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THE CONNEXIONS OF THE STRIATUM AND GLOBUS PALLIDUS: SYNTHESIS AND SPECULATION

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Recent findings on the afferent and efferent connexions of the striatum (the caudate nucleus and putamen) and globus pallidus have been summarized in an orderly sequence. The striatum receives afferent fibres from three main sources, the cerebral cortex, the intralaminar nuclei of the thalamus and the midbrain; the major features of each of these pathways are outlined. The striatum sends efferent fibres to the globus pallidus and the substantia nigra, and the two segments of the globus pallidus in turn project upon the subthalamic nucleus and upon the thalamus and midbrain tegmentum. Through the thalamus the major influence of the striopallidum is upon the motor area of the cerebral cortex, and it is suggested that through the midbrain tegmentum there may also be a descending influence upon the spinal cord. These findings from light microscopical investigations are synthesized with observations made in electron microscopic studies of the striatum and globus pallidus. On the basis of present knowledge of their structure and connexions attention is drawn to several marked similarities between these parts of the basal ganglia and the cerebellum.

Introduction

Knowledge of the anatomical connexions of the striatum (the caudate nucleus and putamen) and globus pallidus was incomplete and confused for a considerable time largely because of two technical reasons. The first of these was related to the situation of these basal ganglia deep within the cerebral hemisphere and the associated difficulty of placing selective lesions within them without damage to adjoining fibre tracts. The second reason was the lack of a neurohistological method for staining fine degenerating axons, as it is now known that most of the afferent pathways to these structures end as axonal branches of fine diameter. During the past two decades, however, these difficulties have, to a large extent, been overcome and as a consequence there has been a marked advance in our understanding of the organization of the afferent and efferent pathways linking the striatum and globus pallidus with each other and with other parts of the cerebral hemisphere. The accurate and reliable stereotaxic atlases which have become available, making it possible to place small electrolytic lesions confined within the limits of these nuclei, and the development of a highly sensitive and specific method for the impregnation of degenerating non-myelinated axons (Nauta & Gygax 1954) have together been the technical basis for most of the recent experimental neurohistological investigations on these regions. The study of normal and experimental material with the electron microscope has elucidated the finer details of the cytological and synaptic organization of these masses, and the interpretation of these observations has been strengthened by considering them in conjunction with those made with one of the oldest of all neurohistological techniques, that of Golgi.

In the present paper an attempt will be made to bring together the major findings on these connexions which have been made with the light microscopical methods during recent years and to summarize the afferent and efferent pathways in an orderly sequence. This information will then be synthesized with the electron microscopic observations which have been described in the preceding papers and in those of other authors. It is considered that the data obtained from these investigations have met the requirement for a physiological analysis of such subcortical structures stated by Eccles in 1953, 'precise physiological investigation has to await the construction of reliable maps of the nerve connexions'. Subsequent to the summary of the connexions of the striatum and globus pallidus, and on the basis of our *present* knowledge of them, certain speculations will be presented and in particular attention will be drawn to several marked similarities in the structure and pattern of connexions of these basal ganglia and the cerebellum. Such similarities in the major afferent and efferent pathways were briefly noted by Nauta & Mehler (1969), but here we will also take into account the more recent electron microscopic evidence. These ideas are being put forward in the hope that they may stimulate further investigation, anatomical and physiological, and also that they may emphasize the value of the correlation of structure and function, an approach that has proved to be so fruitful in the case of the cerebellum.

A detailed and comprehensive review will not be presented and, in particular, little reference will be made to the older literature. The papers dealing with the projection of the cortex upon the striatum (Webster 1961, 1965; Carman, Cowan & Powell 1963; Kemp & Powell 1970) consider the earlier evidence for these connexions, the projection of the thalamus upon the striatum has been discussed recently by Mehler (1966), and the problem of the afferent connexions to the striatum from the midbrain by Nauta & Mehler (1969) and Mettler (1970). The efferent connexions of the globus pallidus have been investigated and reviewed by Nauta & Mehler (1966). For a comprehensive treatment of the connexions of the basal ganglia the review of Mettler (1968) should be consulted. The clinical conditions associated with disease of the basal ganglia and their possible anatomical and physiological basis have recently been the subject of two monographs by Denny-Brown (1962) and Martin (1967).

SYNTHESIS

Light microscopy

Afferent connexions. Cerebral cortex.

A number of observations which have been made on the cortico-striate projection in the monkey (Kemp & Powell 1970) have confirmed those made previously in other species (Webster 1961, 1965; Carman *et al.* 1963). Thus it has been found that the whole of the cerebral cortex sends fibres to both the caudate nucleus and putamen and that the projection is arranged essentially on a topographic basis; the fibres converge upon the striatum as a whole, so that cortical areas appear to be related to a band within the striatum usually including parts of both the caudate nucleus and putamen. All parts of the caudate nucleus and putamen receive afferent fibres from the cortex. Furthermore, the bilateral projection from a limited part of the cerebral cortex to the striatum, seen in other animals (Carman, Cowan, Powell & Webster 1965) is also present in the Primate. As well as confirming these points it has been possible to extend the earlier work. Lesions were usually placed in individual functional areas of the cerebral cortex in order to compare more exactly the volumes of the striatum related to these various areas, and it has been shown that the heaviest projection arises from the somatic sensory and motor regions. That the motor cortex is so strongly related to the striatum is not surprising in view of the known association of the basal ganglia with motor function, but the equally strong projection from the somatic sensory areas of the hemisphere is rather unexpected. A possible explanation may be found in the recent work which shows that Group I muscle afferent fibres terminate in area 3a (Oscarsson & Rosén 1966; Landgren & Silfvenius 1968; Phillips, Powell & Wiesendanger 1970) suggesting that this region is importantly involved in the control of movement. Whether or not area 3a sends a heavier projection to the striatum than the remainder of the somatic sensory cortex is not known as it has not been possible to place lesions restricted to area 3a because it is buried in the depths of the central sulcus. In contrast to the large projection from the somatic sensory and motor areas that from the visual cortex is very small. This finding may be paradoxical in view of Martin's statement (1967) that 'In providing the reflex adjustment and controls for locomotion the basal ganglia are "informed" chiefly by proprioception, and also to an important extent by vision, and only in a minor degree by labyrinthine function'. An alternative interpretation of his observations that visual cues are of great help to Parkinsonian patients who show difficulties in walking is that the visual information is being used by some mechanism which is extrastriatal. The increase in extent of the 'association' cortex in the frontal and parietotemporal lobes in the monkey has been accompanied by a corresponding increase in their cortico-striate projection. These clear differences in the contribution to the cortico-striate projection of the various areas—somatic sensory and motor, visual and 'association'—of the cortex indicate that although the organization of the projection from the cortex upon the striatum is on a simple topographic basis, the *extent* of the caudate nucleus and putamen influenced by any subdivision of the cortex is clearly dependent upon the function of that cortical area and not upon its size.

