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NEOSTRIATUM AND FUNCTIONS OF PREFRONTAL CORTEX

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Abstract. A review of recent anatomical evidence shows that every neocortical area and many nuclei from the dorsal thalamus project to restricted neostriatal regions. The neurobehavioral literature offers many examples of the same results obtained with lesions, stimulations or recordings in a neocortical area and the associated neostriatal region. This evidence is abundant in the case of the prefrontal cortex and rostral neostriatum, but it is available also for other cortico-neostriatal pairs. It seems possible to conclude that the function of a neostriatal region is determined by its cortical and possibly by its thalamic input. However, the possibility that the behavioral effects of lesions and stimulation of neostriatum were in fact produced by involving the fibers passing to and from the overlying cortex has not been convincingly excluded. An attempt was made to develop a simple concept about the relation between the prefrontal cortex and the region of neostriatum associated with it. A serial paradigm, suggesting that prefrontal cortex in adult monkeys and cats acts via neostriatum when mediating performance in certain behavioral tasks, seems to account for most of the available data.

INTRODUCTION

Under the layers of active cortical neurons lies neostriatum[1] — a large, electrically quiet formation, yet an extraordinary consumer of energy and a depot of characteristic neurochemical substances. Among many

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[1] Data from different disciplines suggest that the caudate nucleus and putamen should be considered as one formation. Cytoarchitectonically, they can scarcely by distinguished from each other (Crosby et al. 1962). They seem to originate from the same "anlage" (Hewitt 1961). In those species, like the rat or bat, where capsula

functions attributed to the neostriatum, two have continued to receive attention: motor (e.g. Jung and Hassler 1960) and inhibitory (e.g. Heuser et al. 1961), neither, however, on the basis of solid evidence (Meyers 1953, Laursen 1963). An alternative suggestion, which seems to rest on firmer experimental ground, is that the neostriatum may participate in "complex behavior" (Rosvold 1959) or may function on "a high level of integration" (Laursen 1963).

The caudate nucleus was introduced into the "frontal lobe system" during a previous symposium devoted to frontal granular cortex (Rosvold and Szwarcbart 1964). Subsequent neuropsychological studies confirmed a close functional relationship between the caudate nucleus and the neocortex, but indicated that the neostriatum may be functionally heteregeneous like the neocortex (Divac et al. 1967, Divac 1968*a*). It was suggested that the neostriatum is a "first link in a major pathway providing for cortical regulation of lower centers" (Divac et al. 1967). It was also proposed that the neostriatum may be capable of assuming cortical functions (Divac et al. 1967).

The aim of the present paper is to examine how well the neostriatum conforms to this model. In the first two sections of the paper, data related to the participation of neostriatum in prefrontal[2], as well as other cortical functions are reviewed and discussed. The final section concerns the nature of the functional relation between the two formations.

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interna traverses the neostriatum in thin bundles, the caudate nucleus and putamen are virtually inseparable. In other species the internal capsule separates the two nuclei apparently unsystematically, leaving in some species more tissue on the caudate, and in others more on the putamen side (Bonin and Shariff 1951). In the monkey (Johnson et al. 1968, Kemp and Powell 1970) and other examined species (*see* page 463) the corticofugal axons distribute on both sides of capsula interna in a systematic manner. Substantia nigra projects to the whole neostriatum (Andén et al. 1966) which, in turn, topically projects to the two segments of the globus pallidus and back to the substantia nigra (Szabo 1962, 1967, 1970, Nauta and Mehler 1966). The records of bioelectrical activity in the caudate nucleus and putamen were described as similar in frequency and amplitude (Hayne et al. 1949). Neurons in both structures have a low spontaneous firing rate (Rocha-Miranda 1965, De Long 1971). The caudate nucleus and putamen do not differ in biochemical composition (Manocha and Shantha 1970, Wender and Kozik 1968). In conclusion, there is ground to believe that regions of both caudate nucleus and putamen differ only as much as their cortical and thalamic inputs differ.

