontal-lobe functions, with the significance of the negative evidence still not evident to us.

Septal nuclei

The septal nuclei were not included in the 1962 schema of the frontal-lobe system principally because there were virtually no relevant behavioral data from investigations using monkeys, though evidence from studies using other animals would have been sufficient reason for including them (McCleary 1967). Certainly, the anatomical relationships of the septal nuclei, both with the hippocampus and the prefrontal cortex

are compelling enough (Adey and Meyer 1952, Johnson et al. 1968) to warrant thinking of them as part of the same system. In particular, the selective affinity of the orbital frontal projection for the medial septal nuclei, which are located almost exclusively in a ventral sector of the septum (Johnson et al. 1968), would suggest that lesions placed ventrally rather than dorsally in the septum would mimic the effects of orbital frontal lesions.

One clear selective effect of orbital frontal lesions, as we (Butter, Mishkin and Rosvold 1963) demonstrated some time ago, is an abnormal resistance to extinction of a bar-press habit. It was reasonable to suppose, therefore, that lesions placed ventrally in the septum would also lead to resistance to extinction of a bar-press habit, while lesions placed dorsally would not. Butters and I (1968*b*) showed this to be the case. As may be seen in Fig. 6, only those lesions involving the ventral septum resulted in an abnormal number of responses in extinction.

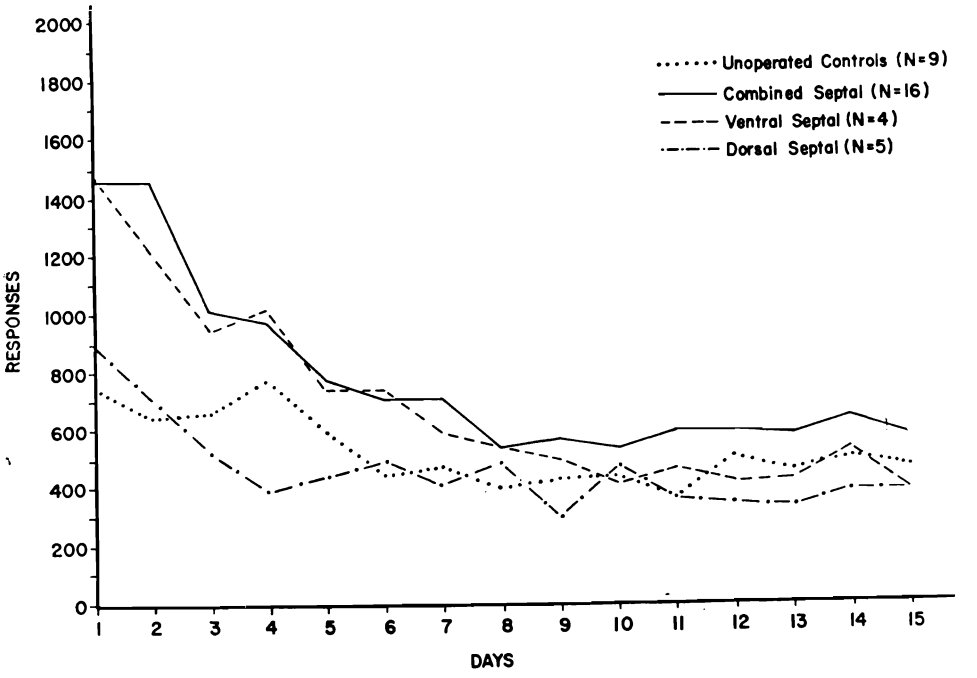

Fig. 6. The mean number of responses emitted during extinction by monkeys with lesions in the dorsal septum, in ventral septum, in both areas of the septum combined, and in normal monkeys. (From Butters and Rosvold 1968*b*.)

We (Butters and Rosvold 1968*b*) also tested the effects of septal nuclei lesions on post-operative initial learning of spatial delayed alternation. None of the lesions resulted in impaired performance on this

test in terms trials and errors to criterion. There was, however, a significant positive correlation between the size of the ventral sector damage and the number of perseverative errors and, as well, with the number of long runs of consecutive errors.