Though the projection from different areas of the cerebral cortex is topographically arranged the termination of the fibres from adjacent regions of the striatum shows considerable overlap in all dimensions. This means that no part of the caudate nucleus or putamen is under the sole influence of one part of the cerebral cortex. Such overlap is the first indication of the considerable convergence which would appear to take place in the striatum and further anatomical evidence for this prediction will be presented when the ultrastructure of the caudate nucleus is considered. This convergence and the resulting integration which must occur, not only between large areas of the cerebral cortex, but also with the input from the thalamus and midbrain seems, on anatomical grounds, to be one of the striking features of the striatum.

The bilateral projection to the striatum has been found to originate in two areas of the cerebral cortex, the supplementary motor area and area 5; the latter appears to correspond to the supplementary sensory area of Penfield & Jasper (1954). The supplementary motor area and area 5 are similar in that both are bilaterally functioning systems (Travis 1955; Penfield & Jasper 1954) and both receive projections from the primary somatic sensory area; in addition area 5 sends fibres to the supplementary motor area (Jones & Powell 1970). Selective ablation of the supplementary motor area results in disturbance in posture and tonus (Travis 1955) and it is perhaps significant that this part of the cerebral cortex should have a bilateral influence on the striatum which is itself involved in the control of posture, muscle tone and movement. One puzzling feature is that in lower forms the bilateral projection is relatively larger than in the monkey suggesting that in the latter species the bilateral influence of the cortex is of less importance. The only explanation that can be put forward at present for this relative diminution of the contralateral projection in the larger animals is that part, at least, of the contralateral projection to the striatum passes via the anterior commissure (van Alphen 1969; Powell &

Cowan 1964, unpublished observations), and that the *relative* size of the contralateral corticostriate projection diminishes in parallel with the *relative* decrease in size of the anterior commissure as compared with that of the corpus callosum. The region of the striatum which receives fibres from the contralateral hemisphere is restricted, being situated in the dorsolateral quadrant of the head of the caudate nucleus and in the dorsolateral part of the body. Careful examination of these areas of the caudate nucleus both with the light and the electron microscope, has failed to reveal any anatomical difference between it and the rest of the nucleus. The difference which would be expected must therefore be subtle, and will probably be found to be a slight variation in the number or distribution of terminals.

There is evidence from studies of Golgi impregnated material that some afferent fibres to the striatum arise as collateral branches from axons in the internal capsule. Whether or not these are efferent fibres from the cerebral cortex cannot be determined. It would be of some importance to know whether the different connexions of a cortical area—cortical and subcortical—arise from different pyramidal cells or are collateral branches of the same pyramidal cells, so that all the projection fields receive identical information. There is some physiological evidence that pyramidal tract fibres do give rise to collateral axons which terminate in the thalamus (Clare, Landau & Bishop 1964; Shimazu, Yanagasiwa & Garoutte 1965), but whether these also send collateral branches to the other regions is not known.

Thalamus

The projection from the thalamus to the striatum has been shown in human neuropathological material (Vogt & Vogt 1941; McLardy 1948), by studies using retrograde cellular degeneration (Droogleever-Fortuyn 1953; Powell & Cowan 1956) and orthograde fibre degeneration methods (Nauta & Whitlock 1954; Mehler 1966), to arise from the intralaminar nuclei and to be well organized. Whether these nuclei also project to the cerebral cortex is questionable, and it seems unlikely that anatomical methods could establish such a connexion. Although it has been customary to consider the intralaminar group of nuclei as the 'non-specific' or 'diffuse' thalamic system there is increasing evidence to indicate that their connexions are well defined and are arranged in parallel with those of the main nuclei. Furthermore, it appears that the individual intralaminar nuclei which receive the same ascending connexions as an adjoining principal nucleus also receive descending fibres from the area of cortex which is related to the same principal nucleus (Jones & Powell 1971). The intralaminar nuclei are, therefore, sites of convergence of fibres from other parts of the brain and the lower levels of the sensory pathways on the one hand and from the cerebral cortex on the other. The efferent fibres of the intralaminar nuclei pass to the striatum and as this group of thalamic nuclei as a whole are equivalent to all of the principal nuclei and receive the same afferent pathways, it appears that the thalamostriate projection is a parallel one to the better known projection of the principal nuclei upon the cerebral cortex. It should be noted that one of the major efferent pathways of the basal ganglia, from the internal segment of the globus pallidus, also terminates in one of the intralaminar nuclei, the centromedian nucleus, and the possible significance of this relationship will be discussed later.