[2] The prefrontal cortex is defined here as the cortical projection area of the mediodorsal thalamic nucleus. This definition is a slight modification of the one proposed by Rose and Woolsey (1948). The term "prefrontal cortex", although not ideal, is preferred to the "frontal granular cortex" because a granular area was not described in the rostral cortex of the cat (Akert 1964) or the rat (Leonard 1969).

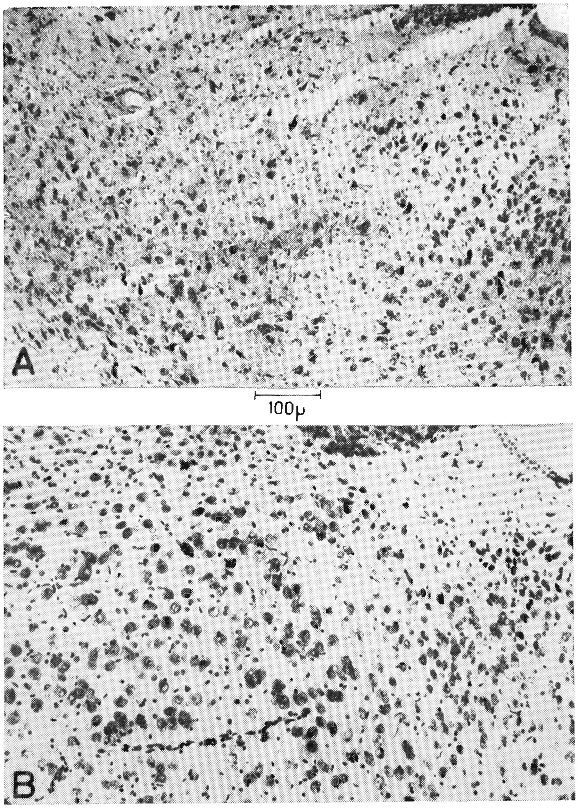

Fig. 1. *A:* The mediodorsal thalamic nucleus of a rat sacrificed 28 days after a mediorostral lesion of the neostriatum. Cresyl violet stain. *B*: As above, but after medial frontal ablation instead of the neostriatal lesion. (From I. Divac, in preparation.)

THE THALAMO-NEOCORTICO-NEOSTRIATAL SYSTEM

Anatomy and electrophysiology

A comprehensive review of the anatomy of the corpus striatum listed cortical projections to the neostriatum from different frontal areas and "suppressor strips", as well as thalamic projections from midline and intralaminar nuclei (Laursen 1963). Recent anatomical data have changed this picture. Impregnation of degenerating axons revealed projections from all neocortical areas terminating in restricted and partially overlapping regions of the neostriatum in animals from many orders: carnivore (Webster 1965), lagomorph (Carman et al. 1963), marsupial (Martin and Hamel 1967), primate (Kemp and Powell 1970) and rodent (Webster 1961). The efferents from the prefrontal cortex to the neostriatum were studied in the monkey by Nauta (1964) and Johson et al. (1968), and in the rat by Leonard (1969). In both species the prefrontal cortex was found to project to the anterior neostriatum. The topical arrangement is maintained also in subsegments: the neurobehaviorally defined sectors of the prefrontal cortex in the monkey project to different, partially overlapping neostriatal regions (Johnson et al. 1968).

Electrophysiological findings support the anatomical data. Rocha-Miranda (1965) found that cells in the head of the caudate nucleus of the cat responded with short latencies and a high probability of firing to electrical stimulation of the anterior cortex. Their discharges followed high rates of cortical stimulation. The same cells responded with longer latencies, a lower probability of responding and without following high rates of stimulation when the marginal gyrus was stimulated. The marginal gyrus, however, projects to the tail of the caudate nucleus (Webster 1965) in which no recordings were made. Neurons in the head of the caudate nucleus of the rat responded with shorter latencies and more readily to electrical stimulation of anterior than posterior cortical loci (Tolkunov 1970).