Thus, on both the bar-press and on the delayed-alternation tasks, monkeys with lesions in the medial septal nuclei exhibit a tendency to perseverate inappropriate responses. They are, in this respect, similar to monkeys with orbital frontal lesions, and, it may be argued, therefore, that at least the medial part of the septal area should be included in the frontal-lobe system.

Centromedian nucleus

Like the septal nuclei, the centromedian nucleus of the thalamus could have been included in the frontal system on the basis of its anatomical relationships with both the frontal cortex and the basal ganglia (Johnson et al. 1968). However, at the time of the 1962 Symposium there were no data to suggest the significance for behavior of these anatomical relationships. Since then, behavioral data have been accumulating from studies, principally in the rat and on aversive conditioning (Delacour 1969), which suggest that the centromedian nucleus is functionally related to the orbital frontal cortex. Until this last year, however, virtually no

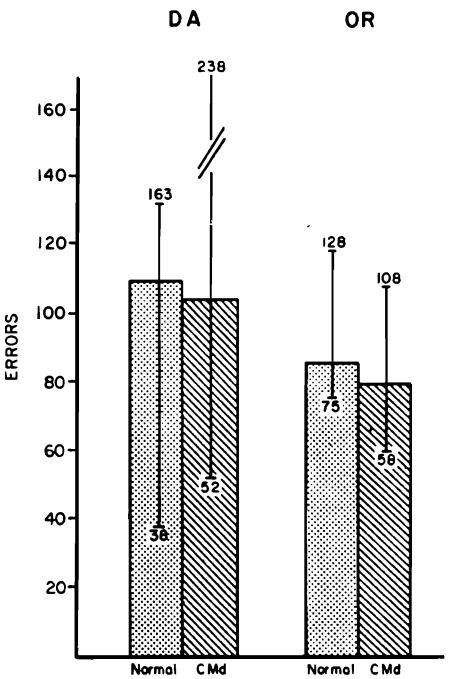

Fig. 7. Initial learning of spatial delayed alternation and object reversal. Mean errors to criterion after centromedian (CMd) lesions. (Based on data in Marburg 1970.)

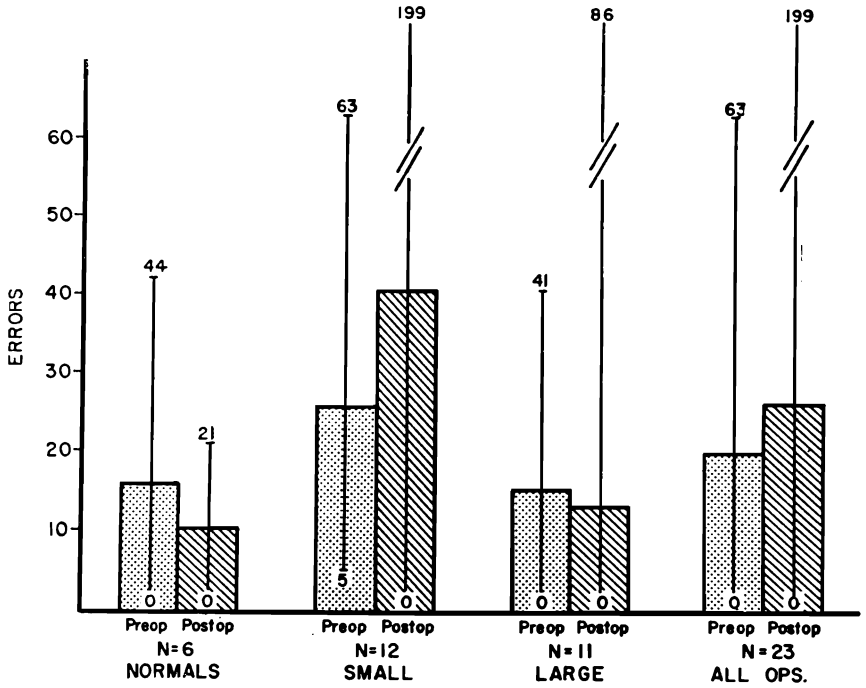

Fig. 8. Post-operative retention of spatial delayed alternation. Mean pre- and post-operative error scores are shown for normals, small-lesion group (less than 30% of CMd), large-lesion group (more than 40% of CMd), and these two groups combined. (Based on data from Marburg 1970.)

