Invited Review

Considerations on the thalamostriatal system with some functional implications

J.M. Giménez-Amaya[1], S. de las Heras[2], E. Erro[1], E. Mengual[1] and J.L. Lanciego[1]
[1]Department of Anatomy, School of Medicine, University of Navarra, Pamplona, Navarra, Spain and
[2]Department of Morphology, School of Medicine, Autonomous University of Madrid, Madrid, Spain

Summary. The thalamostriatal projections are largely neglected in current reviews dealing with basal ganglia function. In the past few years, however, several studies have re-evaluated these projections and have postulated their implication in more complex tasks within the basal ganglia organization. In this review, we try to focus on the morphological and functional importance of this system in the basal ganglia of the rat, cat and monkey. Special attention is paid to the thalamus as an important place for interaction between the input and the output systems of the basal ganglia through the thalamostriatal projections. Thus, we stress on the overlapping thalamic territories between the thalamic projection of the output nuclei of the basal ganglia and the thalamostriatal neurons. Our experimental data support the existence of several thalamic feedback circuits within the basal ganglia functional design. Finally, some considerations are provided upon the functional significance of these thalamic feedback circuits in the overall organization of the basal ganglia in health and disease.

Key words: Thalamostriatal projections, Basal ganglia, Thalamus, Rat, Cat, Monkey, Parkinson's disease

Introduction

The basal ganglia form a group of subcortical structures that are involved in the control of movement as well as in cognitive and emotional tasks and the execution of context-dependent aspects of behavior (Graybiel, 1995; Schultz, 1997; Smith et al., 1998a; Mengual et al., 1999; Mink, 1999). The basal ganglia comprise several interconnected nuclei in the forebrain, diencephalon and midbrain, and their major output is directed to the cerebral cortex via the thalamus (Mink, 1999) (Figs. 1-3). In fact, they are involved in great loop circuits in which cortical and other afferent systems can

Offprint requests to: Dr. J.M. Giménez-Amaya, Departamento de Anatomía, Facultad de Medicina, Universidad de Navarra, C/ Irunlarrea, 1, 31008 Pamplona, Navarra, Spain. Fax: 34-948-425649. e-mail: jmga@unav.es

be brought back onto the frontal cortex after a sequential polysynaptic arrangement between the input and the output nuclei of the basal ganglia (Mengual et al., 1999) (Figs. 1-3). The striatum is the main input nuclei of the basal ganglia and it receives a wide variety of cortical connections. In addition to the cerebral cortex, the thalamus constitutes another important source of excitatory inputs to the striatum (Parent, 1986; Alheid et al., 1990; Mengual et al., 1999). The thalamostriatal projections were firstly demonstrated in humans by Vogt and Vogt (1941) (Parent, 1986) and since then they have been described in the majority of mammalian species (Tanaka et al., 1986; Heras et al., 1997). This striatal afferent system appears to be almost exclusively ipsilateral and it innervates the whole striatum (caudate nucleus and putamen), including its most ventral and medial region, the nucleus accumbens (Parent, 1986; Alheid et al., 1990).

Despite being certainly a major source of excitatory afferents to the basal ganglia, the analysis of the morphological and physiological properties of the thalamostriatal connections has received much less attention than the study of the corticostriatal system (Smith et al., 1998a). In fact, the former connections have been systematically neglected in all classical models of basal ganglia organization (Penney and Young, 1983; Albin et al., 1989; Alexander and Crutcher, 1990; DeLong, 1990; Lang and Lozano, 1998), whereas only very recently they have been timidly included in some functional models of these structures (Levy et al., 1997; Lozano et al., 1998; Smith et al., 1998a,b; Mink, 1999). Interestingly, physiological and clinical studies point to the thalamus as a key structure within the neural circuitry of the basal ganglia (Marsden and Obeso, 1994; Albin et al., 1995; Schneider and Rothblat, 1996; Wichmann and DeLong, 1996; Mengual et al., 1999). Thus, one may expect that this system of striatal afferents is playing a significant role in the overall organization of the basal ganglia response. The goal of this review is to make a brief survey on the thalamostriatal system in mammals. Special attention will be paid to the thalamus as an important place for interaction between the input and the output systems of

the basal ganglia through the thalamostriatal projections (Giménez-Amaya and Scarnati, 1999; Mengual et al., 1999).