Some thalamic nuclei, previously thought to project only to the neocortex (Crosby et al. 1962), send axons or collaterals also to restricted regions of the neostriatum (Nauta and Whitlock 1954, Johnson 1961, Khalifeh et al. 1965, Leonard 1969, Smaha et al. 1969, Graybiel 1970, Hall 1970, Hall and Ebner 1970, Heath 1970). Thus, the neostriatum is heterogeneous with respect to its cortical and thalamic input. The thalamic projections to the neostriatum need to be further worked out.

The relation between the mediodorsal thalamic nucleus and the prefrontal cortico-neostriatal pair differs among species. Ablation of the cortex at the frontal pole of the hemisphere in cat, rabbit and sheep (Rose and Woolsey 1948), dog (Narkiewicz and Brutkowski 1967), monkey (Pribram et al. 1953, Akert 1964) and opossum (Bodian 1942) produced atrophy of the mediorsal thalamic nucleus. In the rat, however, no atrophy was seen in this nucleus when frontal lesions were made (Leonard 1969) or the entire neocortex ablated (Combs 1951, I. Divac, in preparation). Studies of axonal degeneration in the rat demonstrated projections from the mediodorsal nucleus terminating both in the neocortex and in the rostral neostriatum. This part of the neostriatum receives projections also from the prefrontal cortex (Leonard 1969). Thus, fibres from a neocortical area and the corresponding thalamic nucleus converge on one region of the neostriatum. Lesion in the same region produced cell loss in the mediodorsal nucleus (Fig. 1). In the rat, then, the part of neostriatum which receives projections from the prefrontal cortex is possibly the essential projection field of the mediodorsal thalamic nucleus.

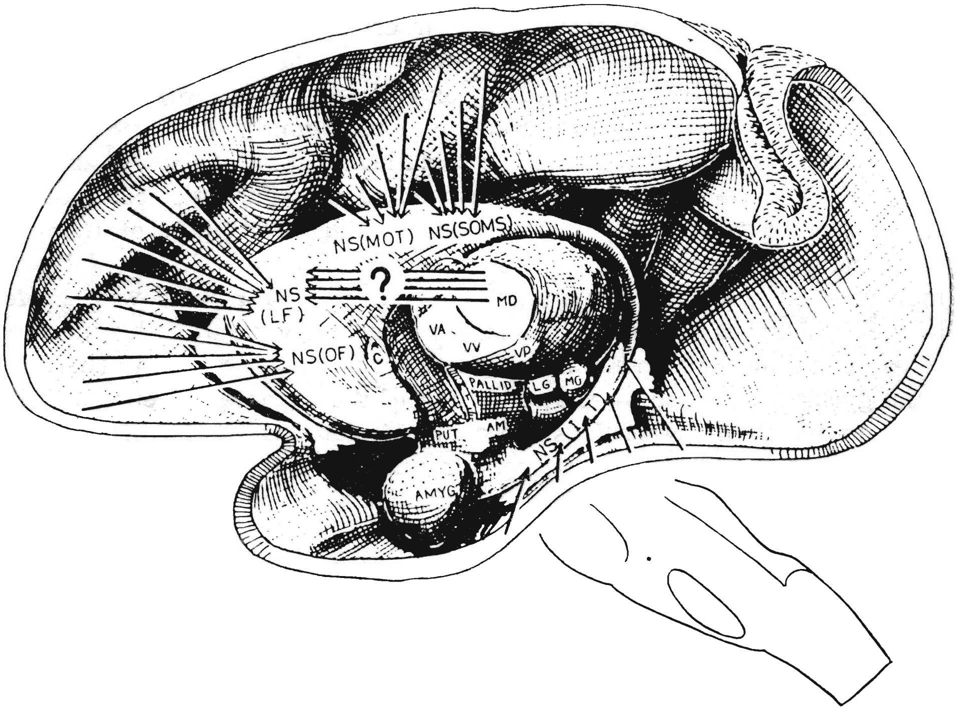

Fig. 2. Schematic representation of the proposed model of the organization of the prosencephalon. To simplify the picture many connections relevant for the model are left out: from many cortical areas to unlabelled regions of the neostriatum, from the thalamus to cortex and, except for the projections from the lateral part of the mediodorsal thalamic nucleus, also from the thalamus to the neostriatum. Neostriatal areas are labelled according to the cortical field where the projections originate. (Modified from Krieg 1963.)