Midbrain

There are two possible sites of origin for fibres to the striatum from the midbrain; the substantia nigra and a region lower in the brain stem adjacent to the red nucleus. Nauta & Kuypers

(1957) showed a projection to the striatum, with fibre degeneration methods, after lesions of the midbrain tegmentum adjacent to the red nucleus while lesions in the substantia nigra are said to give little or no degeneration in the striatum (Cole, Nauta & Mehler 1964; Faull & Carman 1968; Nauta & Mehler 1969; Mettler 1970). Evidence for a projection from the substantia nigra is also derived from histochemical (e.g. Andén, Dahlström, Fuxe & Larsson 1965) and physiological investigation (Frigyesi & Purpura 1967; Connor 1968; Portig & Vogt 1969). The failure of the anatomical techniques to reveal the fibre system may be due to the fibres from the substantia nigra to the striatum being very fine and because they may contain a very high concentration of dopamine. Because it has not proved possible to place large lesions within the substantia nigra without causing ischaemic necrosis of the overlying tegmentum in our electron microscopic study of the termination of afferent fibres in the striatum the controversy about the precise origin of the fibres from the midbrain has been avoided; deliberately large lesions were placed which involved the area which Nauta & Kuypers (1957) showed projects to the striatum and they also encroached upon the substantia nigra. The degenerating terminals, seen with the electron microscope, could therefore have arisen from either of these regions. These findings on the afferent connexions, and of those on the efferent connexions to be discussed below, are summarized schematically in figure 1.

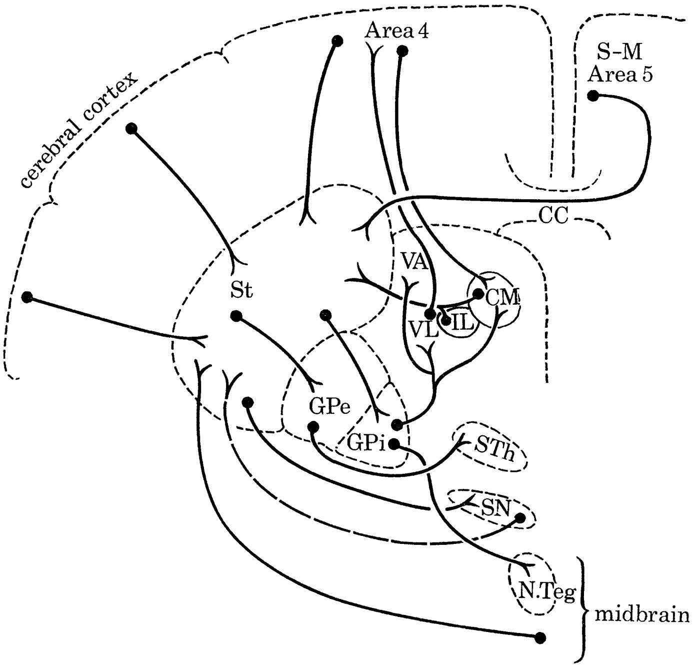

FIGURE 1. Diagram showing the main afferent and efferent connexions of the striatum and globus pallidus. It should be noted that although only the centromedian component of the intralaminar nuclei *receives* fibres from the globus pallidus all of the nuclei of this group (IL) project upon the striatum. Interrupted line indicates a possible connexion *from* substantia nigra (SN) *to* the striatum.

CC	corpus callosum	SN	substantia nigra
CM	centromedian nucleus of the thalamus	St	striatum
GPe	globus pallidus, external segment	STh	subthalamic nucleus
GPi	globus pallidus, internal segment	VA	ventroanterior nucleus of the thalamus
N.Teg	tegmental nuclei	VL	ventrolateral nucleus of the thalamus
S–M	supplementary motor cortex		

Efferent fibres of the striatum

The caudate nucleus and putamen send their efferent fibres to two main sites, the globus pallidus and substantia nigra. The projection to both these structures is topographically well organized, and that to the globus pallidus is, quantitatively at least, the major one. It is probable that only a small proportion of the cells of the striatum contribute to the efferent projection, and although these cells have not been identified with certainty the available evidence from Golgi-impregnated material implicates two types of cell, the large neuron and one variety of the medium-sized cell. It would be of interest to determine, by antidromic stimulation methods, whether the same cell branches to project to both the pallidum and the nigra or whether the projection to these two structures is from different cells.

The efferent fibres from the striatum project radially 'like the spokes of a wheel' (Papez 1942) upon the globus pallidus, and the site of termination of these fibres from all parts of the caudate nucleus and putamen has been determined (Voneida 1960; Szabo 1962, 1967, 1968, 1969; Nauta & Mehler 1966; Cowan & Powell 1966). It has not been established, however, whether the projection is organized upon a simple topographic basis, with the two segments of the globus pallidus receiving fibres from different parts of the striatum, the fibres from peripheral parts of the caudate nucleus and putamen ending in the external segment and those from more central portions ending in the internal segment, or whether all parts of the striatum project in an organized manner upon *both* the external and internal segments (see Cowan & Powell 1966). When the damage is small and is restricted to the peripheral parts of the striatum the axonal degeneration is limited to one or other segment, but with larger lesions of the striatum the degeneration is found in both segments; whether the more extensive degeneration is due to interruption of fibres from more peripheral parts of the striatum is difficult to determine.

The projection of the striatum upon the substantia nigra is similarly organized, with the caudate nucleus, in general, projecting medially and the putamen laterally, and the head of the caudate nucleus is related to rostral parts and the tail to posterior parts of the substantia nigra (Szabo 1962, 1969). The majority of the efferent fibres from the striatum appear to terminate in the pars reticulata although the suggestion from light microscopy that some also end in the pars compacta has been confirmed with the electron microscope (Grofová & Rinvik 1970).