The thalamostriatal system

In mammals, direct thalamic afferents to the striatum originate mainly in the intralaminar and midline thalamic nuclei (Heras et al., 1997; Marín et al., 1998). Other thalamic sources include the ventral, lateral and posterior thalamic groups. The medium-sized spiny neurons are the main target of the thalamostriatal fibers and at least some of them appear to terminate preferentially upon the dendritic shafts of striatal neurons (Smith et al., 1998a). In the rat, Lapper and Bolam (1992) have also demonstrated that the cholinergic neurons of the dorsal striatum, like those of the ventral striatum or nucleus accumbens (Meredith and Wouterlood, 1990), receive a prominent synaptic control by the thalamostriatal system. Also, Rudkin and Sadikot (1999) have described that in the rat the parafascicular thalamic nucleus sends synaptic input to parvalbumin-immunoreactive striatal neurons. In the primate, striatal interneurons immunoreactive for choline acetyl-transferase, parvalbumin and somatostatin appear to receive thalamostriatal fibers as well (Sidibé and Smith, 1996; Smith et al., 1998a). The neurotransmitter involved in the thalamostriatal projections still remains to be determined with certainty. However, there are indications that these projections are excitatory and that they use aspartate or glutamate as the neurotransmitter. Substance P has also been immunohistochemically detected in some thalamic neurons that project to the caudate nucleus (Sugimoto et al., 1984; Parent, 1986). It has also been suggested that thalamostriatal projections may use acetylcholinesterase as a neuromodulator in the striatum (Bernard et al., 1995).

Rat

Many studies have described the anatomical organization of the thalamostriatal connections in the rat

(Jones and Leavitt, 1974; Nauta et al., 1974; van der Kooy, 1979; Veening et al., 1980; Philipson and Griffiths, 1985; Berendse et al., 1988; Dubé et al., 1988; Berendse and Groenewegen, 1990; Féger et al., 1994; Deschênes et al., 1995; Erro et al., 1998, 1999a,b; Funaki et al., 1998), a species in which these projections represent a massive input to the striatum. Early anatomical studies in rats reported a topographical organization of this pathway, so that oblique thalamic zones crossing the borders of several thalamic nuclei were projecting to different transverse striatal segments (Veening et al., 1980). However, the topographical ordering was replaced by another one in which thalamic zones would be projecting to longitudinally oriented striatal areas (Berendse and Groenewegen, 1990).

The use of highly sensitive retrograde tract-tracing methods has allowed further analysis and the description of three major findings in the organization of the thalamostriatal system in the rat (Erro et al., 1998). These findings are as follows: (1) retrogradely labeled thalamostriatal cells were constantly found in the midline and intralaminar nuclei, and inconstantly in the ventral, lateral and posterior thalamic groups; (2) a topographical organization was clearly found in the thalamostriatal neurons of the midline and intralaminar nuclei. Thus, dorsal injections in the striatum elicited lateral thalamic labeling; ventral striatal injections, medial thalamic labeling; medial injections, a predominant dorsal thalamic labeling; and lateral striatal injections, a predominant ventral thalamic labeling; and (3) a predominant labeling was found in the ventral medial and ventral lateral thalamic nuclei after rostral striatal injections whereas the ventral posterior, and the lateral and posterior thalamic groups were mainly labeled after caudal injections.

Interestingly, Deschênes et al. (1995), using single-cell labeling of these projections have observed two types of thalamostriatal fibers in the rat. The first type arises from the bushy relay cells of the central lateral and associative thalamic nuclei. These thalamostriatal fibers arborize sparsely in the striatum by means of long varicose axon collaterals. The second type of
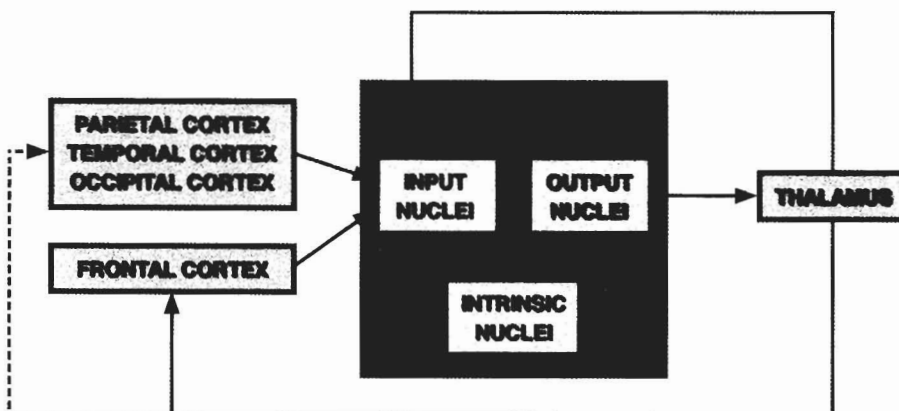