Atrophy of the mediodorsal nucleus after cortical lesions in some species does not rule out that axon collaterals from this nucleus terminate in the neostriatum. In fact, after lesions in the mediodorsal thalamic nucleus of the cat, degenerating axons were found in the rostral portions of the caudate nucleus and putamen by Johnson (1961) and Khalifeh et al. (1965). The latter authors stated that the fibers pass through the caudate nucleus without giving off collaterals. Anterior parts of the caudate nucleus and putamen were found to receive fibers from the prefrontal cortex (Webster 1965). Thus, in the cat, the thalamo-neocortico-neostriatal connections may be arranged in the same way as in the rat. On the other hand, Nauta (1962) did not find degenerating axon branches in the neostriatum after lesions in the mediodorsal nucleus, either in cat or monkey.

To summarize, a region in the rostral neostriatum receives projections from the prefrontal cortex and, at least in some species, from the mediodorsal thalamic nucleus. Axons from both components of other thalamo-neocortical couples may similarly converge on restricted neostriatal regions. As the thalamic projections define functionally meaningful cortical areas, cortical and possibly thalamic projections may define neostriatal regions (Fig. 2).

Neurobehavioral data

Many experiments demonstrated a remarkable similarity between the effects of various operations carried out on the prefrontal cortex and the caudate nucleus. (Tables I and II). In the monkey, Rosvold (1968) found "no exception to the rule that if a frontal lesion results in an impairment on a certain test, so does a caudate lesion". Recently, the same rule was found to apply to nonprimate species. In the cat, lesions of either the gyrus proreus or the rostral part of the caudate nucleus impaired retention of delayed responses (Fig. 3) and delayed alternation (Fig. 4). Similarly, in the rat, retention of spatial reversal (Fig. 5) and of delayed alternation (Fig. 6) was deficient both after prefrontal and anterior neostriatal lesions.

In addition to similar effects of lesions or stimulation, similarities in normal bioelectrical activities were recorded in the prefrontal cortex and the rostral neostriatum during performance of delayed alternation in the monkey. Abplanalp (1969) found the average amplitude of brain waves increased in both structures. The electrocorticogram recorded from the inferotemporal cortex was changed only during visual discriminations. Kubota, Niki and Goto (this Symposium) reported similarities in the discharge patterns of single neurons in the two formations.

Lesions of the neostriatum which produced impairments in prefrontal

TABLE I

Behavioral situations in which procedures carried out on the caudate nucleus or prefrontal cortex produced similar results

	Rat	Cat	Monkey
Delayed alternation	I. Divac, in preration	Divac 1972	Abplanalp 1969 Bättig et al. 1960 Divac et al. 1967 Krauthamer et al. 1967 Kubota et al., this Symposium Rosvold et al. 1958 Rosvold and Delgado 1956
Delayed response	I. Divac, in preparation	Divac 1968*b*	Bättig et al. 1960 Cianci 1965
Spatial reversal	Divac 1971		
Visual go–no go discrimination			Bättig et al. 1962
Auditory go–no go discrimination			Bättig et al. 1962
Delayed successive discrimination			Cohen 1970, and this Symsium
Prism adaptation			Bossom 1965
Self stimulation	Routtenberg 1971		
Bar pressing extinction			Butters and Rosvold 1968
Object reversal			Divac et al. 1967
Activity measures			Rosvold and Delgado 1956

