Full-length review

The connections of the primate subthalamic nucleus: indirect pathways and the open-interconnected scheme of basal ganglia-thalamocortical circuitry

D. Joel, I. Weiner *

Department of Psychology, Tel Aviv University, Ramat-Aviv, Tel Aviv 69978, Israel

Abstract

The current view of basal ganglia organization holds that functionally corresponding subregions of the frontal cortex, basal ganglia and thalamus form several parallel segregated basal ganglia-thalamocortical circuits. In addition, this view states that striatal output reaches the basal ganglia output nuclei (the substantia nigra pars reticulata (SNR) and the internal segment of the globus pallidus (GP_i)) via a 'direct' pathway, and via an 'indirect pathway' which traverses the external segment of the globus pallidus (GP_e) and the subthalamic nucleus (STN). However, the topographical relationships of GP_e and STN, and their topographical relationships with the basal ganglia-thalamocortical circuits are still unclear. The present work reviewed primate data on the topographical organization of STN afferents from GP_e, and STN efferents to the pallidum, striatum and SNR, and examined these data with respect to a tripartite (motor, associative and limbic) functional subdivision of the striatum and pallidum. This examination indicated the following. (1) On the basis of its efferent connections, the STN may be divided into a motor and an associative territories, as well as a smaller limbic territory, each projecting to corresponding areas in the pallidum and striatum. (2) Efferents from GP_e are in a position to contact subthalamic cells projecting to GP_i/SNR, thus providing anatomical support for the existence of indirect pathways. (3) Moreover, given the tripartite division of the striatum, pallidum, and STN, the available data indicate the existence of indirect pathways connecting functionally corresponding subregions of the striatum, pallidum, and STN, as well as indirect pathways connecting functionally non-corresponding subregions. On the basis of the above we suggested that there may be two types of indirect pathways, one which terminates in the same subregion in GP_i/SNR as the direct pathway arising from the same striatal subregion, and another which terminates in a different GP_i/SNR subregion than the direct pathway arising from the same striatal subregion. We termed the former a 'closed indirect pathway' and the latter an 'open indirect pathway'. The application of these concepts to the surveyed data suggested the existence of three closed indirect pathways, each connecting the corresponding functional (motor, associative, and limbic) regions of the striatum, pallidum, STN, and SNR, as well as of two open indirect pathways, one connecting the associative striatum to the motor subregions of the basal ganglia, and the other connecting the associative striatum to the limbic subregions of the basal ganglia. While the organization of the closed indirect pathways fits the closed segregated arrangement of basal ganglia-thalamocortical circuitry, the organization of the open indirect pathways fits the recently suggested open interconnected scheme of basal ganglia thalamocortical circuitry. The clinical implications of this scheme for Huntington's disease are discussed.

Keywords: Basal ganglia; Subthalamic nucleus; Globus pallidus; Indirect pathways; Basal ganglia–thalamocortical circuitry; Primate; Huntington's disease

Contents

---

* Corresponding author. Fax: +972 (3) 640-7391; E-mail: weiner@freud.tau.ac.il

1. Introduction

Although the basal ganglia have long been viewed as playing a central role in motor control and movement disorders, it is now widely accepted that they contribute to a wide variety of behavioral functions, including cognitive and emotional. This functional diversity is also reflected in the complexity of the pathological conditions which are associated with basal ganglia dysfunction, such as Parkinson's disease, Huntington's disease, and schizophrenia [2,5,6,21,22,40,42–44,46,48,69–71,83,92,93,98,108]. This is not surprising given the fact that the basal ganglia receive inputs from virtually all cortical areas, and in turn affect the frontal cortex via their thalamic projections. The understanding of the organization of these connections and the flow of information from the entire cortex via the basal ganglia to the frontal cortex, is essential for unraveling the functions of the basal ganglia, and their involvement in normal and pathological states.

2. The organization of the basal ganglia

The basal ganglia comprise a group of interconnected subcortical nuclei. The striatum is the main input structure of the basal ganglia. Its major inputs arise from the entire cortex, the intralaminar and midline thalamic nuclei, and the midbrain dopaminergic (DA) cell groups in the ventral tegmental area, substantia nigra pars compacta (SNC), and retrorubral area [9,36–38,53,67,83]. The striatal projections can be viewed as participating in two types of connections, external or internal. The external connections carry the output of the striatum to structures outside the basal ganglia. These connections comprise the striatal pro-

jections to the output nuclei of the basal ganglia, the internal segment of the globus pallidus (GP$_i$), the ventral pallidum (VP) (which is the rostroventral extension of the globus pallidus (GP)), and the substantia nigra pars reticulata (SNR); their subsequent projections to thalamic nuclei, including the mediodorsal, ventral anterior and ventral lateral nuclei (all of which innervate the frontal cortex), and the intralaminar and midline thalamic nuclei; superior colliculus; and ponto/mesencephalic tegmentum [2,5–7,46,48,83,85,85,87,92,101]. The internal connections link between the different nuclei of the basal ganglia. These connections include: (1) the striatal projections to the external segment of the globus pallidus (GP$_e$) and to VP, and their subsequent projections to SNR, GP$_i$, and the striatum directly, as well as indirectly via their projections to the subthalamic nucleus (STN) which projects to the pallidum and SNR, and to a lesser extent to the striatum; and (2) The striatal projections to the midbrain DA cell groups [2,5,36,37,49,53,57,59,85,88].

2.1. The external connections of the basal ganglia

In the last 15 years, the most influential model of the organization of the external connections of the basal ganglia views them as components of circuits connecting anatomically and/or functionally distinct frontocortical, basal ganglia, and thalamic areas [7,21,70,92]. The most elaborated circuit model to date is that of Alexander and colleagues [5–7] who proposed that ''the basal ganglia, along with their connected cortical and thalamic areas, are viewed as components of a family of '' basal ganglia-thalamocortical'' circuits that are organized in a parallel manner and remain largely segregated from one another, both structurally and functionally'' ([6], p. 119). Each

basal ganglia-thalamocortical circuit receives input from several separate but functionally related cortical areas, traverses specific regions of the striatum, GP_i, SNR, and thalamus, and projects back upon one of the frontocortical areas providing input to the circuit. Based on the specific regions of the frontal cortex that contribute to the individual circuits, Alexander et al. [6,7] described five basal ganglia-thalamocortical circuits: two motor ('motor' and 'oculomotor'), two associative ('dorsolateral prefrontal' and 'lateral orbitofrontal'), and one limbic ('anterior cingulate'). Most of the data that have given rise to the concept of parallel organization have been collected in primates. In recent years, Groenewegen and his colleges [46,47] have described a number of parallel basal ganglia-thalamocortical circuits in the rat.

While the proponents of circuit models have stressed structural segregation and functional specificity of the basal ganglia-thalamocortical circuits, other writers have emphasized the large degree of structural convergence in the corticostriatal, striatopallidal and striatonigral projections, arguing that convergence within the basal ganglia provides evidence against the concept of parallelism (e.g., [17,94–96]). It is important to realize, however, that the proponents of these seemingly contrasting views use different levels of analysis. Most arguments favoring convergence focus on the structure of the dendritic fields of the neurons in the basal ganglia nuclei, i.e., the convergence within the recipient structure of inputs arising from different parts of the projecting structure, based on the probability that these inputs would synapse on the same neuron (e.g., the convergence in the globus pallidus, see [94–96]). In contrast, the concept of parallel segregated organization was established on the basis of a different level of analysis, namely, the topographical organization of the terminal fields of the projections linking the different nuclei comprising the basal ganglia thalamocortical circuits.

Parent and Hazrati [83,85,87] examined both levels of analysis and concluded that although corticostriatal projections exhibit high degree of convergence, motor, associative, and limbic cortical areas project in a segregated manner onto three distinct striatal subregions. The tripartite principle of organization is maintained at the pallidal level so that the pallidum can also be divided into motor, associative and limbic territories, with high degree of convergence within each territory, but a high degree of segregation between the territories [83,85,87].

The segregation versus convergence debate notwithstanding, it has been increasingly recognized by writers focusing on the topographical level of organization, that interaction between the segregated basal ganglia-thalamocortical circuits is essential for producing coherent behavior as well as the wide variety of symptoms associated with basal ganglia dysfunction (e.g., [29,46,48,53,71]). It has been suggested that such interaction could take place through corticocortical and intrastriatal connections (e.g., [39,46,48,53]). While these connections provide a linkage

between subregions belonging to different circuits, they are not themselves components of the circuits.

Recently, we presented a new scheme of basal ganglia-thalamocortical organization, in which the circuits are connected by pathways which are themselves components of the circuits [64]. The major characteristic of the basal ganglia-thalamocortical circuitry captured by this scheme is the divergence of projections of each circuit-engaged striatal region to the basal ganglia output nuclei and the subsequent segregation of these projections at the thalamic and frontocortical levels. This results in an asymmetry in the frontal cortex–basal ganglia relationships, so that while each frontocortical subfield innervates one striatal region, each striatal region influences the basal ganglia output to two frontocortical subfields. Since this type of organization is not consistent with the closed segregated arrangement, we have revised the basic design of the basal ganglia-thalamocortical circuits, and introduced the concept of a split circuit. A split circuit contains one frontocorticostriatal pathway and two striatofrontocortical pathways. One of the striatofrontocortical pathways reenters the frontocortical area of origin, thus forming a 'closed circuit', and the other leads to a frontocortical area which is the source of a different circuit, thus forming an 'open pathway'. On the basis of the available anatomical data, and using Parent and Hazrati's [83,85] tripartite subdivision of the striatum and pallidum, we tentatively identified a motor, an associative, and a limbic split circuit, each containing a closed circuit and an open pathway. Since split circuits are interconnected via their open pathways, we concluded that the organization of the basal ganglia-thalamocortical circuitry is better described as open interconnected rather than closed segregated [64].

2.2. The internal connections of the basal ganglia

A related question that has arisen recently is to what extent the segregation of the basal ganglia-thalamocortical circuits is maintained in the internal connections of the basal ganglia (e.g., [29,45,53]). It is known that the connections between the striatum and the DA complex do not obey the segregation principle as the ventral striatum is in a position to influence the DA input of the dorsal striatum (e.g., [48–50,76,77,81,107]). In regard to the internal connections formed by GP_e and STN, the conventional view holds that information flows from the striatum to the output nuclei of the basal ganglia via a 'direct' pathway, i.e., the inhibitory striatal projections to GP_i and SNR, and an 'indirect' pathway, i.e., the inhibitory striatal projections to GP_e, the subsequent inhibitory projections from GP_e to STN, and STN excitatory projections to GP_i and SNR (e.g., [2,5,20,93]). In Alexander et al.'s [6] scheme these pathways are incorporated within the parallel segregated arrangement so that each circuit-engaged striatal region is considered to convey cortical information to the output nuclei simultaneously via the direct and indirect

pathways [5,6]. Underlying this suggestion is the assumption that the parallel segregated principle is maintained in the connections between GP$_e$ and STN and in their connections with the structures comprising the basal ganglia-thalamocortical circuits.