relevant information had been available with respect to the functions of this nucleus in the monkey. Marburg (1970), therefore, undertook to investigate the effects of lesions in the centromedian nucleus of the monkey on spatial-delayed alternation, object reversal, and escape from shock. The results for post-operative initial learning of delayed alternation and object reversal are shown in Fig. 7. It may be seen that centromedian lesions do not significantly affect the ability of the monkey to learn these tasks. Figure 8 shows his findings concerning post-operative retention of delayed alternation. Though the lesions have the effect of increasing the range of the scores, they do not result in reliable differences in pre- and post-operative comparisons. Similarly, as may be seen in Fig. 9, lesions of the centromedian nucleus do not affect the retention of object reversal. It should be emphasized that some of these lesions were large, in some cases involving 85% of the nucleus itself as well as substantial amounts of surrounding tissue, and thus it is unlikely that the failure to find an effect on these tests is attributable to the lesion being too small. Rather, it seems reasonable to accept the negative find-

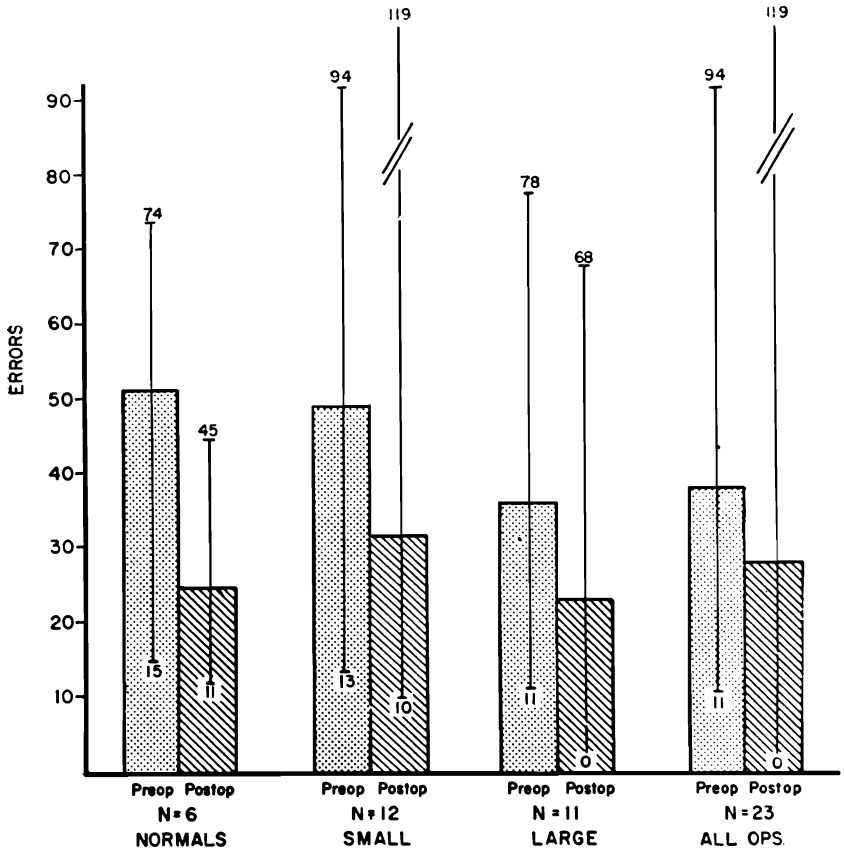

Fig. 9. Post-operative retention of object reversal. Mean pre- and post-operative errors scores are shown for normals, small- (less than 30% of CMd) lesion group, large- (more than 40% of CMd) lesion group, and these two groups combined. (Based on data from Marburg 1970.)

ings on these two tests as indicating that the centromedian nucleus does not participate in all of the functions of the frontal-lobe system.

A probable role for the centromedian nucleus is apparent, however, in the results of the other test which Marburg administered. Figure 10 illustrates that there was an increase in shock-escape thresholds after damage to the nucleus. The difference between the thresholds before and after large (more than 40% of the nucleus) lesions is significant. Thus, in monkeys as well as in other animals the centromedian nucleus is concerned with responses to painful stimuli.