TABLE II

Techniques employed in producing impairments in prefrontal tasks[a]

	Prefrontal cortex	Caudate
Electrical stimulation	Cohen 1970, and this Symposium Stamm 1969 Weiskrantz et al. 1962	Cianci 1965 Cohen 1970, and this Symposium Rosvold and Delgado 1956 Stamm 1969
Cooling	Fuster and Alexander 1970 Shacter and Schuckmann 1967	Krauthamer et al. 1967
Lesion	*See* for review Warren and Akert 1964	High frequency coagulation, Divac et al. 1967 d-c coagulation, stainless steel, Bättig et al. 1960 d-c coagulation, tungsten, Divac 1968*b*
Specific antibodies		Mihailović et al. 1969

[a] A "prefrontal task" is one in which monkeys or other species with prefrontal (*see* Footnote 2) lesions made in adulthood are impaired as compared with intact controls.

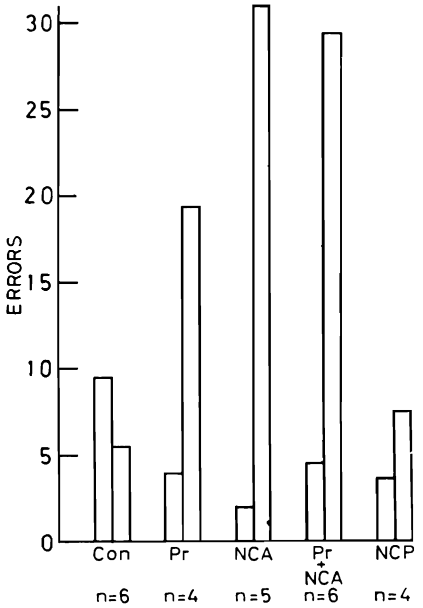

Fig. 3

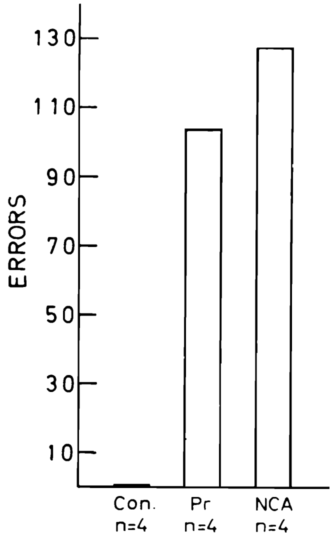

Fig. 4

Fig. 3. Median errors in blocks of 80 trials on 30 sec delayed response in cats. First columns: pre-operative; second columns: post-operative error scores. Con: control; Pr: proreus ablation; NCA: lesion in the rostral part of the caudate nucleus; NCP: lesion in the posterior part of the head of the caudate nucleus. 2 X 2 analysis of variance, including a group with Pr *and* NCA lesions, showed significantly larger effect of the NCA lesions as compared to Pr. (From Divac 1968*b*).

Fig. 4. Median errors in relearning 5 sec delayed alternation after proreal and caudate lesions in cats. Notation as in Fig. 3. The difference between Pr and NCA groups was not statistically significant. (From Divac 1972).

tasks always involved the neostriatal region which receives projections from the prefrontal cortex. Recording electrodes of Abplanalp (1969) and Kubota, Niki and Goto (this Symposium) were placed in the some neostriatal region. On the other hand, deficient performance in prefrontal tasks was not found when neostriatal lesions or stimulations were localized outside the region connected with the prefrontal cortex (Borst et al. 1970, in the rat; Cohen 1970, this Symposium, in the monkey; Divac 1968*b* Fig. 3, in the cat). The only exception to these statements is the delayed alternation impairment found in 2 out of 4 monkeys after lesions in the tail of the caudate nucleus (Divac et al. 1967). Accidental damage of the hippocampus probably caused the impairment (Waxler and Rosvold 1970).