While the interconnections between the STN and pallidum have been the subject of many studies [14–16,24,25,50,65,79,80,90,91,102,104,105], the exact topographical relationships between these structures, and their topographical relationships with the basal ganglia-thalamocortical circuits is still obscure. Although recently several writers have addressed this issue, their conclusions have been inconsistent. In a thorough review of the organization of the basal ganglia, Parent and Hazrati [87,88] questioned the existence of a striato-GP$_e$-STN-GP$_i$ pathway (the indirect pathway), but continued to adhere to the segregation principle in the organization of the internal connections. In contrast to Parent and Hazrati's [87,88] conclusion, the results of a study by Shink et al. [102] on the interconnections between the STN and the two pallidal segments, supported the existence of indirect pathways. Similarly to Parent and Hazrati [87,88] these authors concluded that the connections between the STN and the two pallidal segments respect the known functional subdivision of these structures.

A different view has been advanced by Haber and colleagues [53,106]. According to these authors, strict segregation is not maintained in the internal basal ganglia connections as ''some basal ganglia connections maintain a general separation of different cortical circuits while in others there is a convergence of information from different circuits'' ([53], p. 71). Consequently, the internal connections are viewed as providing an important means of interaction between the basal ganglia-thalamocortical circuits [53,106]. In regard to the connections of the pallidum and STN, Haber et al. [53] concluded that the segregation principle is maintained in the striatopallidal and pallido-subthalamic but not in the pallidostriatal and subthalamopallidal connections, and therefore suggested that these projections can provide a neural substrate for integration between circuits. Other writers also suggested that the connections between STN and the pallidum may subserve interaction between the basal ganglia-thalamocortical circuits. Thus, Groenewegen and Berendse [45] suggested that the STN can be involved to a limited degree in limbic-motor integration, and Feger et al. [29] suggested that VP can influence the STN output to GP, thus enabling 'cross talk between the motor and the so-called associative parts' (p. 378).

3. The connections of the subthalamic nucleus

In the present work we reexamine the internal connections of the basal ganglia involving the STN and GP$_e$ in primates. We review data on the topographical organization of STN afferents from GP$_e$, and STN efferents to GP$_e$, GP$_i$, SNR, VP, and the striatum, with the aim of assessing whether they form indirect pathways. We also examine these data with respect to the tripartite functional subdivision of the striatum and pallidum delineated by Parent and Hazrati [83,85,87], in order to determine to what extent these connections respect such functional subdivision, as would be expected according to the parallel-segregated principle. Our main conclusion is that these connections indeed form indirect pathways but their organization does not maintain strict segregation, thereby providing an additional mechanism of between-circuit interaction.

3.1. The functional subdivision of the striatum, pallidum, and SNR

The corticostriatal projections are believed to impose a functional organization upon the striatum and, subsequently, upon other nuclei of the basal ganglia (e.g., [2,5–7,29,53,70,83,85,92,96]). While several versions of striatal subdivision have been proposed (e.g., [6,7,23,53,70,92,96]) we shall adopt here the tripartite anatomofunctional subdivision of the striatum suggested by Parent and Hazrati [83,85,87], which was used in our previous work describing the organization of the external connections of the basal ganglia [64]. According to this arrangement, motor, associative, and limbic cortical areas project in a segregated manner onto three distinct striatal subregions referred to as motor, associative, and limbic striatal territories. The motor striatum comprises the dorsolateral postcommissural putamen and a dorsolateral region in the caudate nucleus; it is innervated by the primary motor cortex (MI), premotor cortex (PMC), supplementary motor area (SMA), and postarcuate premotor area. The associative striatum comprises large parts of the putamen rostral to the anterior commissure and most of the head, body, and tail of the caudate nucleus; it receives input from associative areas of the cortex, including areas 8, 9, 10, and 46 of the prefrontal cortex (PFC). The limbic striatum comprises the nucleus accumbens and the most ventral parts of both putamen and caudate nucleus; it receives extensive input from limbic structures, such as the hippocampus and amygdala, as well as from prefrontal areas assumed to subserve limbic and autonomic functions, i.e., orbitofrontal, infralimbic, and prelimbic cortices (see also [6,7,53,100,114]).

Parent and Hazrati [83,85,87] showed that the tripartite principle of organization is maintained at the pallidal level, so that the pallidum can also be divided into motor, associative and limbic territories. The motor GP$_e$ comprises the ventrolateral two thirds of the post-commissural GP$_e$ and the motor GP$_i$ comprises the ventrolateral two thirds of the post-commissural GP$_i$. The associative GP$_e$ comprises most of GP at anterior commissural levels and the dorsomedial third of the post-commissural GP$_e$, and the associative GP$_i$ comprises the dorsomedial third of the

post-commissural GP_i. The limbic pallidum comprises the VP, the ventromedial rim of rostral GP_e, and the medial tip of GP_i (for a similar subdivision see [53]).

There is still a controversy regarding the extent of segregation of the striatal projections to SNR (e.g., [35,53,60,68,86,87,95]). Parent and Hazrati [86,87] concluded that the projections of the three striatal territories overlap extensively in SNR (for a similar conclusion see [53], for discussion of the controversy regarding this issue see [64]).

3.2. The subthalamic nucleus

The STN is a small structure located between the zona incerta dorsally and the cerebral peduncle ventrally. It is encapsulated by major myelinated fiber bundles and is thus considered a 'closed' nucleus, except for its medial border that merges into the lateral hypothalamic area [13,88].

3.3. The efferents of the subthalamic nucleus

The STN projects to GP_e, GP_i, and SNR, and to a lesser extent to the striatum [14–16,25,79,80,88,90,91,104,105]. A thorough description of the organization of STN terminal fields and their relation to the dendritic trees in each of these structures has been provided recently by Parent and Hazrati [87,88]. These authors concluded that STN terminal fields in GP_e, GP_i and SNR are similar in organization to the striatal terminal fields in these structures [55,87,88]. Projections from different striatal subterritories are restricted to the corresponding subterritory in the pallidum, but intermingle in SNR. Therefore, although subthalamic axons arborize throughout large caudorostral portions of the pallidum [88], STN projections can be expected to respect the functional subdivision of the pallidum. Consequently, inspection of the topography of STN projections is important for revealing the relationships between different subareas of STN and the functional subdivisions of the structures to which it projects.

STN projects densely to both pallidal segments [14–16,25,55,56,58,80,88]. In order to delineate the topographical organization of STN projections to GP_e and GP_i, data from different experiments must be combined. Using retrograde and anterograde tracing techniques, Carpenter and colleagues [14–16] concluded that the medial third of the middle third of STN [1] projects to rostral GP_e; most of the rostral third of STN and the central third of the middle third of STN project to central GP_e; and the lateral (especially more caudal) STN innervates the caudal GP_e. Projec-

tions to GP_i arise primarily from the medial third of the caudal two thirds of STN and not from rostral STN.

Carpenter and colleagues' [14–16] description of the distribution of STN cells projecting to GP_e seems to be in accord with other reports, while that of STN cells projecting to GP_i seems to be more restricted compared with other reports in both the rostrocaudal and mediolateral extents. In an anterograde tracing study by Nauta and Cole [80] it was found that projections from a medial region of the more rostral STN reach rostral GP_e and ventromedial part of rostral GP_i including VP, and projections from a more caudal and dorsal region of STN reach an area in GP_e and GP_i that roughly corresponds to the motor pallidum, i.e., there were projections to the ventrolateral two thirds of GP_e and GP_i reaching the caudal parts of these nuclei, and no projections to the rostral GP_e. These results also seem to support Carpenter et al.'s [14,15] conclusion regarding the dorsoventral organization of the projections to GP, namely, that there is an inverse dorsoventral topography in these projections with dorsal STN projecting more ventrally, and ventral STN more dorsally in GP. In a retrograde study by DeVito et al. [25] it was reported that cells projecting to GP_e are found in more rostral and lateral regions of STN and cells projecting to GP_i are found in more medial and caudal regions.

Subsequent results of Parent and colleagues [84,90,91,104] are generally in accord with the previous findings. Thus, in two retrograde tracing studies [84,90] retrograde tracer was injected to either substantia nigra (SN) (including SNR and SNC) or GP (in the first study tracer was injected mainly to central GP_i but there was some involvement of the adjacent GP_e; in the second study injections were made into the dorsolateral two thirds of the pallidum, involving GP_e and GP_i; in both studies injections did not include the rostral GP_e). Many labelled cells were found throughout STN, particularly in its rostral and dorsolateral two thirds, after pallidal injections, while a lesser number of labelled cells was found after SN injections. These cells were located in the ventral part of STN after injections that included the entire SN [84], and were confined mostly to the ventromedial third of STN after injections into the medial two thirds of SN [90]. In another study [91], retrograde tracer was injected into either GP_e or GP_i (not including their most rostral and caudal regions). From Fig. 2 of this study which illustrates the distribution of retrogradely labelled cells in the striatum, it may be concluded that GP_e injection involved mostly the motor part of GP_e (retrogradely labelled cells predominated in the dorsolateral striatum) while GP_i injection involved mostly the associative part of GP_i (retrogradely labelled cells predominated in the rostral and ventromedial striatum). After both injections numerous retrogradely labelled cells were found in the entire rostrocaudal extent of STN, with cells labelled after injections to GP_e being located more lateral than those labelled after GP_i injections. In the rostral STN GP_e projecting cells were found in its lateral

---

[1] Following Carpenter et al. [19,20], the STN was divided into medial, central, and lateral thirds along the mediolateral axis, and to rostral, middle, and caudal thirds along the rostrocaudal axis, whereas GP was divided into rostral, central, and caudal thirds along the rostrocaudal axis.

half, and GP$_i$ projecting cells in its medial half. In the middle STN GP$_e$ projecting cells were found in its central part and GP$_i$ projecting cell in its medial part, while in the caudal STN GP$_e$ projecting cells were found in the dorsal central part of STN, while GP$_i$ projecting cells were confined to the most medial corner of the nucleus.

Following anterograde injections into different areas of STN, Smith et al. [104] found a gross rostrocaudal topography, with more rostral injections reaching more rostral GP$_e$ and GP$_i$ and more caudal injections labeling more densely more caudal regions of GP$_e$ and GP$_i$. In addition, injection into more rostromedial area in STN resulted in labeling of more rostral GP$_e$, VP, and more rostral and ventromedial GP$_i$ (an area which may correspond to the associative and limbic pallidum), while injection into a more caudal and lateral area in STN resulted in labeling in more caudal and dorsolateral areas of GP$_e$ and GP$_i$ (an area which may correspond to the motor pallidum) [104]. The latter results are very similar to those of Nauta and Cole [80] cited above (i.e., the dorsal part of the caudal two thirds of STN projects to ventral and lateral regions of the caudal and central GP$_e$ and GP$_i$, and a rostromedial region of STN innervates the rostral GP$_e$ and ventral and medial areas of more rostral GP$_i$).