This pattern of deficits, namely, no impairment on delayed alternation or object reversal, but a clear-cut change in response to aversive stimuli, is similar to that found after damage to the dorsomedial nucleus

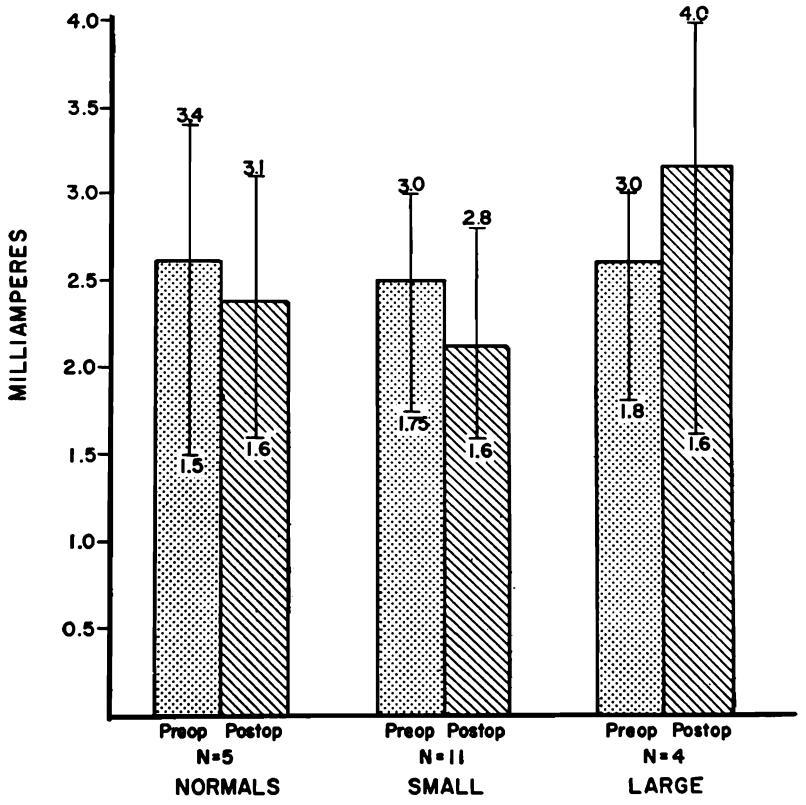

Fig. 10. Shock-escape threshold changes after CMd lesions. Pre- and post-operative thresholds are shown in milliamperes for normals, small- (less than 30% of CMd) lesion group, and large-(more than 40% of CMd) lesion group. (Based on data from Marburg 1970.)

of the thalamus (Peters et al. 1956, Roberts 1962). No satisfactory explanation can be offered for the apparent lack of effect on delayed response-type tests of lesions in these structures which are so intimately related anatomically to the frontal lobes. It is, of course, possible to suggest that these nuclei have so many connections with other structures in the frontal-lobe system that in their absence their functions are subsumed by alternate structures. There is little evidence bearing on this question, but Marburg's observations in two monkeys suggests that it is not, at least, the dorsomedial and the centromedian nuclei which substitute for one another. These two additional animals were given massive lesions involving both these structures, but, even so, their performance on delayed alternation and object reversal remained unaffected.

It seems indicated, then, that if the centromedian nucleus is to be included in the frontal-lobe system on the basis of behavioral evidence,

it is because of its participation in functions related to the response to painful stimuli rather than in the functions involved in spatial delayed-alternation and object-reversal tasks.

Hypothalamus

Few would object to including the hypothalamus in a frontal-lobe system; indeed, in many respects the hypothalamus appears to be continuous both in structure and function with the posterior orbital frontal cortex (Nauta 1964, Robinson and Mishkin 1968, Nauta and Haymaker 1969, MacLean 1969). It is somewhat surprising then to find so little correlative behavioral analysis which attempts to relate the functions of the hypothalamus to those of the prefrontal cortex in terms of the tests with which we have been concerned. Much of what has been done has, in fact, been done in Poland by Romaniuk (1962) and by Balińska, Brutkowski and Stefanicka (1966). Their data, derived principally from studies on the rabbit, would support the contention that the hypothalamus should be included in the frontal-lobe system on behavioral as well as on anatomical bases.