Efferent connexions of the globus pallidus and substantia nigra

If the connexions of these basal ganglia are followed in sequence by considering in turn the efferent connexions of the globus pallidus and substantia nigra one obtains what is perhaps the strongest clue to the functional significance of these large masses of neurons. The precise site of termination of the efferent fibres from the substantia nigra is still a matter of debate: whether they are predominantly to the thalamus (Cole *et al.* 1964; Faull & Carman 1968), the globus pallidus (Mettler 1970), or the striatum itself (Andén *et al.* 1965; Nauta & Mehler 1969). As our own investigations have not contributed to the elucidation of this problem, and because the available evidence has been critically reviewed by Mettler (1970), it will not be discussed further, but it may be noted that, depending upon which of these respective sites is shown to receive the major projection from the substantia nigra, the afferent fibres to the substantia nigra from the striatum together with the nigral efferents would form either a second pathway from the striatum to the thalamus (parallel to that through the globus pallidus), or an indirect pathway through the substantia nigra from the striatum to the globus pallidus, or a direct feedback to the striatum.

In contrast, however, the efferent connexions of the globus pallidus have recently been considerably clarified by Nauta & Mehler (1966), and for the detailed results of this investigation and for an authoritative review of the earlier literature on these pathways the original paper should be consulted. These authors have shown that the two segments of the globus pallidus differ considerably in their projections, the external segment sends fibres to the subthalamic nucleus and the internal segment to the thalamus and midbrain tegmentum. It is especially significant that the thalamic nuclei, the principal nuclei ventralis anterior and ventralis lateralis and the centromedian nucleus of the intralaminar group, in which these fibres end, are all closely related to the motor cortex, the ventral nuclei being reciprocally connected to this cortical area while the centromedian nucleus receives a substantial projection from it. Furthermore, the site of termination of the pallidal fibres in the ventral nuclei (VA, VLo and VLm) overlaps with that of those from the cerebellum. As the centromedian nucleus is a site of convergence of fibres from the motor cortex and the globus pallidus on the one hand and sends its efferent fibres to the caudate and putamen on the other it could well serve as a feed-back mechanism to modulate the activity of *both* parts of the striatum—peripheral and medial—consequent upon changes in the activity of the motor cortex. It appears, therefore, that the strio-pallidum is strategically placed to sample the activity of the entire cerebral cortex (through the cortico-striate connexions), to integrate this with the resultant activity of the intralaminar nuclei of the thalamus and the midbrain tegmentum and to affect in turn the activity of one component of the intralaminar system (the centromedian nucleus) and the motor area of the cortex. It is also probable from the organized nature of these connexions that, despite the fact that there is considerable overlap in the termination of fibres from adjoining areas of the cortex, different regions within the striatum as a whole are under the influence of cortical areas which have distinctly different functions, and, because of the organization of the strio-pallidal projection, parts of the globus pallidus (and perhaps the two pallidal segments) are also being influenced predominantly by one or other area of the cortex.

If the strio-pallidal projection is arranged such that peripheral parts of the striatum are related to the external pallidal segment and more central parts of the striatum to the internal segment then the peripheral parts of the striatum would be expected to influence mainly the subthalamic nucleus while more medial parts of the caudate nucleus and putamen would probably influence the thalamus and midbrain tegmentum. Although there is no evidence of a clear-cut difference, in terms of structural or functional subdivisions, in the origin of the cortical afferents to the peripheral and central parts of the striatum, a synthesis of the findings made in studies on the monkey allowed certain correlations to be made (Kemp & Powell 1970). Most of the cortical areas which were damaged in the monkey (including the motor cortex, the somatic sensory and visual areas) project to peripheral parts of the striatum, the medial surface dorsally, the lateral surface of the parietal and occipital lobes and most of the temporal lobe laterally. It is probable, therefore, that through the striatum these are regions of cortex which influence the external segment of the globus pallidus and then the subthalamus. The orbital cortex, the insula and its opercula appear to project upon the medial part of the striatum, and it is these areas, therefore, that would ultimately influence the medial segment of the globus pallidus and the thalamus and midbrain tegmentum. It was suggested that the significance of this organization lay in the recent evidence for a final convergence of the three major sensory pathways, through association cortical connexions, in the depths of the superior temporal sulcus, at the frontal pole and in the cortex of the frontal operculum, and that all these regions are interconnected with each other and with the cortex on the orbital surface of the frontal lobe and with the temporal pole (Jones & Powell 1970). It is possible, therefore, that through these regions of cortex the medial parts of the striatum and the internal segment of the globus pallidus are receiving an influence which represents a complex integration not only of all the sensory pathways but also of the areas of 'association' cortex of the frontal and parietotemporal lobes. As the internal segment of the globus pallidus projects upon the ventrolateral nucleus of the thalamus, which in turn sends fibres to the motor cortex, it would mean that this is a pathway, of increasing convergence, to areas 4 and 6. It is significant that these regions of 'association' cortex have undergone a considerable expansion in the Primate brain, and also that this has been associated with an enlargement of the putamen and with the differentiation of the internal segment of the globus pallidus from the entopeduncular nucleus of other mammals. As these structures are successive relays in a pathway ultimately influencing the motor cortex it is clear that through this pathway, at least in the Primate, there is an increase in the influence upon the motor cortex of the other neocortical areas.