Recently, Shink et al. [102] investigated the interconnections between the STN and the two pallidal segments by making small deposits of biotinylated dextran amine (which is transported both anterogradely and retrogradely) in the central part of GP$_e$ or GP$_i$. Their figures reveal that the dorsal third of central GP$_e$ (part of the associative GP$_e$) is innervated by neurons scattered in the lateral and central

thirds of the rostral two thirds of STN and in the caudomedial STN. The labeling mostly spared the most dorsal STN. The ventral two thirds of the central GP$_e$ (part of the motor GP$_e$) are innervated by neurons scattered in the dorsal half of the lateral third of the rostral STN and in the dorsal half of the central third of the middle third of STN. The dorsal third of the central GP$_i$ (part of the associative GP$_i$) is innervated by neurons scattered in the ventral part of the central and part of the lateral thirds of middle STN. The ventral two thirds of the central GP$_i$ (part of the motor GP$_i$) are innervated by neurons scattered in the dorsal half of the central and part of the lateral thirds of the rostral two thirds of STN. Shink et al.'s [102] results are in accord with earlier findings in several respects: They reinforce the topographical organization of STN projections to the central parts of GP$_i$ and GP$_e$, described previously [14–16,80,84,90,91,104]; they support Carpenter et al.'s [14,15] conclusion that there is an inverse dorsoventral topography in STN projections to GP; as other studies [80,84,90,91,104], they show that STN neurons projecting to GP$_i$ are located also in the rostral parts of STN, and are not restricted to the more caudal parts, as reported by Carpenter and colleagues [14–16].

STN projections to VP arise from its medial part, but the extent of the area from which the projections arise is controversial. While Parent and Hazrati [88] suggest that it is confined to the medial tip of STN, Haber et al. [53] suggest that it arises from the medial half of STN.

A summary diagram of STN projections to the pallidum is presented in Fig. 1a. Combining the different findings regarding these projections, it may be concluded that the
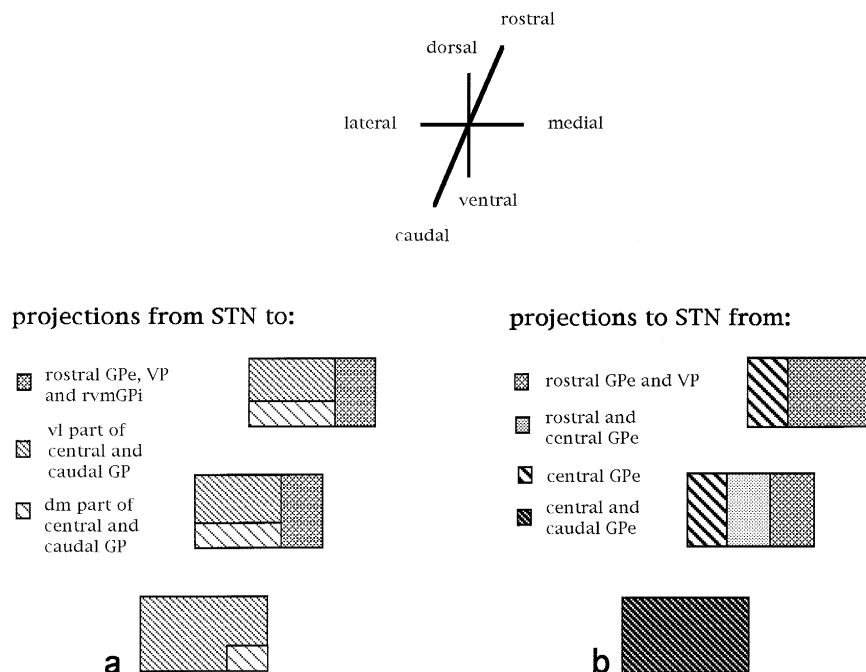

Fig. 1. A schematic representation of the localization of STN regions projecting to different regions of the pallidum (a) and of terminal fields in STN arising from different regions of the GP$_e$ (b).

rostral two thirds of the medial STN projects primarily to the rostral GP_e, which is part of the associative GP_e, to VP, which is part of the limbic pallidum, and to rostral-ventromedial GP_i, which includes parts of associative and limbic GP_i. The rostral two thirds of the lateral two thirds of STN project primarily to central and caudal GP_e and GP_i (in both pallidal segments these areas include associative and motor subfields dorsomedially and ventrolateraly, respectively). The ventral third of this STN region projects to the dorsomedial third of GP_e and GP_i, which are parts of the associative pallidum. Complementarily, the dorsal two thirds of this region project to the ventrolateral GP_e and GP_i, which are parts of the motor pallidum. Most of the caudal STN projects to the motor pallidum, except for a small ventromedial region which projects to the associative pallidum. Thus, the dorsolateral two thirds of the rostral two thirds of STN and most of the caudal third of STN innervate the motor pallidum, while the medial and ventral parts of the rostral two thirds of STN innervate the associative and limbic pallidum.

STN projections to SN seem to be not as dense as those to the pallidum [15,80,104]. The subthalamonigral fibers terminate mostly in SNR in a patchy manner, but some fibers ascend along the dopaminergic cell columns of the SNC that invade the SNR. Thus, STN influences mainly non-dopaminergic cells in SN but can also influence dopaminergic cells [80,84,104]. STN projections to SN arise mainly from the ventral part of STN [90,104] and seem to display a crude mediolateral topography, with medial STN projecting to medial SN and lateral STN projecting to lateral SN [80,88,90,104].

STN projections to the striatum are much scarcer than those to the pallidum and nigra and arise mainly from the rostral two thirds of STN. The projections terminate mostly in the motor striatum, i.e., putamen and lateral caudate and arise from the more lateral and dorsal aspects of STN. There is some innervation of the associative striatum, i.e., more medial caudate and rostral putamen, which arises from more medial and ventral STN [79,80,88,90,103,104].

3.4. The afferents of the subthalamic nucleus

The main inputs to STN arise from the frontal cortex and GP_e. The cortical projections arise mainly from the primary motor cortex, which innervates the dorsal and lateral STN, and more so in its rostral part, preserving a crude somatotopy with the face represented more laterally and the leg more medially. Weaker projections arise from other frontal regions. Projections from PMC arise mainly from its ventral part, and to a lesser extent from its dorsal and medial (including SMA) parts, and terminate ventral and medial to the projections from MI. The projections from area 8 terminate ventral to the projections from the face area, in the ventrolateral STN throughout most of its rostrocaudal extent. Projections from area 9 are confined mainly to a small rostral and ventromedial region of STN,

just medial to the projections from PMC [78]. The most medial part of STN was free of labeling in this experiment [78], and an interesting question is whether this area is innervated by limbic frontal regions. It should be noted that there may be important differences between species regarding the extent and area of termination of the cortico-subthalamic projections. For example, Huerta et al. [61] found considerable input to STN from area 8 in the owl monkey and in the macaque, but virtually no such input in the squirrel monkey.

The projections from GP_e to STN are topographically organized. Although STN neurons have rather large dendritic arborizations, pallidal afferents form synapses predominantly with proximal dendrites and soma [88,102], suggesting that their influence is mainly restricted to subthalamic neurons located within their terminal fields. Therefore the examination of the topographical organization of the pallidal terminal fields in STN is important for revealing the relationships between the functional subdivisions of the GP_e and subareas of STN.

The first thorough study of the pallidal projections to STN was carried out by Carpenter and colleagues using a series of anterograde and retrograde tracing experiments [14–16]. Summarizing the results of these papers the organization of GP_e projections is as follows: the rostral GP_e projects to the medial two thirds of the rostral two thirds of STN. The central GP_e, particularly its dorsal two thirds, innervates mainly the lateral STN (these projections are denser towards the more caudal areas of STN), and in addition projects to the central third of the rostral two thirds of STN. The caudal GP_e innervates the caudal STN, but these projections are weaker compared with the projections from the more rostral parts of GP_e. These findings seem to be in accord with several anterograde tracing studies. Kim et al. [65] found that the ventral part of the caudal and central GP_e innervates the caudal STN and the lateral (particularly the ventrolateral) STN. DeVito and Anderson [24] reported that the central part of GP_e projects to the caudal STN and to the lateral part of the middle STN. Shink et al. [102] found that the dorsal third of central GP_e (part of the associative GP_e) innervates an area in the ventral half of the lateral third of the rostral two thirds of STN and in the ventral half of the central third of the middle third of STN. The ventral two thirds of the central GP_e (part of the motor GP_e) was found to innervate an area in the dorsal half of the lateral and central thirds of the rostral two third of STN. Contrary to the results of Carpenter et al. [14–16], this study suggests that the ventral third of central GP_e contributes a greater projection to STN and that this projection is directed more rostrally than was previously thought.

In addition to this general topography, the organization of the projections from rostral GP_e can be further specified, such that the dorsolateral rostral GP_e innervates the medial part of the middle STN (from which the STN projection to rostral GP_e arises); the ventrolateral rostral GP_e innervates

the central third of rostral STN (from which part of the STN projection to central GP$_e$ arises); and the rostromedial GP$_e$ innervates the medial third of STN [14,15]. Complementarily, the VP, which is the rostroventral extension of GP, innervates the most ventromedial STN. There is a mediolateral topography of VP projections to STN that is continuous medially with that of the adjacent lateral hypothalamus, with lateral VP projecting more densely to STN and medial VP terminating more densely in the lateral hypothalamus [52].

A summary diagram of the pallidal projections to STN is presented in Fig. 1b. When considering the topographical organization of STN afferents from GP$_e$ in relation to its efferents to the other nuclei of the basal ganglia, the following picture emerges: Rostral GP$_e$ (part of associative GP$_e$) innervates the medial two thirds of rostral STN and the central third of middle STN, all of which project to central GP$_e$, and projects to a lesser extent to the medial third of middle STN, which innervates the rostral GP$_e$ itself. Regarding the central GP$_e$ (which includes associative and motor areas, dorsomedially and ventrolaterally, respectively), most of the projections to STN arise from its dorsal two thirds and are directed mainly to the lateral STN and more so more caudally (the area which innervates primarily the motor GP$_i$), and only weakly to the central part of the rostral two thirds of STN (which is part of the STN area from which it receives projections). In addition, there is an inverse dorsoventral topography in the projections from the central GP$_e$, with dorsal GP$_e$ projecting more ventrally, and ventral GP$_e$ more dorsally in STN. The ventral part of central GP$_e$ as well as caudal GP$_e$ (both parts of the motor GP$_e$) contribute the weakest projection to STN, compared with the other GP$_e$ areas, and this projection is directed to lateral and caudal STN (which project back to these areas). As can be seen when comparing Fig. 1a and Fig. 1b, STN afferents from GP$_e$ are not fully in register with STN efferents to the pallidum.

Interestingly, Shink et al. [102] reported some results which are relevant to this conclusion. Thus, after injection into the dorsal part of central GP$_e$, the correspondence between the pallidal terminal field in STN and the STN area containing neurons projecting to this pallidal region was not absolute, but rather, the retrogradely labelled cells were scattered throughout a much wider area than that containing the anterogradely labelled terminals. As can be seen in Fig. 4 in Shink et al. [102], the neurons that were found outside the area of termination were located mainly in the central STN, which according to previous studies, is innervated by the rostral GP$_e$, which was not investigated in Shink et al.'s [102] study.