Only in the past few months, however, has any similarly relevant data become available for the monkey. This has been provided in a study with Vereczkei (L. Vereczkei, P. S. Goldman and H. E. Rosvold, unpublished data) of the University of Pecs, Hungary, who has just completed a year with us. We placed lesions in the anterior, ventromedial, or lateral areas of the hypothalamus, and as well, large lesions in these three areas combined, and observed the effects on tests of visual pattern discrimination, spatial delayed alternation, and object reversal. The data have not yet been completely analyzed, particularly with respect to the precise boundaries of the lesions; nevertheless, a preliminary analysis of the data suggests that initial learning of each of the tasks is impaired to some extent after each of the lesions, except perhaps after the lateral lesion on delayed alternation (Table I). Indeed, the magnitude of these deficits (some animals failed to learn delayed alternation in 1000 trials), often as great as one expects from cortical lesions, is particularly impressive when one considers how small the subcortical lesion is in comparison with the cortical lesion. Another suggestion in the data is apparent in the pattern of the effects of the lesions — impairment on spatial delayed alternation, visual pattern discrimination, and on object reversal; such a pattern is similar to that seen after orbital lesions (Goldman et al. 1970).

If these encouraging findings are borne out in the more systematic

TABLE I

Effects of hypothalamic lesions: mean scores to criterion on visual pattern discrimination, spatial delayed alternation and object reversal[a]

Groups[b]	VD		DA		OR
	Trials	Errors	Trials	Errors	Errors
N	115	47	238	80	36
AH	305	142	510	160	90
VM	281	122	508	160	90
LH	290	125	360	100	98
AH+VM+ +LH	393	184	793	296	100

a Abbreviations: VD, visual pattern discrimination; DA, spatial delayed alternation; OR, object reversal; N, normal; AH, anterior hypothalamic area; VM, ventromedial area; LH, lateral hypothalamic area.

b The assignment of animals to groups is based on a preliminary study of the brains and should be considered tentative. While there may be reassignments of some animals when the lesion sites are more systematically verified, the preliminary analysis suggests that there are not likely to be so many as to invalidate the general points made in the text.

analysis of the data now under way, it would then seem justified to include the hypothalamus in the frontal-lobe system, and probably in that part related to the orbital frontal cortex.

Caudate nucleus

It will be recalled that at the time of the Pennsylvania Symposium, of all the structures alleged to belong to a frontal-lobe system, the head of the caudate nucleus seemed most to warrant a place. Its intimate relationship with the frontal lobes had been established on the basis of anatomical connections, electrophysiological interrelationships, and similarities in the behavior subserved. Indeed the similarities in function based on behavioral evidence were so compelling that it seemed justified to conclude that there is an identity of function between these two structures. The results of studies since then have continued to support this conclusion. For example, on two other tests of frontal-lobe function (conditional position response and auditory go–no go) on which Ławicka, Mishkin and I (1966) found monkeys with frontal cortical lesions to be impaired, B. Vest and I (unpublished data) later found, as may be seen in Fig. 11, equally severe impairments in monkeys with lesions in the head of the caudate nucleus. There seems to be no exception, then, to the rule that whenever a frontal-lobe lesion results in impaired performance on a test, so do lesions in the head of the caudate.