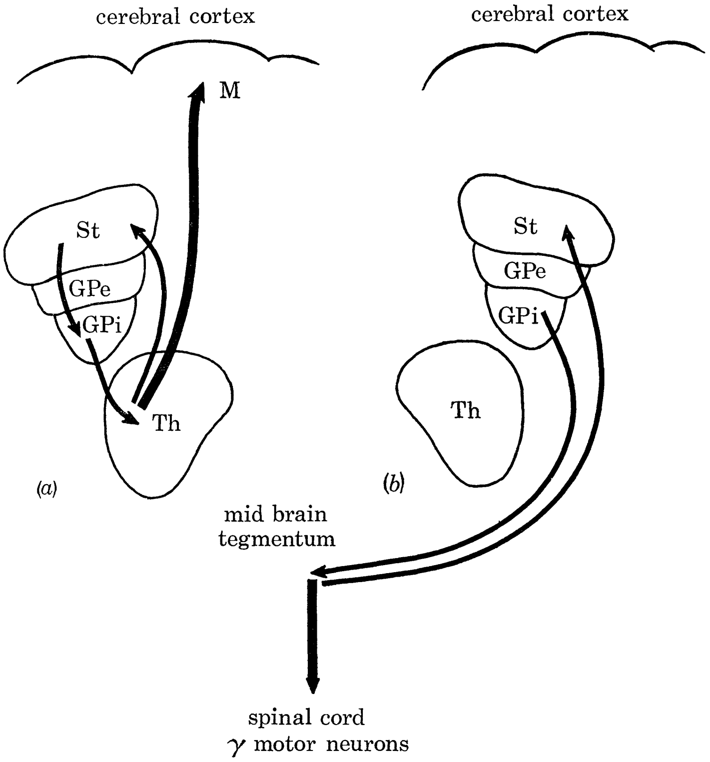

FIGURE 2. Schematic figure to show the similarity of the reciprocal relationship of the basal ganglia with (*a*) the thalamus (and thence the motor cortex) and (*b*) the midbrain (and thence the spinal cord).

GPe	globus pallidus, external segment	St	striatum
GPi	globus pallidus, internal segment	Th	thalamus
M	motor cortex		

The connexions of the globus pallidus with the thalamus have been considered at some length because the elucidation of the details of the projection to the centromedian and ventral nuclei (Nauta & Mehler 1966) has been one of the most important contributions in recent years, and also because of its probable functional significance.

Until relatively recently the midbrain connexions of the basal ganglia received much less attention, and most interest has been shown in the relationship with the substantia nigra, particularly with regard to the question of an afferent pathway to the striatum from this structure. From a correlation of the findings of Nauta & Mehler (1966) on the site of termination of the pallidal efferent fibres in the midbrain tegmentum with certain observations made in neurophysiological experiments, however, certain tentative speculations may be made. The internal segment of the globus pallidus projects to the nucleus tegmenti pedunculopontinus which is in the immediate vicinity of the site of origin of the mesencephalic fibres to the striatum. Whether these two regions are identical or adjoining each other cannot be stated on the evidence available, but their close proximity does raise the possibility of a reciprocal relationship between the midbrain and the striatum and pallidum comparable to that between the thalamus (especially the centromedian nucleus) and the striatum and pallidum (figure 2). As the thalamic nuclei which receive pallidal efferent fibres are closely related to the motor cortex and are probably implicated in the control of movement the question may be asked whether the midbrain connexions of the basal ganglia are also implicated in this activity. That this is possible is suggested by the observation that stimulation of a region which appears to be close to the site of termination of the fibres from the globus pallidus gives facilitation of the gamma motor neurons (Granit & Kaada 1952; Shimazu, Hongo & Kubota 1962; Vedel & Mouillac-Baudevin 1969) and that stimulation of the caudate nucleus can also increase gamma fibre activity (Granit & Kaada 1952; Vedel & Mouillac-Baudevin 1969). There is the possibility, therefore, of a descending influence of the striatum upon the spinal cord, in addition to its effect upon the cerebral cortex through the thalamus (figure 2).

Electron microscopy

The aim of the electron microscopic study, the results of which have been described in the preceding papers, was to define the precise mode and site of termination of the different afferent fibres upon the cells of the caudate nucleus in experimental material. After lesions in the cerebral cortex, thalamus and midbrain, the degenerating terminals of the fibres from these regions were all found to have asymmetrical membrane thickenings and to end mainly upon dendritic spines. It was not possible, however, to determine whether the fibres from these three different pathways ended upon spines on different parts of the dendritic tree of the same cell, or upon the dendritic spines of different cells. Because of this inconclusive result Golgi impregnated material was prepared in order to compare the distribution of spines in the normal, and after interruption of the main afferent pathways; failure of impregnation of spines has been shown to occur in pyramidal cells of the cerebral cortex after prolonged deafferentation (Globus & Scheibel 1966; Valverde 1967). In the course of this part of the investigation certain observations were made on normal material with the Golgi method, and from these it has been possible to make a number of useful correlations with the electron microscopic appearance of the nucleus. Examination of the putamen with both the light and electron microscopes has shown that it is similar in all respects to the caudate nucleus. Since this is the case, where the caudate nucleus is specifically referred to, the observations may be considered to apply to the striatum as a whole.

Although the caudate nucleus is apparently homogeneous, in that the various elements are scattered uniformly throughout its neuropil, a number of cell varieties can be recognized with both the light and electron microscopes. There is a great preponderance of one cell type which is densely covered with spines, has a short axon which branches profusely and probably receives most of the axon terminals from all sources. There appear to be few long axon, efferent neurons so that the majority of cells in the striatum are interneurons. A striking feature of the nucleus is the dense axonal plexus; this receives a major contribution from the collateral branches of the short axon cells, as well as a few from the cells with long axons and from the incoming afferent fibres. Perhaps the most important characteristic of the axonal plexus is that all the component fibres *cross* dendrites rather than lie parallel to them. In the Golgi impregnated material the axons are beaded, and the beads almost certainly correspond to the vesicle-filled enlargements on non-myelinated fibres which can be seen with the electron microscope and which form *en passant* synaptic contacts. These fibres, therefore, have a wide sphere of influence passing across parts of one cell to another cell and terminating on each in turn.