Shink et al. [102] also reported that following injections in the motor part of the central GP$_i$ some retrogradely labelled cells were found outside the cluster of labelled varicosities [102]. Since neurons in GP$_e$ which send collaterals to STN and GP$_i$ are thought to be the main source of these labelled varicosities (see Shink et al. [102]), it is

possible that the STN labelled cells that were found outside the cluster of labelled varicosities, are innervated by pallidal neurons which do not send collaterals to the STN and to the injected GP$_i$ region. Such neurons are unlikely to be located in any of the central GP$_e$ areas injected, since after injection of tracer into these regions labelled varicosities in STN did not overlap the area of retrogradely labelled cells that were found outside the cluster of labelled varicosities after injection of tracer into the motor GP$_i$. This suggests that correspondence between the GP$_e$ terminal field in STN and the STN area containing neurons projecting to the corresponding GP$_i$ region was also not absolute. The other possible pallidal sites of inputs to this STN area are the caudal and rostral thirds of GP$_e$ which were not injected. Since other authors reported that the caudal GP$_e$ projects only lightly to the STN, and that these projections terminate mainly in the caudal and lateral STN (see elsewhere in this subsection), it seems unlikely that the caudal GP$_e$ innervates the STN cells projecting to the motor part of the central GP$_i$. In contrast, the rostral GP$_e$ was reported to project densely to the medial and central STN (see elsewhere is this subsection). Taken together, these findings make it likely that the rostral GP$_e$ (which is part of the associative GP$_e$) is in a position to influence some of the subthalamic neurons projecting to the motor part of the central GP$_i$.

When examining the topographical organization of the connections between the pallidum and STN with respect to the tripartite functional subdivision of the striatum and pallidum, it can be concluded that the associative GP$_e$ is reciprocally connected with part of STN, but innervates in addition a different part of STN which projects primarily to the motor pallidum. The motor GP$_e$ appears to have a more limited influence on this STN area. Regarding the VP, it seems clear that this structure reciprocates at least part of its STN projections. The situation is less clear regarding the extent of interactions with other pallidal inputs to STN, and its resolution depends on the extent of the STN field which projects to VP. As mentioned above, according to Parent and Hazrati [88] the projections to VP arise only from the medial tip of STN. If this were the case, the VP would have reciprocal connections with STN, with only minimal influence from other pallidal areas. However, according to Haber et al. [53] the projections to VP arise from the medial half of STN. Were this the case then the associative GP$_e$ would be in a position to influence the STN input to the limbic pallidum, similarly to its position in relation to the motor pallidum.

4. Summary of the data: indirect pathways

4.1. Summary of the anatomical data

Before summarizing the anatomical data presented above and suggesting a general scheme of indirect path-

ways, it should be noted that a description of such pathways based on anatomical analysis at the topographical level has several serious limitations. The anatomical evidence upon which our descriptions are based remains incomplete and is derived from comparisons of anterograde and retrograde labeling studies performed in different sets of animals. Moreover, different primate species are likely to differ in the specific details of organization. However, most of the studies on which our analysis relies used squirrel monkeys [14,15,55,56,58,84,90,91,102,104]. More importantly, the main conclusions that emerge from our examination when the data are combined across experiments are supported by data presented within single studies [14,15], as well as within single animals [102]. In this context, it is worthwhile to point out that Shink et al.'s [102] recent study, which used small deposits of a tracer which is transported both anterogradely and retrogradely, confirmed previous findings on the topographical organization of the subthalamopallidal and pallidosubthalamic projections. In addition, the results of their electron microscopic analysis were consistent with conclusions derived from analysis at the topographical level. Definitive evidence for the precise description of the connections requires additional studies at the synaptic level using electron microscopy, double- and multiple-label tract-tracing experiments, and studies involving transneuronal transport of viruses which appear particularly suited to identify multisynaptic pathways, as well as physiological data. Such future studies are likely to clarify and revise the details of organization described here that must now be considered provisional.

Bearing these limitations in mind, the present data suggest that on the basis of its efferent connections, the STN may be divided into a motor and an associative territories, as well as a smaller limbic territory, each projecting to corresponding areas in the striatum, GP_e and GP_i. More specifically, the dorsolateral two thirds of the rostral two thirds of STN and most of the caudal third of STN project to the motor pallidum and motor striatum, and thus comprise the motor STN. The ventral and medial parts of the rostral two thirds of STN project mainly to the associative pallidum, associative striatum, and SNR, and to a lesser extent to the limbic pallidum. These parts of STN comprise the associative STN and the limbic STN. The exact definition of the limbic STN according to relevant STN efferents is still unclear (see above).

The cortical afferents of STN seem to obey this functional division. The motor STN receives its major cortical input from MI and a smaller input from PMC. These cortical areas provide also a major input to the motor striatum. Part of the associative and limbic STN is the recipient of projections from areas 8 and 9 (associative PFC), which also provide input to the associative striatum. This part of STN receives also input from PMC, which is not a contributor of innervation to the associative striatum, and thus cannot be regarded as part of an associative

circuit according to the parallel segregated scheme. However, in the open interconnected scheme, the PMC is the target of the open associative pathway (which traverses the associative GP_i and thalamus) and therefore is part of the associative split circuit [64].

In contrast to the segregated organization of STN efferents, it seems that its afferents from GP_e do not maintain this segregation, since the main input to STN arises from the associative GP_e (i.e., the rostral GP_e and dorsal part of post-commissural GP_e) while the main output of STN is directed to the motor parts of GP_e and GP_i. More specifically, there are reciprocal connections between the motor GP_e and motor STN as well as between the associative GP_e and associative STN, but the afferents from the associative GP_e also project to the motor STN, which does not provide a reciprocal input. A similar organization might exist in the STN input to the limbic pallidum. As detailed above, there are reciprocal connections between VP and the limbic STN, but it is possible that the associative GP_e contributes a significant input to the STN region which innervates the VP.

4.2. Indirect pathways

The present data suggest that in general, efferents from GP_e are in a position to contact subthalamic cells projecting to GP_i/SNR, and thus provide anatomical support for the existence of an indirect pathway, i.e., a set of connections from the striatum, via GP_e and STN, to GP_i/SNR. This conclusion differs from that of Parent and Hazrati [88] although most of the data on which it is based are the same. Parent and Hazrati concluded that inputs from GP_e seem to spare the area containing subthalamic cells projecting to GP_i/SNR, and therefore, that there is no firm anatomical support for the existence of the indirect pathway. They based this conclusion on the findings of Carpenter et al. [14,15] but later findings [80,91,104] showed that cells projecting to GP_i can be found throughout most rostrocaudal extent of STN (for details see above). The latter results lead us to conclude that the indirect pathway may exist. While this conclusion is primarily based on analysis at the topographical level, it is reinforced by Shink et al.'s [102] findings at the electron microscopic level that GP_e terminals form synapses with STN neurons projecting to GP_i.

Moreover, given the tripartite division of the striatum, pallidum, and STN, the parallel segregated principle predicts the existence of indirect pathways connecting functionally corresponding subregions of the striatum, GP_e, STN, and GP_i. The available data indicate that this organizational principle holds true for the three functional subregions of the striatum, pallidum, and STN, and in addition point to a different organizational principle which does not obey this functional subdivision.

More specifically, segregation seems to be maintained with regard to the associative subregions of the striatum,

pallidum and STN. Thus, the anatomical data support the existence of an indirect pathway passing from the associative striatum, via the associative GP_e and associative STN, to the associative GP_i and SNR. This conclusion is supported by Shink et al.'s [102] findings at the electron microscopic level that terminals from part of the associative GP_e form synapses with STN neurons projecting to part of the associative GP_i. The available data are not sufficient to determine whether different neurons in the associative parts of the striatum, GP_e, and STN are involved in the transfer of information to the associative GP_i and SNR, thus giving rise to two segregated indirect pathways rather than to one pathway which diverges at one of these stations to reach SNR and the associative GP_i.

The anatomical data seem also to support the existence of an indirect pathway connecting the motor subregions of the basal ganglia, passing from the motor striatum, via the motor GP_e and motor STN, to the motor GP_i. This suggestion is again supported by Shink et al.'s [102] findings at the electron microscopic level that terminals from part of the motor GP_e form synapses with STN neurons projecting to part of the motor GP_i.

Strict segregation, however, does not seem to be maintained in the connections of the motor STN, since this subregion is innervated not only by the motor GP_e but also by the associative GP_e. This raises the possibility that there may be an indirect pathway connecting functionally non-corresponding subregions of the basal ganglia, i.e., the associative striatum and the motor GP_i, via the associative GP_e and motor STN.

The available data do not suffice to determine the degree of segregation between the motor and associative pallidal inputs in the motor STN. If the projections from the motor and associative pallidal subregions converge on the same neurons in STN, the motor STN would relay to the motor GP_i the combined inputs from the associative and motor GP_e. If these projections remain segregated, some of STN neurons would channel information from the motor striatum via the motor GP_e and motor STN, to the motor GP_i (i.e., an indirect pathway from the motor striatum to the motor GP_i, as described above), while others would channel information from the associative striatum, via the associative GP_e and motor STN, to the motor GP_i (i.e., an indirect pathway from the associative striatum to the motor GP_i). While Shink et al.'s [102] demonstration that terminals from part of the motor GP_e form synapses with STN neurons projecting to part of the motor GP_i, supports the existence of indirect pathway connecting the motor striatum to the motor GP_i, it does not suffice to determine whether these STN neurons are contacted by motor pallidal neurons only, or by motor and associative pallidal neurons. However, their report that some retrogradely labelled cells were found outside the cluster of labelled varicosities following the injections in part of the motor GP_i, suggests that some STN neurons may convey information from the associative GP_e only. The central point here is that, regardless of whether the projections from the motor and associative GP_e remain segregated in the motor STN or converge on the same neurons, there is transfer of information from the associative striatum, via the associative GP_e and motor STN to the motor GP_i, which is the pallidal target of the motor and not of the associative striatum.

The anatomical data seem also to support the existence of an indirect pathway connecting the limbic subregions of the basal ganglia, passing from the limbic striatum, via the VP and limbic STN, to the VP. Since there are different views in regard to the exact STN territory which innervates the VP (see above), it is not clear whether the limbic STN is innervated only by the VP or also by the associative GP_e. If the VP is the only pallidal input to the limbic STN, then strict segregation is maintained in the connections of the limbic subregions of the basal ganglia, similar to the connections of the associative subregions. If the limbic STN is innervated also by the associative GP_e, then there is (indirect) transfer of information from the associative striatum to the VP, via the associative GP_e and limbic STN, similar to the transfer of information from the associative striatum to the motor GP_i.

As stated in the introduction, the possibility that the STN may provide a substrate for interaction between functionally different subregions within the basal ganglia has been raised before [29,45,53]. Moreover, the proposition that the subthalamopallidal pathway has a reciprocal but also a non-reciprocal component can be found in the work of Haber et al. [53]. These authors concluded that discrete pallidal regions project to restricted regions of STN, while specific regions of STN project to a large area of the VP, and thus suggested that specific parts of STN modulate also regions of GP_e and VP from which they do not receive input. We concur with Haber et al.'s [53] general position that in addition to a reciprocal component there is also a non-reciprocal component in the connections of the pallidum and STN, so that areas of STN can influence pallidal areas which do not reciprocate their projections. However, the details of the organization described here differ from that of Haber et al.'s [53] in that we suggest that discrete projections exist in both directions although their extent is not symmetrical, so that an area which is a major contributor of projections may not be a major recipient of reciprocal projections (e.g., associative pallidum) and vice versa (e.g., motor pallidum). This gives rise to a specific mode of interaction between the pallidum and the STN.