At a more recent meeting I (Rosvold 1968) described how this simi-

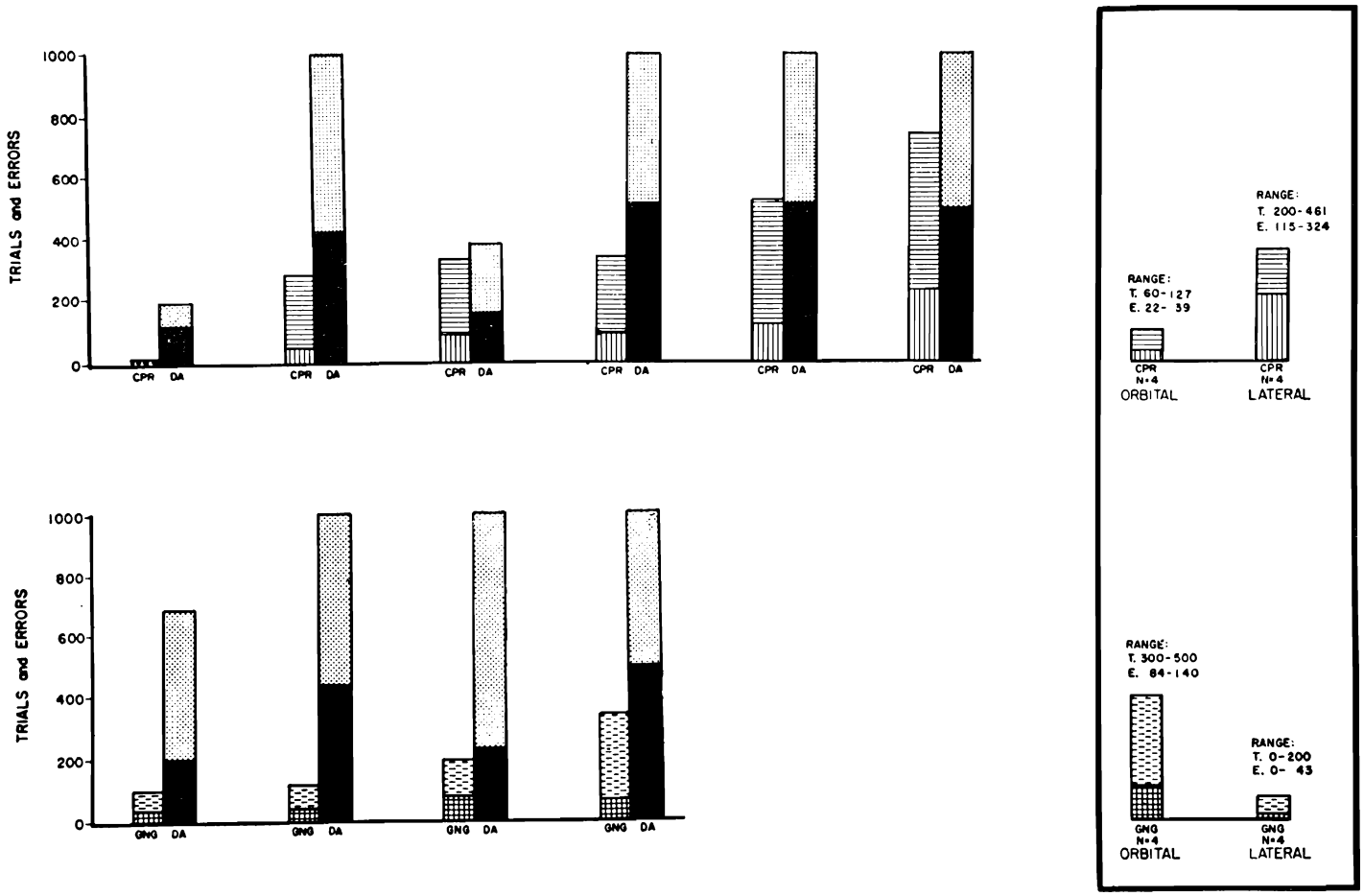

Fig. 11. Effects of lesions in the head of the caudate nucleus on the conditional position response test (CPR), the go–no go test (GNG), and spatial delayed alternation (DA). The total length of the bars indicates trials; the bottom division, errors. To the right of the Figure are the same comparisons for animals with lateral and orbital frontal lesions; the data used to prepare this part of the Figure are from the study by Ła wicka, Mishkin and Rosvold (1966).

larity in function could be extended to encompass the implications of newly discovered topographical relationships between parts of the frontal cortex and parts of the head of the caudate. Anatomical studies from several laboratories (Nauta 1964, Kemp and Powell 1970), ours among them (Johnson et al. 1968), had demonstrated that the head of the caudate nucleus was not a homogeneous mass, but rather, had a clearly definable topography based on differential projections from the cortex. Of special relevance to our work was the finding that the dorsolateral frontal cortex projected selectively on an anterodorsal sector of the head of the caudate nucleus, while the orbital frontal cortex directed its fibers to a ventrolateral sector of the head of the caudate.