Lesions or stimulation confined to restricted neostriatal regions produced the same effect as ablation or stimulation of the associated neo-

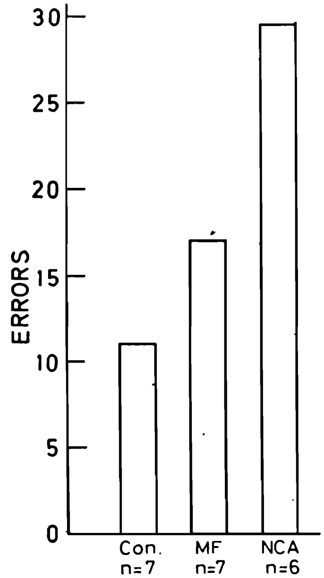

Fig. 5

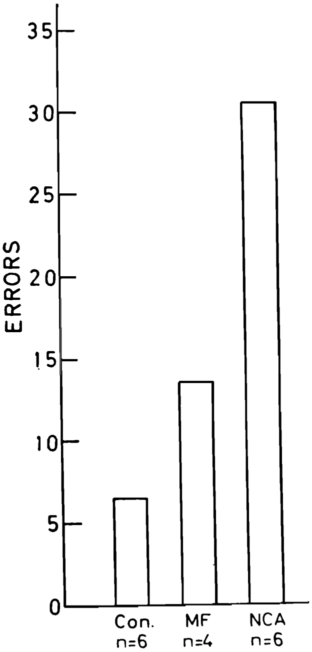

Fig. 6

Fig. 5. Median errors to criterion in two spatial reversals in rats. MF: mediofrontal ablation. Other notation as in Fig. 3. Mann-Whitney U test showed significant differences in each comparison. (From Divac 1971.)

Fig. 6. Median errors in the first 60 trials of post-operative retention of spatial alternation in rats. Notation as in Fig. 5. (From I. Divac, G. Wikmark and R. Weiss, in preparation.)

cortical region. Stimulation (Cohen 1970, and this Symposium) or destruction (Divac et al. 1967) of the tail of the caudate nucleus impaired visual discrimination. Lesion in the medial part of the head of the caudate nucleus impaired passive avoidance (Fox et al. 1964). Anterodorsal lesion interfered with learning of delayed alternation only, while ventrolateral lesion impaired only object reversal (Divac et al. 1967).

I summarize by paraphrazing Rosvold (1968): In fact, in no species have we found any exception to the rule that if lesion or stimulation in an "associative" neocortical area results in impairment on a certain test, so does lesion or stimulation in the associated part of the neostriatum.

IS THE EVIDENCE FOR PARTICIPATION OF THE CAUDATE NUCLEUS IN PREFRONTAL FUNCTION UNEQUIVOCAL?

The question to be discussed in this section derives from the astonishing fact that effects of various procedures carried out in the prefrontal cortex and the caudate nucleus, two structures different in many respects (*see* p. 470), are so strikingly similar (Tables I and II). Could this be an artifact?

Prefrontal afferent and efferent fibers pass either through or near the anterior neostriatum in the cat (Khalifeh et al. 1965, Krnjević and Silver 1965, Murray 1966, Scheibel and Scheibel 1967, Rinvik 1968) and monkey (Nauta 1962, 1964). In the rat, the capsula interna perforates the neostriatum in dispersed bundles. The available procedures for making lesions always damage the fibers which pass through the neostriatum. The fibers passing near the neostriatum are difficult to avoid, and in no illustration of the papers listed in Table I were the lesions confined to the caudate nucleus.

The effects described after lesions or stimulation of the caudate nucleus could have been produced by disturbed input or output of the overlying cortex. Gross recording in the caudate nucleus (e.g. Abplanalp 1969) can similarly pick up the activity of corticofugal or corticopetal fibers or both.