Though the experimental Golgi study was confined to the axospinous terminals on the one cell type which is densely covered with spines, it should be noted that this cell is by far the most common and that the majority of afferent fibres terminate on spines. The fibres from both the cerebral cortex and thalamus terminate over the whole length of the dendrite of the same cell, so that there is integration of information from these two sources. However, if the hypothesis which has been proposed by Diamond, Gray & Yasargil (1970) is correct, 'that the dendritic spine provides a postsynaptic region which is effectively isolated from other synapses in the neuron, in such a way that the immediate and the long-term effects of presynaptic activity at the spine occur with little or no interference from synaptic activity generated elsewhere in the cell', these fibres from the cortex and the thalamus could, initially at least, have quite separate influences upon this type of neuron. Since the projections overlap completely it would seem reasonable to suppose that the influence of each of these pathways is susceptible to modification, from mutual interaction and from the general properties of the dendrite, before reaching the cell body. Too many spines remain on the dendrites of these cells after a combined lesion of the cerebral cortex and thalamus to be accounted for by the terminals of afferents from the midbrain. It may, therefore, be inferred that a number of axospinous terminals are those of axons intrinsic to the nucleus. Furthermore, the number of spines remaining after a combined lesion in the cerebral cortex and thalamus are distributed in the same way as in the normal, which suggests that the fibres from the midbrain, and those arising in the nucleus, are also distributed along the whole course of the dendrite. Some of the terminals with asymmetrical membrane thickenings in contact with dentritic shafts and cell somata are also intrinsic as a number of them are seen, with the electron microscope, to be normal after a combined lesion of the cerebral cortex and thalamus. Though they could all arise in the midbrain this seems unlikely as this projection is very sparse. An experiment with a lesion within the caudate nucleus cannot show directly which terminals with asymmetrical membrane thickenings are intrinsic as some of the afferent fibres to the nucleus would also be interrupted. Such an experiment, however, does confirm that all terminals with symmetrical membrane thickenings arise from the cells of the caudate nucleus as this is the only type of lesion which results in their degeneration. Degenerating terminals with symmetrical contact regions also appear in the globus pallidus and substantia nigra after damage to the caudate nucleus indicating that some of this type of terminal in the caudate nucleus could arise from the collateral axons of the long axon cells of the caudate nucleus. The normal material of the caudate nucleus shows that terminals with symmetrical contact membrane thickenings may be of two types, and as well as being in contact with dendritic spines and shafts, and cell bodies, they are also found in contact with the initial segments of axons.

All the techniques which have been used have indicated that considerable convergence occurs in the striatum and a correlation of the observations made with these diverse methods also suggests a mechanism by which it could occur. The investigation of the cortico-striate projection in the monkey has shown that there is definite overlap in the termination of the fibres from adjacent functional areas so that any neuron will receive fibres from at least two adjoining areas of the cerebral cortex. Furthermore, there is electron microscopical evidence that individual fibres have a wide distribution as such degenerating fibres have been found to have numerous terminals *en passant*. Similar degenerating terminals *en passant* have been seen after a lesion in the thalamus, and it is possible that fibres arising here also have a comparatively widespread distribution. In addition, in Golgi impregnated material incoming afferent fibres have been seen to branch quite extensively. The ultimate convergence of these two major pathways onto the same cells, as well as the possible convergence of the midbrain pathway, has already been discussed. Each cell, as well as receiving these afferent fibres, also obtains integrated information from other cells within the nucleus. The collateral axons crossing from one cell to another, together with the spreading of afferent fibres, will tend to homogenize the output from adjacent regions of the striatum. Final convergence within the striatum occurs upon the efferent cells and, if these have been identified correctly, they appear to form only a very small proportion of the total number of neurons in the region. Consequently, the information passing to the globus pallidus and substantia nigra represents a highly integrated and modified version of the total input to the area.

The details of the organization of the pallidum have not been investigated here, but Fox, Hillman, Siegesmund & Sether (1966) have found in Golgi impregnated material that the long dendrites of the pallidal neurons are ensheathed by axons which lie parallel to them, and with the electron microscope it can be seen that the dendrites are studded with terminals. This arrangement suggests that the output from the striatum is focusing down upon the cells of the globus pallidus. Whether or not there is a significant degree of convergence at this level cannot be stated: the large size of the striatum compared with the globus pallidus suggests that there is, but it must be remembered that probably only 2 or 3 % of the cells of the striatum are of the efferent variety. It would be interesting to compare the number of long axon cells in the caudate nucleus with the number of cells in the globus pallidus.

It has been proposed that terminals with asymmetrical membrane thickenings and round vesicles are excitatory in function while those axons with symmetrical thickenings and containing flattened vesicles have an inhibitory influence (see Gray 1969). This correlation of morphology and function is not conclusively established, but if it is correct, the findings in this study would suggest that all the afferent fibres to the striatum have an excitatory effect upon the cells on which they terminate, that a large number of the neurons in the striatum function as inhibitory interneurons (though some of the intrinsic cells are excitatory) and that the major effect of the efferent cells upon the globus pallidus is also inhibitory. To a large extent these correlations are in accord with the physiological observations which have been made on the caudate nucleus and globus pallidus (see Kemp & Powell 1971).

Speculations

In 1928 Wilson noted a similarity between the basal ganglia and the cerebellum, and he suggested that 'The play of striatal impulses upon the optic thalamus may resemble that of the cerebello-mesencephalo-thalamic system, in the sense that both are afferent or thalamopetal, and that in circumstances not yet elucidated, lesions on either pathway may occasion choreoathetoid movement via the cortico-spinal system'. In the forty years which have passed since Wilson made this suggestion there has been a considerable increase in our knowledge of both these parts of the brain, and in the past decade, particularly, there has been a marked advance in our understanding of the cerebellum. Can the new data which has become available in this time be considered to support Wilson's suggestion? In the following pages the available evidence on the structure and connexions of the basal ganglia will be used to compare them, from an anatomical point of view, with the cerebellum (figure 3). As the interrelationships of the cerebellum and cerebral hemispheres have recently been considered in an authoritative review by Evarts & Thach (1969), it will be useful to make the present comparison of the basal ganglia and the cerebellum not only with the conclusions drawn by these authors but in essentially the same order.