The possibility that there may be an additional principle of organization of the connections of the STN and pallidum, in addition to the parallel segregated principle, has also been raised by Shink et al. [102]. Although the bulk of their data could be accomodated by the principle of parallel organization, their finding that following deposits of tracer in GP_i occasionally retrogradely labelled cells were located outside of the region of terminal labeling in STN,

has led them to suggest that "another alternative is that the organizational principle that we have identified, overlies an additional, albeit less prominent, system in which there is not a correspondence between functionally related neurons" (p. 354). It should be reiterated in this context that Shink et al. [102] did not study the organization of the connections of the rostral GP$_e$, which is part of the associative GP$_e$. This pallidal area seems to be particularly relevant as a potential neural substrate of the connections between associative and motor subregions of the basal ganglia, since other studies pointed to this region as a major contributor of innervation to the subthalamic area we defined here as motor STN.

We suggest that the anatomical data reviewed here can be interpreted as indicating that different principles of organization apply to different pallidal regions. The motor and limbic pallidum seem to have reciprocal connections with STN, as expected according to the parallel segregated principle. The associative pallidum seems not to obey such segregation, but rather to be involved in an asymmetrical relations with the STN, in that it innervates a wider area of STN than the area from which it receives its innervation.

It has long been recognized, in both primates and rats, that different principles govern the organization of the nigrostriatonigral connections of different striatal regions. Thus, while the motor and associative striatum have reciprocal connections with the SNC, the connections of the limbic striatum with the DA system are asymmetrical, in that the limbic striatum innervates a wider area of the DA cell groups than the area from which it receives its innervation [34,49,51,53,62,63,67,68,76,77,81,86,87,89,107]. The operation of different organizational principles in different subregions of the same structure may, therefore, be a general characteristic of the internal connections of the basal ganglia.

4.3. Open and closed indirect pathways

The analysis of the topographical relations between STN afferents and efferents, raises the possibility that there may be two types of indirect pathways. One type of indirect pathway terminates in the same GP$_i$/SNR subregion as the direct pathway arising from the same striatal subregion, thus connecting functionally corresponding subregions of the striatum, pallidum, and STN, as conceived by the parallel segregated scheme. The second type of indirect pathway terminates in a different GP$_i$/SNR subregion than the direct pathway arising from the same striatal subregion, thus connecting functionally non-corresponding subregions of the striatum, pallidum, and STN. We suggest to term the former a 'closed indirect pathway' and the latter an 'open indirect pathway'. Fig. 2 presents a schematic diagram of a closed indirect pathway (panel a) and an open indirect pathway (panel b). Closed indirect pathways contribute to the processing of information within basal ganglia-thalamocortical circuits, while open indirect pathways connect between circuits.
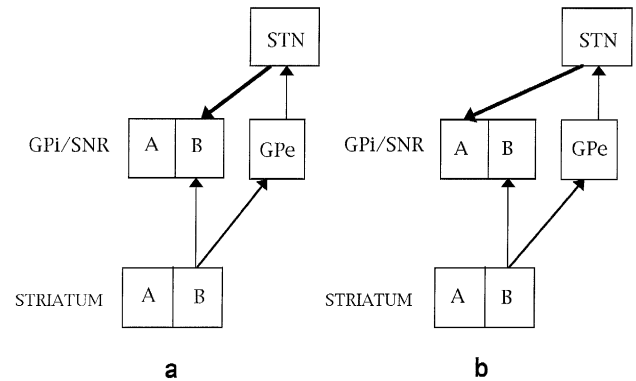

Fig. 2. A schematic diagram of a direct and an indirect pathway. Both pathways originate in the same striatal subregion, but the former leads directly to its target in the output nuclei, whereas the latter traverses parts of GP$_e$ and STN before reaching the output nuclei. a: a closed indirect pathway terminates in the same subregion in the output nuclei as the direct pathway arising from the same striatal subregion. b: an open indirect pathway terminates in a different subregion in the output nuclei than the direct pathway arising from the same striatal subregion. A and B represent corresponding subregions in the striatum and in GP$_i$/SNR.

While future studies are needed to substantiate the concept of closed and open indirect pathways, the application of this concept to the data surveyed here suggests that there may be: (1) three closed indirect pathways, each connecting the corresponding functional (motor, associative, and limbic) regions of the striatum, pallidum, STN, and SNR; and (2) two open indirect pathways, one connecting the associative striatum to the motor GP$_i$, via the associative GP$_e$ and motor STN, and the other connecting the associative striatum to the VP, via the associative GP$_e$ and limbic STN.

4.4. The indirect pathways and the split-circuit scheme

A novel feature that emerges in the organization of the internal connections of the basal ganglia described here, is that indirect pathways can connect between functionally non-corresponding subregions of the basal ganglia. This reinforces the newly suggested concept of open interconnected organization of the basal ganglia-thalamocortical circuitry [64]. According to this concept, connectivity is inherent in the neural architecture of the basal ganglia-thalamocortical connections, so that the same set of connections subserves both segregated and integrated processing. Thus, the basic design of the external connections is that of striatofrontocortical pathways which consist of a set of connections from a striatal subregion via parts of GP$_i$ or SNR and the thalamus to a frontocortical region. A striatofrontocortical pathway that reenters the frontocortical area which is the source of cortical input to this striatal subregion, forms a closed circuit and thus subserves segregated processing. A striatofrontocortical pathway that terminates in a frontocortical area which innervates a different striatal subregion, forms an open pathway and thus subserves integrated processing. This characteristic of the

basal ganglia-thalamocortical circuitry has been captured by the concept of split circuit [64]. We suggest that the same principle governs the organization of the internal connections. Thus, the basic design of the internal connections is that of indirect striatopallidal/nigral pathways which consist of a set of connections from a striatal subregion, via parts of GP$_e$ and STN, to a GP$_i$/SNR subregion. An indirect pathway which terminates in the same GP$_i$/SNR subregion as the direct pathway originating from the same striatal subregion, forms a closed indirect pathway, and thus contributes to segregated processing. An indirect pathway which terminates in a different GP$_i$/SNR subregion than the direct pathway, forms an open indirect pathway, and thus contributes to integrated processing. Thus, both the external and the internal connections of the basal ganglia provide a neural substrate for the transfer of information within as well as between basal ganglia-thalamocortical circuits.

5. Some clinical implications: Huntington's disease

Huntington's disease (HD) is an inherited progressive neurodegenerative disorder of mid-life onset. Clinically this disease is characterized by progressive involuntary choreiform movements, cognitive decline, and personality changes [2,28,33,72,73,92,93,113]. The first and most severely affected neurons are in the striatum [2,54,66,72,73,93,109–111,115]. In later stages death of neurons occurs in other brain regions, including the cortex [72,73]. In addition, the early stages of the disease are marked by a selective loss of striatal neurons projecting to GP$_e$ and SNR, while neurons projecting to GP$_i$ are lost only in later stages ([3,4,97,99], but see [31]).

The leading model of HD, launched by Penney and Young [2,92,93], views this disease as a dysfunction of the motor circuit resulting from abnormal functioning of the indirect pathway. More specifically, loss of striatal innervation to GP$_e$ results in overactivity of GP$_e$ which leads to underactivity of STN, which in turn leads to underactivity of GP$_i$ and thus overactivity of the thalamus, resulting in chorea [2,10,18,74,75,93]. Alexander et al. [6] suggested that in addition to the degeneration of neurons in the putamen, which results in the disruption of the motor circuit, there should be a degeneration of neurons in the caudate nucleus, i.e., a disruption in the associative circuits, which subserves the cognitive symptoms of this disease.

A survey of the relevant literature points to two bodies of relevant data for delineating specific subregions that are likely to be involved in Huntington's chorea. (a) Data from human and non-human primate research implicate the motor parts of STN, GP$_i$, and thalamus in the production of chorea [2,8,10,18,19,27,41,74,75,82]. The involvement of these subregions in Huntington's chorea is only suggestive, and awaits confirmation by functional neuroimaging in HD patients. (b) Anatomical and physiological studies in HD patients reveal that in the early stages of HD, when chorea is most prominent, striatal dysfunction is most evident in the associative striatum (as defined here) [32,54,66,109,111,115]. Only in later stages, which are marked clinically by the replacement of chorea with rigidity, bradykinesia and dystonia, the motor striatum is involved as well [2,30,32,54,66,75,97,109,111,115]. Relatedly, in patients with benign hereditary chorea there is caudate hypometabolism [106a], and although chorea is a rare outcome after striatal lesions in humans, it is much more common after caudate than after putamen lesion [10].

It follows from the above that the basal ganglia subregions likely to subserve Huntington's chorea include the motor parts of STN, GP$_i$, and thalamus, which are known to subserve the production of chorea in humans and animals, and the associative striatum, which is affected in HD patients. Therefore, a model of HD should account for a dysfunction of the motor circuit that results from damage to the associative striatum. This poses a serious difficulty for the parallel segregated scheme because in this scheme, abnormal functioning of the motor STN can stem only from pathology in the motor GP$_e$ or motor striatum. In contrast, the topographical organization of the internal connections outlined here is congenial to a constellation in which pathology in the associative striatum leads to dysfunction of the motor STN. Since one of the inputs to the motor STN arises from the associative GP$_e$, abnormal functioning of the motor STN can result from a pathology in the associative GP$_e$ or associative striatum. Indeed, abnormal functioning of the motor STN following pathology of the associative striatum can be viewed as a dysfunction of the open indirect pathway which connects the associative striatum with motor subregions of the basal ganglia.

As stated above, the early stages of HD are marked by cognitive and emotional symptoms, in addition to motor symptoms. This symptomatology presumably results from the selective loss of the associative striatal projections to SNR and GP$_e$ (which is the main pathological change found in HD patients at this stage), and the resulting abnormalities in their projections. As detailed in this work, the associative GP$_e$ projects to the motor and associative STN, which project to the motor GP$_i$ and to the associative GP$_i$ and SNR, respectively. In describing the projections of GP$_i$ and SNR to the thalamus and cortex we will rely on the split circuit scheme of the basal ganglia-thalamocortical circuitry described in our previous work [64].

The projections of the associative striatum to the associative GP$_i$ and to SNR and their subsequent projections, via the thalamus, to the frontal cortex, as well as the projections of the associative striatum to the associative GP$_e$ and the subsequent projections, via the STN, to the SNR and pallidum, are depicted in Fig. 3. We suggest that loss of the associative striatal projections to the associative GP$_e$ and SNR can give rise to the complex motor, cogni-
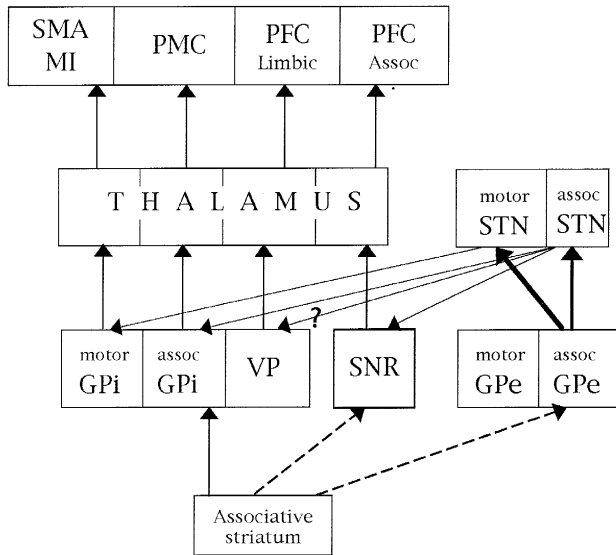
Fig. 3. Summary diagram of the areas and projections affected following selective loss of the associative striatal projections to GP_e and SNR in the early stages of HD. The degenerated projections are depicted in dashed lines. The loss of associative striatal input to the associative GP_e leads to overactivity of the associative GP_e and a resultant underactivity of both the associative and motor STN. Motor symptoms result from disrupted input from the motor STN to the motor GP_i (which projects via the thalamus to the MI and SMA), as well as from disrupted input from the associative STN to the associative GP_i (which projects via the thalamus to the PMC). Frontal-like cognitive deficits result from disrupted input from the associative STN and the associative striatum to SNR (which projects via the thalamus to the associative PFC). Emotional symptoms may result from disrupted input from the limbic STN to VP (which projects via the thalamus to the limbic PFC). The corticostriatal projections and the subthalamic projections to GP_e and the striatum are not depicted.

tive and emotional symptomatology of the early stages of HD in the following manner (see Fig. 3).