No direct attempt has been made to assess the role of corticofugal and corticopetal fibers in the effects produced by lesions or stimulation of the caudate nucleus. The following results suggest that destruction of the caudate tissue and not damage to the passing fibers is responsible for the deficits in the prefrontal tasks. Some of these results, however, may be differently interpreted. (i) Lesions confined to the white matter adjoining the caudate nucleus did not produce the deficits which were found when the lesions invaded the caudate tissue (Rosvold and Delgado 1956, Divac et al. 1967). (ii) In cats (Fig. 3) and rats (Fig. 5 and 6) rostral neostriatal lesions had more effect on the performance of frontal tasks than the cortical ablations. The larger impairments seen after neostriatal lesions could not be attributed to undercutting cortical areas wider than those removed by ablation of the prefrontal cortex because ablation in the cat of the periproreal cortex in addition to removal of the gyrus proreus did not further disturb performance of delayed responses (I. Divac, in preparation). Similarly, in rats, lesions of the fronto-polar cortex, which is probably undercut by rostral neostriatal lesions, did not disturb retention of spatial reversals (Divac 1971) or delayed alternation (I. Divac, G. Wikmark and R. Weiss, in preparation). (iii). In infant monkeys, prefrontal cortical ablation alone did not produce prefrontal symptoms; when caudate lesions were added, performance of delayed responses was impaired. The groups were, however, not comparable. Only monkeys with both cortical and caudate lesions were reared away from their mothers and had epileptic seizures (Kling and Tucker 1967). (iv) Time-locked firing of caudate neurons during delayed alternation performance may suggest that the caudate nucleus is involved in "prefrontal functions" (Kubota et al., this Symposium). Only one behavioral task was used, however, and the firing of the caudate cells during delayed alternation may not be specific for this task.

In conclusion, it is unlikely, but not excluded, that the effects of lesion or stimulation of the neostriatum are artifacts of involvement of corticofugal or corticopetal fibers.

FUNCTIONAL RELATION BETWEEN THE PREFRONTAL CORTEX AND THE ASSOCIATED NEOSTRIATUM

The following anatomical characteristics of the prefrontal cortex and the associated neostriatum must be taken into account in speculations about the relation between them. The prefrontal cortex and the associated part of neostriatum differ cytoarchitecturally (Crosby et al. 1962) and biochemically (Friede 1966). The prefrontal cortex receives projections, from many cortical areas (Jones and Powell 1970) as well as thalamus, and projects to a restricted region of the neostriatum as well as various diencephalic and rhombencephalic nuclei (Kuypers and Lawrence 1967, Johnson et al. 1968, Rinvik 1968, Leonard 1969, Brodal 1971). The neostriatal region associated with the prefrontal cortex does not receive input from distant parts of neostriatum (Voneida 1960, Szabo 1962, 1967, 1970, Nauta and Mehler 1966) but receives axons from substantia nigra (Andén et al. 1966), thalamus and prefrontal cortex, and projects to the two segments of globus pallidus and to substantia nigra (Voneida 1960, Szabo 1962, 1967, 1970, Nauta and Mehler 1966).

The listed anatomical data permit two conclusions. First, the differences in biochemical composition, cytoarchitecture *and* connections rule out similar modes of operation and interchangeable outputs of the two formations. Secondly, both "in parallel" and "in series" relations between the two formations are possible.

A lesion in either of the two formations affects the other. Prefrontal ablation does not cause cell loss in the neostriatum of the monkey (Burandt et al. 1961), cat (Wang and Akert 1962) or rat (Knook 1965), but deprives it of prefrontal input and, in the cat at least, of the input from the mediodorsal thalamic nucleus which in this species probably projects to the rostral neostriatum but degenerates after prefrontal ablation. The lesion in the part of the neostriatum associated with the prefrontal cortex deprives the latter of one of its output targets and may, as discussed in the preceding section, accidentally interfere with the afferent and efferent systems of the prefrontal cortex. It is, therefore, impossible to postulate that the effects of lesion in the two formations are independent.