Divac, Szwarcbart and I (1967) provided evidence of behavioral relevance for these findings in demonstrating that the functions of these two sectors of the head of the caudate could be dissociated in much the same way as the functions of the dorsolateral and orbital cortex, respectively. Monkeys with anterodorsal lesions were impaired on delayed alternation but not object reversal; monkeys with ventrolateral lesions were impaired on object reversal but not on delayed alternation. Furthermore, Butters and I (1968*a*) later showed that the effects of ventrolateral caudate lesions mimicked orbital cortical lesions in another way; that is to say, either lesion resulted in an abnormal resistance to extinction of a bar-press habit. It seems justified to conclude, then, that the anterodorsal sector of the head of the caudate, like the dorsolateral frontal cortex, is concerned with the spatial factors in a test while the ventrolateral sector of the caudate, like the orbital frontal cortex, is concerned with the inhibition of prepotent response tendencies.

The similarity in function between parts of the frontal cortex and parts of the head of the caudate nucleus, determined, it seemed, by selective anatomical connections between them, led us to ask if, in turn, each part of the caudate directed fibers selectively to other structures and similarly determined their functions. Accordingly, Johnson and I (1971) undertook an anatomical study seeking to determine if the efferents of the two sectors of the caudate could be distinguished. We placed lesions selectively in one or the other sector or the head of the caudate nucleus and traced the consequent degeneration of fibers. Degenerating fibers from the selectively placed lesions could be traced along separate trajectories to different areas of termination in the globus pallidus, those from the anterodorsal caudate terminating more laterally in the pallidum than those from the ventrolateral caudate. I have summarized these findings in Fig. 12. Also shown in the Figure is the significant fact, demonstrated some years ago by Nauta and Mehler (1966),

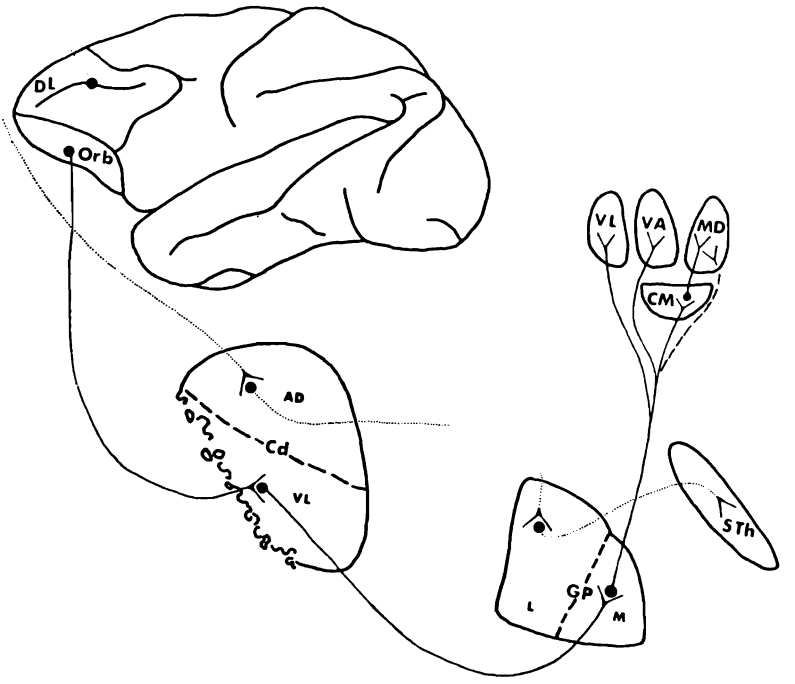

Fig. 12. Schematic representation of the "dorsal" and the "orbital" frontal system as determined by fiber degeneration following selectivedy placed lesions at each successive relay.

that the principal efferent projections of the medial and the lateral segments of pallidum also tend to take different courses; the medial by way of the thalamic fasciculus to the dorsal thalamus, and the lateral by way of the subthalamic fasciculus to the subthalamic nucleus. Thus, at least two well-defined systems originating in the cortex and maintaining their integrity through successive subcortical relays may be distinguished. The first is a "dorsal" system which finds its way from the dorsolateral prefrontal cortex, through the anterodorsal caudate and lateral pallidum to the subthalamic nucleus, and the other is an "orbital" system which finds its way from the orbital cortex through the ventrolateral caudate and medial pallidum to the dorsal thalamus.