The loss of associative striatal projections to the associative GP_e should result in disruption of the subsequent projections, via the STN, to the pallidum and SNR, i.e., disruption of the indirect pathways arising from the associative striatum. Disruption of the indirect pathway connecting the associative striatum to the motor GP_i, via the associative GP_e and motor STN, can account for the chorea exhibited by HD patients. Disruption of the indirect pathway connecting the associative striatum to the associative GP_i, via the associative GP_e and associative STN, is also expected to result in motor symptoms, since according to the split circuit scheme, the output from the associative GP_i reaches (via the thalamus) the PMC [64].

Disruption of the indirect pathway connecting the associative striatum to SNR, via the associative GP_e and associative STN, should disrupt SNR output (via the thalamus) to the associative PFC. Further disruption of this output is expected to result from degeneration of the associative striatal projections to SNR. Disruption of SNR output will result in the dysfunction of the associative PFC, leading to prefrontal-like cognitive deficits observed in HD patients [11,12,26,111,113]. Interestingly, although chorea is usu-

ally considered the first sign of HD, cognitive changes are usually present when the movement disorder begins and may even precede it by a decade or more [26,69,77].

Finally, as was noted above, the associative GP_e projections to STN may form also an open indirect pathway connecting the associative striatum, via the associative GP_e and limbic STN, to the VP. Disruption of this pathway may result in emotional disturbances. Some of the emotional symptoms reported in HD, such as aggression, increased irritability, impulsivity, erratic behavior, and emotional outbursts [25,26,32,112] were suggested to be striatal release symptoms [112]. It is possible that emotional 'release' symptoms could result from a dysfunction of the open indirect pathway from the associative striatum to the VP, similarly to the motor 'release' symptoms which result from disruption of the open indirect pathway from the associative striatum to the motor GP_i (a detailed application of the split circuit model to HD will be presented in Joel & Weiner, in preparation).

The pathological mechanism suggested here to underlie the symptomatology of HD raises a possibility of a treatment for this disease. According to the present model, in the early stages of the disease, associative striatal pathology results in overactivity of the associative GP_e which leads, via the resultant underactivity of STN, to motor, cognitive, and emotional abnormalities observed in the early stages of HD. We suggest that lesion of the overactive associative GP_e could ameliorate some of these symptoms. The rational for this treatment is based on the assumption that it is better to have no input from a component of a system than to have an abnormal 'noisy' input [71], similar to the rational underlying lesioning of the overactive motor GP_i in order to ameliorate some of the hypokinetic symptoms in Parkinson's disease (e.g., [22,71]). There is some evidence that stereotaxic pallidal lesions can ameliorate hyperkinetic movements in affected patients [1] [2].

6. Parallel segregated versus open interconnected organization and neuropathology

Models of basal ganglia-thalamocortical organization have major implications for the construction of models of neuro- and psychopathology. The pioneer circuit models of basal ganglia related disorders of Penney and Young [92] and Swerdlow and Koob [108] have had a major impact in this respect by promoting the view that complex behavioral pathology must reflect a malfunction of a circuit rather than of a lesion in an isolated brain structure. This view has received a powerful impetus from the concept of

---

[2] The possibility that GP_e lesions might result in Parkinsonian symptoms and the possible mechanisms that can prevent such symptoms, are discussed in detail elsewhere (Joel and Weiner, in preparation).

parallel segregated organization of the basal ganglia-thalamocortical circuits [7]. A major advantage of the parallel organization principle is that it enables to delimit the scope of symptoms of the different basal ganglia related disorders that can be attributed to specific functions of individual circuits, and moreover, to specific alterations in the components within each circuit. However, the emphasis on the closed segregated nature of the parallel circuits has a serious drawback, in view of the fact that during recent years it has become increasingly apparent that most of the basal ganglia-related pathologies comprise motor, cognitive and emotional symptoms, and are not limited to one class of symptoms, as would be expected according to the principle of functional segregation [53]. Since according to this scheme, dysfunction of a circuit can result only from a pathology of a station within this circuit, the only way that a closed segregated model can explain symptom coexistence is by postulating a disruption in each of the relevant circuits, as was the case for HD (see above). Likewise, DeLong and Wichmann [22] recently suggested that the segregated circuit model predicts that the behavioral deficits of Parkinson's disease reflect abnormal processes in the motor, oculomotor, and the associative circuits, and possibly in the limbic circuit.

A major strength of the open interconnected model for explaining neuropathological mechanisms is its ability to accommodate coexistence of different classes of symptoms as a result of damage to only one station in one of the circuits, as was exemplified above with regard to HD. Thus, whereas the closed segregated organization provides a framework whereby damage to different stations of an individual circuit results in selective disturbances of motor, cognitive, or emotional behaviors, the open interconnected organization provides in addition a framework whereby such damage may lead to different combinations of motor, cognitive, and emotional behaviors. Thus, the spectrum of the symptoms in a given disorder will result from specific disturbances at one or more of the different levels of a given circuit (frontal cortex, basal ganglia, thalamus) as well as from a subsequent disruption of the normal interaction and flow of information between the different circuits that enable to produce integrated output.

Acknowledgements

References

[1] Aizawa, H., Kwak, S., Shimizu, T., Goto, J., Nakano, I., Mannen, T. and Shibasaki H., A case of adult onset pure pallidal degeneration. I. Clinical manifestations and neuropathological observations, *J. Neurol. Sci.*, 102 (1991) 76–82.

[2] Albin, R.L., Young, A.B. and Penney, J.B., The functional anatomy of basal ganglia disorders, *Trends Neurosci.*, 12 (1989) 366–375.

[3] Albin, R.L., Reiner, A., Anderson, K.D., Penney, J.B. and Young, A.B., Striatal and nigral neuron subpopulations in rigid Huntington's disease: implications for the functional anatomy of chorea and rigidity-akinesia, *Ann. Neurol.*, 27 (1990) 357–365.

[4] Albin, R.L., Young, A.B., Penney, J.B., Handelin, B., Balfour, K.D., Markel, D.S., Tourtelotte, W.W. and Reiner, A., Abnormalities of striatal projection neurons and *N*-methyl-D-aspartate receptors in presymptomatic Huntington's disease, *N. Engl. J. Med.*, 322 (1990) 1293–1298.

[5] Alexander, G.E. and Crutcher, M.D., Functional architecture of basal ganglia circuits: neural substrates of parallel processing, *Trends Neurosci.*, 13 (1990) 266–271.

[6] Alexander, G.E., Crutcher, M.D. and Delong, M.R., basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, 'prefrontal' and 'limbic' functions, *Prog. Brain Res.*, 85 (1990) 119–146.

[7] Alexander, G.E., Delong, M.R. and Strick, P.L., Parallel organization of functionally segregated circuits linking basal ganglia and cortex, *Annu. Rev. Neurosci.*, 9 (1986) 357–381.

[8] Aziz, T.Z., Peggs, D., Sambrook, M.A. and Crossman, A.R., Lesion of the subthalamic nucleus for the alleviation of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced parkinsonism in the primate, *Movement Disorders,* 1 (1991) 288–292.

[9] Berendse, H.W. and Groenewegen, H.J., Organization of the thalamostriatal projections in the rat, with special emphasis on the ventral striatum, *J. Comp. Neurol.*, 299 (1990) 187–228.

[10] Bhatia, K.P. and Marsden, C.D., The behavioural and motor consequences of focal lesions of the basal ganglia in man, *Brain,* 117 (1994) 859–876.

[11] Brandt, J. and Butters, N., The neuropsychology of Huntington's disease, *Trends Neurosci.*, 9 (1986) 118–120.

[12] Butters, N., Albert, M.S. and Sax, D., Investigations of the memory disorders of patients with Huntington's disease, *Adv. Neurol.*, 23 (1979) 203–213.

[13] Carpenter, M.B., Interconnections between the corpus striatum and brain stem nuclei. In J.S. McKenzie, R.E. Kemm and L.N. Wilcock (Eds.), *The Basal Ganglia: Structure and Function,* Plenum Press, New York, 1984, pp. 1–68.

[14] Carpenter, M.B., Batton, R.R., Carleton, S.C. and Keller, J.T., Interconnections and organization of pallidal and subthalamic nucleus neurons in the monkey, *J. Comp. Neurol.,* 197 (1981) 579–603.

[15] Carpenter, M.B., Keller, J.T. and Conte, P., Connections of the subthalamic nucleus in the monkey, *Brain Res.,* 224 (1981) 1–29.

[16] Carpenter, M.B. and Jayaraman, A., Subthalamic nucleus afferents: anatomical and immunocytochemical features. In G. Bernardi, M.B. Carpenter, G. Di Chiara, M. Morelli and P. Stanzione (Eds.), *The Basal Ganglia III*, Plenum Press, New York, 1991, pp. 109–117.

[17] Chevalier G. and Deniau, J.M., Disinhibition as a basic process in the expression of striatal functions, *Trends Neurosci.*, 13 (1990) 277–280.

[18] Crossman, A.R., Primate models of dyskinesia: the experimental approach to the study of basal ganglia-realted involuntary movement disorders, *Neuroscience*, 21 (1987) 1–40.

[19] DeLong, M.R., Primate models of movement diorders of basal ganglia origin, *Trends Neurosci.*, 13 (1990) 281–285.

[20] DeLong, M.R., Crutcher, M.D. and Georgopoulos, A.P., Primate globus pallidus and subthalamic nucleus: functional organization, *J. Neurophysiol.,* 53 (1985) 530–543.

[21] DeLong, M.R. and Georgopoulos, A.P., Motor functions of the basal ganglia. In J.M. Brookhart, V.B. Mountcastle and V.B. Brooks (Eds.), *Handbook of Physiology, Vol. II*, American Physiological Society, Bethesda, MD, 1981, pp. 1017–1061.

[22] DeLong, M.R. and Wichmann, T., Basal ganglia-thalamocortical circuits in parkinsonian signs, *Clin. Neurosci.*, 1 (1993) 18–26.

[23] Deniau, J.M. and Chevalier, G., Functional architecture of the rodent substantia nigra pars reticulata: evidence for segregated channels. In G. Percheron, J.S. McKenzie and J. Feger (Eds.), *The Basal Ganglia IV: New Ideas and Data on Structure and Function*, Plenum Press, New York, 1994, pp. 63–70.