Neurobehavioral evidence may lead to the erroneous conclusion that the functions of the prefrontal cortex and the associated neostriatum are similar enough to substitute for each other: First, Kling and Tucker (1967, 1968) found impairment in delayed response in infant monkeys with combined lesions in the prefrontal cortex and rostral neostriatum. Either prefrontal ablations alone or combined with removal of the posterior association cortex did not produce the impairment. The multivariable defferences between the groups (*see* p. 469) preclude the inference that neostriatum carries on the function for which the prefrontal cortex is still immature. Secondly, together with similar effects of lesions or stimulation of the two formations (Tables I and II), the successful retraining of animals with prefrontal ablations (Ławicka and Konorski 1959), 1961, Bättig et al. 1960, Pinsker and French 1967, Divac 1972), may lead to the hypothesis that the neostriatum is "capable of assuming cortical functions" (Divac et al. 1967). Direct tests of this hypothesis did not bear out its predictions. Lesion in the rostral neostriatum either in cats which learned delayed response without the prefrontal cortex (Wikmark and Divac 1972) or in monkeys which relearned delayed matching from sample after lateral prefrontal topectomy (J. S. Stamm, personal communication), did not impair the performance in these tasks. Thirdly, similarities in bioelectrical activities of the two formations (Abplanalp 1969, Kubota et al., this Symposium) and Cohen's (1970, this Symposium) results of stimulation suggest only that the two formations work in synchrony, not that their operations are similar and can substitute for each other. Fourthly, similarities in effects of lesions and stimulation (Tables I and II) imply only that the prefrontal cortex and the rostral neostriatum participate in mediation of the same behavior. If their operations were identical, and if mass action were not involved, lesion of either of the two formations should be without an effect.

Some data rule out mass action: no additivity of effects of combined lesions was found (Divac 1968*b*); the degree of effect did not vary with the size of lesion but it did vary with its location, though the neostriatal was not larger than prefrontal lesion, it produced a larger deficit (Fig. 3); finally, the lesion of the remaining formation in the experiments of J. S. Stamm (personal communication) and Wikmark and Divac (1972) did not produce the impairment.

In conclusion, both anatomical and neurobehavioral evidence concur in ruling out that the operations of the prefrontal cortex and the associated neostriatum are similar enough to substitute for each other.

The anatomy permits both "in parallel" and "in series" relation between the prefrontal cortex and the associated neostriatum. Both paradigms are in agreement with the effects of lesions in adult monkeys (Tables I and II). The "in parallel" paradigm, however, does not agree with the finding that effects of lesions of the two formations were not additive (Divac 1968*b*), and with the effects of sequential lesions: destruction of the neostriatum in cats or monkeys which learned a prefrontal task with ablated prefrontal cortex did not produce the impairment (J. S. Stamm, personal communication, Wikmark and Divac 1972). In the inverse sequence of the two lesions, the second operation was also without an effect (J. S. Stamm, personal communication).

All reviewed results, except the stronger effect of the neostriatal lesion as compared with the proreal one (Fig. 3) are in agreement with the "in series" paradigm. The serial relationship favored by this analysis applies to the prefrontal cortico-neostriatal system in adult cats and monkeys and to the functions revealed by the contemporary neurobehavioral techniques. Relations between the members of other neocortico-neostriatal systems may be different, e.g. no neostriatal lesion replicated the effects of ablations of the motor cortex. Other relations may exist in the infant brain (Kling and Tucker 1968), or in adult brains of other species, notably rat, in which the rostral neostriatum continues to receive input from the mediodorsal nucleus after ablation of the prefrontal cortex. Finally, some other functions mediated by the prefrontal cortex and the associated neostriatum may be discovered, for which other paradigms will be suitable.

It may be concluded (i) that the prefrontal cortex and the associated part of the neostriatum perform different operations both needed for the same behavior, (ii) that some operations of the two formations are organized "in series", and (iii) that some operations of the two formations are interdependent.

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