As we have discussed in our published report of this study, the data from behavioral studies are consistent in demonstrating that the cortical and caudate components of the "dorsal" and of the "orbital" systems subserve different functions. Whether or not the behavioral distinctions between the two systems are maintained at successive relays beyond the caudate nucleus is at present unclear. There have been no studies relating the effects of selctive lesions in the pallidum to prefrontal

functions on the basis of the customary behavioral problems, and only one relevant study involving lesions in the subthalamic nucleus; and this study did not attempt to distinguish between "dorsal" and "orbital" functions. The evidence from studies concerning the function of the dorsal thalamus is equally unsatisfactory for making a distinction between the two systems. On the one hand, lesions in the dorsomedial (Peters et al. 1956) or the centromedian (Marburg 1970) nucleus do not affect performance on any of the tests on which the dissociation between the two systems rests. On the other hand, lesions in these thalamic nuclei do impair responses to noxious stimuli (Roberts 1962, Delacour 1969, Marburg 1970); effects which are probably more closely related to "orbital" (limbic) than to "dorsal" system lesions.

Clearly, what is now required is a comprehensive investigation comparing the effects of selectively placed lesions in all of the structures in the system on a battery of tests which samples the entire gamut of frontal-lobe functions. Only then will it be possible to avoid the bias, evident in this presentation, of making the most of the positive evidence favoring the hypothesis. Furthermore, if the systems concept is to become meaningful, it will be necessary ultimately to provide behavioral and electrophysiological evidence not only that these interrelated structures do, in fact, function as a system, but also to give some indication as to the functional contribution which each component makes to the system. In the meantime, accepting the available evidence as consistent with the notion that there are two dissociable frontal-subcortical systems serves to suggest what research remains to be done if this goal is to be achieved.

Conclusion

The evidence available at the time of the Pennsylvania Symposium justified thinking of the prefrontal cortex and certain subcortical structures as parts of a functional system. In the years between that Symposium and this one, a clear dissociation between the functions of the dorsolateral and the orbital parts of the prefrontal cortex has evolved and, as I have described in this review, it has been possible to align subcortical structures with one or the other part of the prefrontal cortex. Thus there appears to be a "dorsal" system and an "orbital" system composed of structures which have functions similar to those subserved by the division of the prefrontal cortex with which it is related.

While this review has emphasized the evidence supporting the concept of anatomically interrelated structures forming two distinguishable

functional systems, there are important questions remaining to be answered if the concept is to continue to be useful. It is a fact, for example, that the two systems, though clearly dissociable structurally and functionally, also converge upon one another at several levels: the "dorsal" system meets the "orbital" system at the level of the medial pallidum through reentrant fibers from the subthalamic nucleus, and the "orbital" system reaches the "dorsal" system through projections from medial pallidum to the thalamus and thence back to the cortex and to the striatum. The significance for behavior of this interdigitation is not apparent, though it obviously provides a mechanism for activity in one system to influence activity in the other.

Another question requiring explanation concerns the finding that lesions in subcortical structures may produce some but not all of the effects associated with lesions in their affiliated cortical areas. Thus, lesions in the hippocampus result in deficits on delayed-alternation but not on delayed response. Septal lesions increase resistance to extinction of a bar-press habit but do not result in severe delayed alternation deficits. And ventrolateral caudate lesions, though resulting in impairment on object reversal and on bar-press extinction, do not affect performance on delayed alternation. Given that there is support for including each of these structures in the system indicated, it can be concluded that the functions of the cortex need not be replicated in detail by each of the subcortical structures. If it could be determined what factor in a test is particularly vulnerable to the effects of a certain subcortical lesion, much could be said concerning the unique contribution of that structure to the function of the frontal-lobe system.

Many other questions could be raised, both with respect to other structures to be incorporated into the system, and also concerning such behaviorally anomalous structures as the centromedian and the dorsal medial nuclei which on anatomical grounds seem so much to be an integral part of the system. Ferreting out the answers to these many questions poses a challenge for future research.

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