[24] DeVito, J.L. and Anderson, M.E., An autoradiographic study of efferent connections of the globus pallidus in the *Macaca mulatta*, *Exp. Brain Res.,* 46 (1982) 107–117.

[25] DeVito, J.L., Anderson, M.E. and Walsh, K.E., A horseradish peroxidase study of afferent connections of the globus pallidus in *Macaca mulatta*, *Exp. Brain Res.*, 38 (1980) 65–73.

[26] DiFiglia, M., Excitotoxic injury of the neostriatum: a model for Huntington's disease, *Trends Neurosci.*, 13 (1990) 286–289.

[27] Emerich, D.F. and Sanberg, P.R., Animal models of Huntington's disease. In A.A. Boulton, G.B. Baker and R.F. Butterworth (Eds.), *Neuromethods 21: Animal Models of Neurological Disease, I. Neurodegenerative Diseases,* Humana Press, NJ, 1992, pp. 65–134.

[28] Fedio, P., Cox, C.S., Neophytides, A., Conal-Frederick, G. and Chase, T.N., Neuropsychological profile of Huntington's disease: patients and those at risk, *Adv. Neurol.*, 23 (1979) 239–255.

[29] Feger, J., Mouroux, M., Benazzouz, A., Boraud, T., Gross, C. and Crossman, A.R., The subthalamic nucleus: a more complex structure than expected. In G. Percheron, J.S. McKenzie and J. Feger (Eds.), *The Basal Ganglia IV: New Ideas and Data on Structure and Function*, Plenum Press, New York, 1994, pp. 371–382.

[30] Fenske, T., Martin, W.R.W., Ammann, W., Clark, C. and Hayden, M.R., Specificity of cerebral metabolic abnormalities in Huntington's disease, *Neurology*, 38 (Suppl. 1) (1988) 359.

[31] Ferrante, R.J., Beal, M.F. and Kowall, N.W., Mechanisms of neural degeneration in Huntington's disease. In G. Percheron, J.S. McKenzie and J. Feger (Eds.), *The Basal Ganglia IV: New Ideas and Data on Structure and Function*, Plenum Press, New York, 1994, pp. 149–161.

[32] Ferrante, R.J., Kowall, N.W., Richardson, E.O., Bird, E.D. and Martin, J.B., Topography of enkephalin, substance P and acetylcholinesterase staining in Huntington's disease striatum, *Neurosci. Lett.*, 71 (1986) 283–288.

[33] Folstein, S.E., Folstein, M.F. and McHugh, P.R., Psychiatric syndromes in Huntington's disease, *Adv. Neurol.*, 23 (1979) 281–289.

[34] Francois, C., Percheron, G. and Yelnik, J., Localization of nigrostriatal, nigrothalamic and nigrotectal neurons in ventricular coordinates in macaques, *Neuroscience*, 13 (1984) 61–76.

[35] Francois, C., Yelnik, J. and Percheron, G., Gologi study of the primate substantia nigra II. Spatial organization of dendritic arborizations in relation to the cytoarchitectonic boundaries and to the striatonigral bundle, *J. Comp. Neurol.*, 265 (1987) 473–493.

[36] Gerfen, C.R., The neostriatal mosaic I. Compartmental organization of projections from the striatum to the substantia nigra in the rat, *J. Comp. Neurol.*, 236 (1985) 454–476.

[37] Gerfen, C.R., The neostriatal mosaic: multiple levels of compartmental organization in the basal ganglia, *Annu. Rev. Neurosci.*, 15 (1992) 285–320.

[38] Gerfen, C.R., Herkenham, M. and Thibault, J., The neostriatal mosaic II. Patch- and matrix-directed mesostriatal dopaminergic and non-dopaminergic systems, *J. Neurosci.*, 7 (1987) 3915–3934.

[39] Goldman-Rakic, P.S., Topography of cognition: parallel distributed networks in primate association cortex, *Annu. Rev. Neurosci.*, 11 (1988) 137–156.

[40] Goldman-Rakic, P.S. and Selemon, L.D., New frontiers in basal ganglia research, *Trends Neurosci.*, 13 (1990) 241–244.

[41] Graham, W.C., Robertson, R.G., Aziz, T.Z., Peggs, D., Mitchell, I.J., Sambrook, M.A. and Crossman, A.R., The role of the internal segment of the globus pallidus in mediating dyskinesia. In G. Percheron, J.S. McKenzie and J. Feger (Eds.), *The Basal Ganglia IV: New Ideas and Data on Structure and Function*, Plenum Press, New York, 1994, pp. 349–355.

[42] Gray, J.A., Feldon, J., Rawlins, J.N.P., Hemsley, D.R. and Smith, A.D., The neuropsychology of schizophrenia, *Behav. Brain Sci.*, 14 (1991) 1–84.

[43] Graybiel, A.M., Neurochemically specified subsystems in the basal ganglia. In D. Evered and M. O'Connor (Eds.), *Functions of the Basal Ganglia, Ciba Foundation Symposium 107*, Pitman, London, 1984, pp. 114–149.

[44] Graybiel, A.M., Neurotransmitters and neuromodulators in the basal ganglia, *Trends Neurosci.*, 13 (1990) 244–254.

[45] Groenewegen, H.J. and Berendse, H.W., Connections of the subthalamic nucleus with ventral striatopallidal parts of the basal ganglia in the rat, *J. Comp. Neurol.*, 294 (1990) 607–622.

[46] Groenewegen, H.J. and Berendse, H.W., Anatomical relationships between the prefrontal cortex and the basal ganglia in the rat. In Sherry, Glowiki, Goldman-Rakic and Christen (Eds.), *Motor and Cognitive Functions of the Prefrontal Cortex*, Springer-Verlag, 1993.

[47] Groenewegen, H.J., Berendse, H.W., Meredith, G.E, Haber, S.N., Voorn, P., Wolters, J.G. and Lohman, A.H.M., Functional anatomy of the ventral, limbic system-innervated striatum. In P. Willner and J. Scheel-Kruger (Eds.), *The Mesolimbic Dopamine System: From Motivation to Action*, John Wiley, Chichester, 1991, pp. 19–59.

[48] Groenewegen, H.J., Berendse, H.W., Wolters, J.G. and Lohman, A.H.M., The anatomical relationship of the prefrontal cortex with the striatopallidal system, the thalamus and the amygdala: evidence for a parallel organization, *Prog. Brain Res.*, 85 (1990) 95–118.

[49] Groenewegen, H.J., Berendse, H.W. and Wouterlood, F.G., Organization of the projections from the ventral striatopallidal system to ventral mesencephalic dopaminergic neurons in the rat. In G. Percheron, J.S. McKenzie and J. Feger (Eds.), *The Basal Ganglia IV: New Ideas and Data on Structure and Function*, Plenum Press, New York, 1994, pp. 81–93.

[50] Haber, S.N., Groenewegen, H.J., Grove, E.A. and Nauta, W.J.H., Efferent connections of the ventral pallidum: evidence of a dual striatopallidofugal pathway, *J. Comp. Neurol.*, 235 (1985) 322–335.

[51] Haber, S.N., Lynd, E., Klein, C. and Groenewegen, H.J., Topographic organization of the ventral striatal efferent projections in the rhesus monkey: an anterograde tracing study, *J. Comp. Neurol.*, 293 (1990) 282–298.

[52] Haber, S.N., Lynd-Balta, E. and Mitchell, S.J., The organization of the descending ventral pallidal projections of the monkey, *J. Comp. Neurol.*, 329 (1993) 11–128.

[53] Haber, S.N., Lynd-Balta, E. and Spooren, W.P.J.M., Integrative aspects of basal ganglia circuitry. In G. Percheron, J.S. McKenzie and J. Feger (Eds.), *The Basal Ganglia IV: New Ideas and Data on Structure and Function*, Plenum Press, New York, 1994, pp. 71–80.

[54] Hayden, M.R., Martin, W.R.W., Stoessl, A.J., Clark, C., Hollenberg, S., Adam, M.J., Ammann, W., Harrop, R., Rogers, J., Ruth, T., Sayre, C. and Pate, B.D., Positron emission tomography in the early diagnosis of Huntington's disease, *Neurology*, 36 (1986) 888–894.

[55] Hazrati, L.-N. and Parent, A., Convergence of subthalamic and striatal efferents at pallidal level in primates: an anterograde-labeling study with biocytin and PHA-L, *Brain Res.*, 569 (1992) 336–340.

[56] Hazrati, L.-N. and Parent, A., Differential patterns of arborization of striatal and subthalamic fibers in the two pallidal segments in primates, *Brain Res.*, 598 (1992) 311–315.

[57] Hazrati, L.N. and Parent, A., The striatopallidal projection displays a high degree of anatomical specificity in the primate, *Brain Res.*, 592 (1992) 213–227.

[58] Hazrati, L.-N. and Parent, A., Striatal and subthalamic afferents to the primate pallidum: interactions between two opposite chemospecific neuronal systems, *Prog. Brain Res.*, 99 (1993) 89–104.

[59] Hazrati, L.-N., Parent, A., Mitchell, S. and Haber, S.N., Evidence

for interconnections between the two segments of the globus pallidus in primates: a PHA-L anterograde tracing study, *Brain Res.*, 87 (1990) 171–175.

[60] Hedreen, J.C. and DeLong, M.R., Organization of striatopallidal, striatonigral and nigrostriatal projections in the macaque, *J. Comp. Neurol.*, 304 (1991) 569–595.

[61] Huerta, M.F., Krubitzer, L.A. and Kaas, J.H., Frontal eye field as defined by intracortical microstimulation in squirrel monkeys, owl monkeys, and macaque monkeys: I. Subcortical connections, *J. Comp. Neurol.*, 253 (1986) 415–439.

[62] Jimenez-Castellanos, J. and Graybiel, A.M., Subdivisions of the dopamine-containing A8-A9-A10 complex identified by their differential mesostriatal innervation of striosomes and extrastriosomal matrix, *Neuroscience*, 23 (1987) 223–242.

[63] Jimenez-Castellanos, J. and Graybiel, A.M., Evidence that histochemically distinct zones of the primate substantia nigra pars compacta are related to patterned distributions of nigrostriatal projection neurons and striatonigral fibers, *Exp. Brain Res.*, 74 (1989) 227–238.

[64] Joel, D. and Weiner, I., The organization of the basal ganglia-thalamocortical circuits: open interconnected rather than closed segregated, *Neuroscience*, 63 (1994) 363–379.

[65] Kim, R., Nakano, K., Jayaram, A. and Carpenter, M.B., Projections of the globus pallidus and adjacent structures: an autoradiographic study in the monkey, *J. Comp. Neurol.*, 169 (1976) 263–290.

[66] Kowall, N.M., Ferrante, R.J. and Martin, J.B., Patterns of cell loss in Huntington's disease, *Trends Neurosci.*, 10 (1987) 24–29.

[67] Lynd-Balta, E. and Haber, S.N., The organization of midbrain projections to the striatum in the primate: sensorimotor-related striatum versus ventral striatum, *Neuroscience*, 59 (1994) 625–640.

[68] Lynd-belta, E. and Haber, S.N., Primate striatonigral projections: a comparison of the sensorimotor-related striatum and the ventral striatum, *J. Comp. Neurol.*, 345 (1994) 562–578.