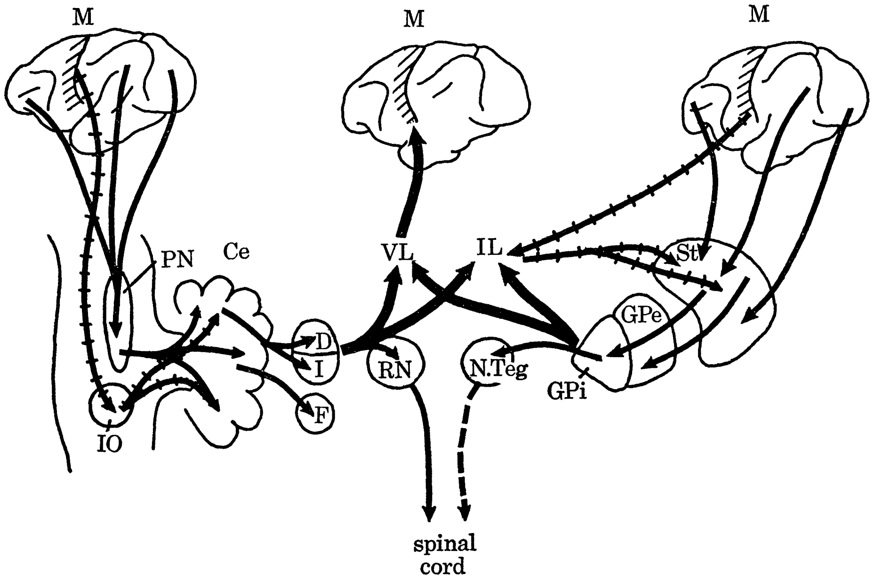

FIGURE 3. Schematic figure to summarize the main points of similarity in the organization of the cerebral connexions of the cerebellum and basal ganglia. Presumed equivalent pathways in the two systems are shown by the same kinds of symbols. Interrupted lines indicate possible connexions.

Ce	cerebellar cortex	IO	inferior olive
D	dentate nucleus	M	motor cortex
F	fastigial nucleus	N.Teg	tegmental nuclei
GPe	globus pallidus, external segment	PN	pontine nuclei
GPi	globus pallidus, internal segment	RN	red nucleus
I	interpositus nucleus	St	striatum
IL	intralaminar nuclei of the thalamus	VL	ventrolateral nucleus of the thalamus

The first point of similarity is that in both the cerebellum and the basal ganglia there are two distinct subdivisions, the first of which is predominantly in receipt of a great majority of the extrinsic afferent fibres, which is densely cellular and which projects upon the second subdivision composed of relatively few efferent neurons. In the cerebellum these are the cortex and the deep nuclei respectively, and in the basal ganglia, the striatum (caudate nucleus and putamen) and the globus pallidus. In this discussion it is assumed that the cerebellar cortex is essentially equivalent to the striatum and the deep nuclei to the globus pallidus. Although it is immediately apparent that the lamination of the cerebellar cortex forms a marked contrast to the striatum it can be argued that in most respects the structure of these two parts of the brain are remarkably similar:

(*a*) Both are homogeneous throughout, with the corollary that any difference in functions between various parts must be the result solely of differences in the connexions of the parts.

(*b*) Both contain cells with the highest concentration of dendritic spines in the nervous system.

(*c*) A dense plexus made up largely of intrinsic axons is a characteristic feature, and in each case the axons *cross* dendrites making numerous endings *en passant*.

(*d*) There are several types of interneurons in each, in the cerebellar cortex these have symmetrical membrane thickenings and flat vesicles and are inhibitory in influence and as far as the evidence permits it appears that the same is true of a great number of the intrinsic cells of the striatum; the structural arrangement of the cerebellar cortex has been shown to be the basis of marked convergence and divergence of afferent impulses, and the most reasonable interpretation of the intrinsic organization of the striatum suggests that the same is true here.

Although Evarts & Thach (1969) concluded that not all of the cerebral cortex projected to the cerebellum, it can now be stated that the part of the cerebral cortex about which they were most doubtful, the visual area, does send fibres to the pontine nuclei (Garey, Jones & Powell 1968; Spatz, Tigges & Tigges 1970) which project to the cerebellum. In this respect, therefore, the cerebellum and basal ganglia are similar in being influenced by the entire neocortex. In addition, all regions of the cerebellum which have been investigated have been found to receive an input from the neocortex and this is true of the striatum. The sensori-motor area of the cerebral cortex projects to very wide areas of both the cerebellum and the striatum, but it is significant that *there is an exceptionally small projection to each from the visual cortex.*

The cerebral cortical projection upon the cerebellum can be divided into two distinct categories on the basis of the type of afferent fibre—mossy or climbing—involved in the final relay. The climbing fibre pathway is mediated through the inferior olive and is of long latency, whereas the mossy fibre input passes through a synapse in the pontine or reticular nuclei and is of short latency. The cortical projection upon the striatum may also be separated into a direct cortico-striate pathway and an indirect one through the intralaminar nuclei. It should be pointed out, however, first that the direct pathway differs from its presumed equivalent mossy fibre projection in not having a synapse before the striatum is reached, and, secondly, that the entire neocortex would be involved in the indirect path as it projects upon all the intralaminar nuclei whereas only the motor cortex (Sousa-Pinto & Brodal 1969) is related to the inferior olive. The latter discrepancy may only be apparent as there is increasing evidence to suggest that the inferior olive may not be the only source of climbing fibres (Evarts & Thach 1969; Sousa-Pinto & Brodal 1969). Although there is no evidence to indicate that the afferent fibres to the striatum from the cortex and thalamus resemble the mossy and climbing fibre respectively, it is noteworthy that the area of neocortex related to the inferior olive, the motor cortex, is also related to the centromedian nucleus which differs from the rest of this group in receiving fibres from the globus pallidus and in being the only intralaminar nucleus to increase relatively in size in the primate.