[69] Marsden, C.D., The mysterious motor function of the basal ganglia, *Neurology*, 32 (1982) 514–539.

[70] Marsden, C.D., Movement disorders and the basal ganglia, *Trends Neurosci.*, 9 (1986) 512–515.

[71] Marsden, C.D. and Obeso, J.A., The functions of the basal ganglia and the paradox of stereotaxic surgery in Parkinson's disease, *Brain*, 117 (1994) 877–897.

[72] Martin, J.B., Huntington's disease: new approaches to an old problem, *Neurology*, 34 (1984) 1059–1072.

[73] Martin, J.B. and Gusella, J.F., Huntington's disease: pathogenesis and management, *N. Engl. J. Med.*, 315 (1986) 1267–1276.

[74] Mitchell, I.J., Brotchie, J.M., Graham, W.C., Page, R.O., Robertson, R.G., Sambrook, M.A. and Crossman, A.R., Advances in the understanding of neural mechanisms in movement disorders. In G. Bernardi, M.B. Carpenter, G. Di Chiara, M. Morelli and P. Stanzione (Eds.), *The Basal Ganglia III*, Plenum Press, New York, 1991, pp. 607–616.

[75] Mitchell, I.J., Jackson, A., Sambrook, M.A. and Crossman, A.R., The role of the subthalamic nucleus in experimental chorea, *Brain Res.*, 112 (1989) 1533–1548.

[76] Mogenson, G.J., Jones, D.L. and Yim, C.Y., From motivation to action: functional interface between the limbic system and the motor system, *Prog. Neurobiol.*, 14 (1980) 69–97.

[77] Mogenson, G.J., Swanson, L.W. and Wu, M., Neural projections from nucleus accumbens to globus pallidus, substantia innominata and lateral preoptic-lateral hypothalamic area: an anatomical and electrophysiological investigation in the rat, *J. Neurosci.*, 3 (1983) 189–202.

[78] Monakow, K.H., Akert, K. and Kunzle, H., Projections of the precentral motor cortex and other cortical areas of the frontal lobe to the subthalamic nuclei in the monkey, *Exp. Brain Res.*, 33 (1978) 395–403.

[79] Nakano, K., Hasegawa, Y., Tokushige, A., Nakagawa, S., Kayahara, T. and Mizuno, N., Topographic projections from the

[80] Nauta, H.J.W. and Cole, M., Efferent projections of the subthalamic nucleus: an autoradiographic study in monkey and cat, *J. Comp. Neurol.*, 180 (1978) 1–16.

[81] Nauta, H.J.W., Smith, G.P., Faull, R.L.M. and Domesick, V.B., Efferent connections and nigral afferents of the nucleus accumbens septi in the rat, *Neuroscience*, 3 (1978) 385–401.

[82] Obeso, J.A., Guridi, J. and Herrero, M.-T., Role of the subthalamic nucleus in normal and pathological conditions. In G. Percheron, J.S. McKenzie and J. Feger (Eds.), *The Basal Ganglia IV: New Ideas and Data on Structure and Function*, Plenum Press, New York, 1994, pp. 365–370.

[83] Parent, A., Extrinsic connections of the basal ganglia, *Trends Neurosci.*, 13 (1990) 254–258.

[84] Parent, A., Bouchard, C. and Smith, Y., The striatopallidal and striatonigral projections: two distinct fiber systems in primates, *Brain Res.*, 303 (1984) 385–390.

[85] Parent, A. and Hazrati, L.N., Anatomical aspects of information processing in primate basal ganglia, *Trends Neurosci.*, 16 (1993) 111–116.

[86] Parent, A. and Hazrati, L.-N., Multiple striatal representation in primate substantia nigra, *J. Comp. Neurol.,* 344 (1994) 305–320.

[87] Parent, A. and Hazrati, L.-N., Functional anatomy of the basal ganglia. I. The corticobasal ganglia-thalamocortical loop, *Brain Res. Rev,* 20 (1995) 91–127.

[88] Parent, A. and Hazrati, L.-N., Functional anatomy of the basal ganglia. II. The place of subthalamic nucleus and external pallidum in basal ganglia circuitry, *Brain Res. Rev.,* 20 (1995) 128–154.

[89] Parent, A., Mackey, A. and De Bellefeuille, L., The subcortical afferents to caudate nucleus and putamen in primate: a fluorescence retrograde double labeling study, *Neuroscience,* 10 (1983) 1137–1150.

[90] Parent, A. and Smith, Y., Organization of efferent projections of the subthalamic nucleus in the squirrel monkey as revealed by retrograde labeling methods, *Brain Res.*, 436 (1987) 296–310.

[91] Parent, A., Smith, Y., Filion, M. and Dumas, J., Distinct afferents to internal and external pallidal segments in the squirrel monkey, *Neurosci. Lett.*, 96 (1989) 140–144.

[92] Penney, J.B. and Young, A.B., Speculations on the functional anatomy of basal ganglia disorders, *Annu. Rev. Neurosci.*, 6 (1983) 73–97.

[93] Penney, J.B. and Young, A.B., Striatal inhomogeneities and basal ganglia function, *Movement Disorders*, 1 (1986) 3–15.

[94] Percheron, G. and Filion, M., Parallel processing in the basal ganglia: up to a point, *Trends Neurosci.*, 14 (1991) 55–56.

[95] Percheron, G., Francois, C. and Yelnik, J., Spatial organization and information processing in the core of the basal ganglia. In M.B. Carpenter and A. Jayaraman (Eds.), *The Basal Ganglia II: Structure and Function–Current Concepts,* Plenum Press, New York, 1987, pp. 205–226.

[96] Percheron, G., Francois, C., Yelnik, J., Fenelon, G. and Talbi, B., The basal ganglia related systems of primates: definition, description and informational analysis. In G. Percheron, J.S. McKenzie and J. Feger (Eds.), *The Basal Ganglia IV: New Ideas and Data on Structure and Function*, Plenum Press, New York, 1994, pp. 3–20.

[97] Reiner, A., Albin, R.L., Anderson, K.D., D'Amato, C.J., Penney, J.B. and Young, A.B., Differential loss of striatal projection neurons in Huntington's disease, *Proc. Natl. Acad. Sci. USA*, 85 (1988) 5733–5737.

[98] Robbins, T.W. and Brown, V.J., The role of the striatum in the mental chronometry of action: a theoretical review, *Rev. Neurosci.*, 2 (1990) 181–213.

[99] Sapp, E., Ge, P., Aizawa, H., Bird, E., Penney, J., Young, A.B., Vonsattel, J.-P. and DiFiglia, M., Evidence for a preferential loss of enkephalin immunoreactivity in the external globus pallidus in low

grade Huntington's disease using high resolution image analysis, *Neuroscience*, 64 (1995) 397–404.

[100] Selemon, L.D. and Goldman-Rakic, P.S., Longitudinal topography and interdigitation of corticostriatal projections in the rhesus monkey, *J. Neurosci.*, 5 (1985) 776–794.

[101] Selemon, L.D. and Goldman-Rakic, P.S., Topographic intermingling of striatonigral and striatopallidal neurons in the rhesus monkey, *J. Comp. Neurol.*, 297 (1990) 359–376.

[102] Shink, E., Bevan, M.D., Bolam, J.P. and Smith, Y., The subthalamic nucleus and the external pallidum: two tightly interconnected structures that control the output of the basal ganglia in the monkey, *Neuroscience*, 73 (1996) 335–357.

[103] Smith, Y. and Parent, A., Differential connections of caudate nucleus and putamen in the squirrel monkey (*Saimiri sciureus*), *Neuroscience*, 18 (1986) 346–371.

[104] Smith, Y., Hazrati, L.-N. and Parent, A., Efferent projections of the subthalamic nucleus in the squirrel monkey as studied by the PHA-L anterograde tracing method, *J. Comp. Neurol.*, 294 (1990) 306–323.

[105] Smith, Y., Wichmann, T. and DeLong, M.R., The external pallidum and the subthalamic nucleus send convergent synaptic inputs onto single neurons in the internal pallidal segment in monkey: anatomical organization and functional significance. In G. Percheron, J.S. McKenzie and J. Feger (Eds.), *The Basal Ganglia IV: New Ideas and Data on Structure and Function*, Plenum Press, New York, 1994, pp. 51–62.

[106] Spooren, W.P.J.M., Lynd-Balta, E., Mitchell, S. and Haber, S.N., The (ventral) pallidostriatal pathway in the monkey: evidence for integration of basal ganglia circuits, *Soc. Neurosci. Abstr.*, 19 (1993) 1435.

[106a] Suchowersky, O., Hayden, M.R., Martin, W.R.W., Stoessl, A.J., Hildebrand, A.M. and Pate, B.D., Cerebral metabolism of glucose in benign hereditary chorea, *Movement Disorders,* 1 (1986) 33–44.

[107] Swanson, L.W. and Mogenson, G.J., Neural mechanisms for the functional coupling of autonomic, endocrine and somatomotor responses in adaptive behavior, *Brain Res. Rev.*, 3 (1981) 1–34.

[108] Swerdlow, N.R. and Koob, G.F., Dopamine, schizophrenia, mania and depression: toward a unified hypothesis of cortico-striato-pallido-thalamic function, *Behav. Brain Sci.*, 10 (1987) 215–217.

[109] Vonsattel, J.-P., Myers, R.H., Stevens, T.J., Ferrante, R.J., Paskevich, P.A., Richardson, E.P. and Bird, E.D., Huntington's disease: neuropathological grading. In M.B. Carpenter and A. Jayaraman (Eds.), *The Basal Ganglia II: Structure and Function – Current Concepts,* Plenum Press, New York, 1987, pp. 515–531.

[110] Waters, C.M., Peck, R., Rossor, M., Reynolds, G.P. and Hunt, S.P., Immunocytochemical studies on the basal ganglia and substantia nigra in Parkinson's disease and Huntington's chorea, *Neuroscience*, 25 (1988) 419–438.

[111] Weinberger, D.R., Berman, K.F., Iadarola, M., Driesen, N. and Zec, R., Prefrontal cortical blood flow and cognitive function in Huntington's disease, *J. Neurol. Neurosurg. Psychiatry*, 52 (1988) 94–104.

[112] Wichmann, T., Baron, M.S. and DeLong, M.R., Local inactivation of the sensorimotor territories of the internal segment of the globus pallidus and the subthalamic nucleus alleviates parkinsonian motor signs in MPTP treated monkeys. In G. Percheron, J.S. McKenzie and J. Feger (Eds.), *The Basal Ganglia IV: New Ideas and Data on Structure and Function*, Plenum Press, New York, 1994, pp. 357–363.

[113] Wilson, R.S. and Garron, D.C., Cognitive and affective aspects of Huntington's disease, *Adv. Neurol.*, 23 (1979) 193–201.

[114] Yeterian, E.H. and Pandya, D.N., Prefrontostriatal connections in relation to cortical architectonic organization in rhesus monkeys, *J. Comp. Neurol.*, 312 (1991) 43–67.

[115] Young, A.B., Penney, J.B., Starosta-Rubinstein, S., Markel, D.S., Berent, S., Giordani, B., Ehrenkaufer, R., Jewett, D. and Hichwa, R., PET scan investigations of Huntington's disease: cerebelar metabolic correlates of neurological features and functional decline, *Ann. Neurol.*, 20 (1986) 296–303.