After reviewing the literature on the connexions *from* the cerebrum *to* the cerebellum Evarts & Thach considered the details of the projection of the cerebellum *upon* the cerebral hemisphere. This cerebello-cerebral projection is in two stages, the first from the cerebellar cortex to the deep nuclei and the second from these nuclei to the thalamus. The projection of the cerebellar cortex upon the deep nuclei is definitely arranged in a longitudinal pattern, the medial vermis being related to the fastigial nucleus, the intermediate cortical zone projecting to the interpositus nucleus and the lateral part of the hemisphere to the dentate nucleus. The corresponding projection from the striatum to the globus pallidus appears to be similarly arranged if allowance is made for the difference in form of the basal ganglia, the striatum being clearly a three-dimensional structure in contrast to the two-dimensional sheet of the cerebellar cortex. The most reasonable interpretation of the pattern of the strio-pallidal projection is that the striatal efferents project radially, like the spokes of a wheel, upon the globus pallidus and the medial and lateral segments of the globus pallidus receive fibres from the corresponding parts of the striatum (Cowan & Powell 1966). It is worth emphasizing that this second component of both the cerebellum and basal ganglia is divided into more than one part—the three of the deep nuclei and the two segments of the globus pallidus; in each case these parts differ in receiving afferent fibres from different portions of the cerebellar cortex or striatum and in sending their efferents to different parts of the brain. The cortico-nuclear and strio-pallidal projections are similar functionally also: Purkinje cells exert inhibitory effects upon the neurons of the deep nuclei (Eccles, Ito & Szentagothai 1967); inhibition of cells in the globus pallidus has also been found after stimulation of the striatum (Malliani & Purpura 1967) and the terminals of striatal efferent fibres in the globus pallidus have the morphological features presumed to be those of inhibitory fibres.

Although, as Evarts & Thach point out, there are minor discrepancies between the results of different workers in regard to the projection of the cerebellar nuclei upon the thalamus, it is clear that the majority of the fibres arise in the dentate nucleus and terminate in the ventrolateral and ventroanterior principal nuclei and certain of the intralaminar group. The inner segment of the globus pallidus also projects upon the same principal nuclei of the thalamus and upon the centromedian nucleus of the intralaminar group. As these ventral nuclei project upon the motor cortex, the major cerebral influence of *both* the cerebellum and the basal ganglia is upon the motor area of the cortex. A point which has been emphasized about the connexions between the cerebral cortex and the cerebellum is that they are non-reciprocal, in that all the neocortex projects upon the cerebellum whereas the cerebellum projects back only upon the motor cortex: precisely the same is true of the relationship between the cortex and the basal ganglia. Furthermore, Evarts & Thach noted that 'the bulk of the cerebellar input to the motor cortex comes from the more lateral portions of the cerebellar cortex' and that 'these parts of the cerebellum themselves are activated...especially from association cortex'; from the findings of the study of the cortico-striate projection in the monkey it was also suggested that the pallido-thalamic pathway transmitted an 'influence which represents a complex integration...of the areas of "association" cortex of the frontal and parietotemporal lobes' (Kemp & Powell 1970). In addition to their projections to the thalamus it is perhaps significant that the dentate nucleus and the internal segment of the globus pallidus each project to the midbrain—to the red nucleus and the tegmentum respectively—and it is possible that these pathways are equivalent and that both ultimately influence the spinal cord. While the principal nuclei of the thalamus to which both the cerebellum and basal ganglia send fibres are projecting to the motor cortex, the other thalamic nuclei which receive fibres from the cerebellum and basal ganglia, those of the intralaminar group, project back to the caudate nucleus and putamen. Through this pathway the cerebellum is exerting an influence upon the striatum. The ultimate cerebral projection of the cerebellum is therefore upon the motor cortex and the striatum, and in the latter there is further convergence of neocortical and cerebellar activity which in turn projects back upon the motor cortex. Whether the basal ganglia also project back indirectly upon the cerebellum is not so clear, but there is some evidence that they may do so (Sedgwick & Williams 1967).

With regard to their cerebral connexions it can be said that the cerebellum and the basal ganglia both receive fibres, by two pathways, from most of the neocortex, and, through the same principal nuclei of the thalamus, they both influence the motor cortex (figure 3). They both have a similar intrinsic structure, which can be the basis of convergence and divergence, and through the intralaminar nuclei the cerebellum can exert an effect upon the striatum. The connexions which the cerebellum and the basal ganglia have with structures outside the cerebral hemisphere will not be considered except that it is perhaps worth noting that in addition to their major projections, to the deep cerebellar nuclei and the globus pallidus respectively, both the cerebellar cortex and the striatum send fibres *directly* to one other structure, to the vestibular nuclei from the cortex of the floccular-nodular lobe and to the substantia nigra from the caudate nucleus and putamen.

The final problem which Evarts & Thach considered was the role of the cerebellum in the initiation of movement. It is significant that though these authors concluded that the evidence was in favour of the cerebellum having such a function they also accept Wilson's opinion that lesions of the striatum more obviously impair movement initiation. Mettler (1967) has also emphasized the inability of the patient with Parkinson's disease to make a decision, and that these patients are stimulus bound and unable to initiate movements.

In the foregoing account an attempt has been made to show certain similarities in the anatomical structure and connexions between the basal ganglia and the cerebellum, mainly in the hope that this comparison may provide certain clues about the functions of the basal ganglia. It is perhaps significant that Evarts & Thach, from a completely different approach, may have implicitly reached a like conclusion about the similarity of these two parts of the brain when they wrote 'it is likely that the cerebellum and the pallidum act in parallel to set up patterns of thalamo-cortical output necessary for the appropriate activation of cortico-spinal neurons'.

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