Fig. 1. Block diagram illustrating the general features of the input-output organization of the basal ganglia including the thalamostriatal projections.

thalamostriatal fibers arises from large, reticular-like, relay cells located in the parafascicular and ethmoid nuclei. These fibers form dense clusters of terminations in the striatum and they send branches to other nuclei of the basal ganglia as well. This study, therefore, suggests the existence of different types of thalamostriatal projections in the rat that might subserve different roles in the basal ganglia functional organization (see also Deschênes et al., 1996).

Regarding their termination in the caudate putamen, these projections have been reported to innervate different neurochemical striatal compartments. Thus, Herkenham and Pert (1981) have demonstrated that thalamostriatal projections from the parafascicular nucleus terminate upon the matrix compartment of the rat striatum. In the ventral striatum, thalamic afferent

Fig. 2. Schematic diagram illustrating the basal ganglia circuitry. The excitatory connections are indicated in black lines whereas the inhibitory ones are shown in grey lines. The dopaminergic projections from the pars compacta of the substantia nigra are both excitatory and inhibitory, depending on the postsynaptic receptor. DA: dopamine; enk: enkephalin; GABA: γ-aminobutyric acid; glu: glutamate; LGP: globus pallidus, lateral part; MGP: globus pallidus, medial part; SNC: pars compacta of the substantia nigra; SNR: pars reticulata of the substantia nigra; SP: substance P; STh: subthalamic nucleus; Thal: thalamus.

fibers in the 'shell' region of the nucleus accumbens avoid areas of weak enkephalin immunoreactivity (Berendse and Groenewegen, 1990). In the 'core' region of this nucleus and in the adjacent ventral part of the caudate putamen, thalamostriatal fibers generally avoid areas of strong enkephalin immunoreactivity (Berendse and Groenewegen, 1990). Thalamostriatal projections from the paraventricular and rhomboid nuclei, however, selectively concentrate in areas of strong enkephalin immunoreactivity of the ventral striatum (Berendse and Groenewegen, 1990).

Cat

Thalamostriatal projections in the cat have also been studied by retrograde and anterograde labeling methods (Jones and Leavitt, 1974; Royce, 1978a,b; Sato et al., 1979; Beckstead, 1984a,b; Macchi et al., 1984; Jayaraman, 1985; Royce and Mourey, 1985; Takada et al., 1985; Ragsdale and Graybiel, 1991; Heras et al., 1997, 1998a,b, 1999). Beckstead (1984a) has suggested that the general distribution of the projection regions in the striatum from each thalamic nucleus surrounding the mediodorsal nucleus (rostral intralaminar and midline nuclei) and the fasciculus retroflexus (caudal intralaminar nuclei) displays a general relationship between each other in keeping with their topographical relationship within the thalamus. However, more recent studies with fluorescent tracers could not detect any clear topographical arrangement in the thalamocaudate projections from the rhomboid, dorsal mediodorsal, centrolateral and paracentral thalamic nuclei, although the ventral group was found to project almost exclusively to rostral sectors of the caudate nucleus (Heras et al., 1998b).

Furthermore, studies using double injections of retrograde fluorescent tracers in the cat caudate nucleus have resulted in several findings (Heras et al., 1999). There were few double-labeled cells overall, indicating little collateralization of these projections. However, a large proportion of double-labeled cells were seen after injections in dorsal and ventral regions of the caudate nucleus as compared to injections placed in rostral and caudal portions of the caudate nucleus or in medial and lateral regions of it. In all instances, a relatively larger proportion of double-labeled cells were seen where injections were placed in close proximity to each other, as compared to injections separated at a greater distance. These neurons were mainly located in the caudal intralaminar nuclei, rhomboid nucleus and dorsal mediodorsal thalamic nucleus. Interestingly, the presence of a cluster-like organization of thalamocaudate neurons in the rhomboid and dorsal mediodorsal thalamic nuclei projecting to different sectors of the striatum could also be detected.

The thalamostriatal projections in the cat are also organized following the chemical architecture of the striatum in matrix and striosomes (Graybiel and Ragsdale, 1978; Graybiel, 1990). Furthermore, Ragsdale
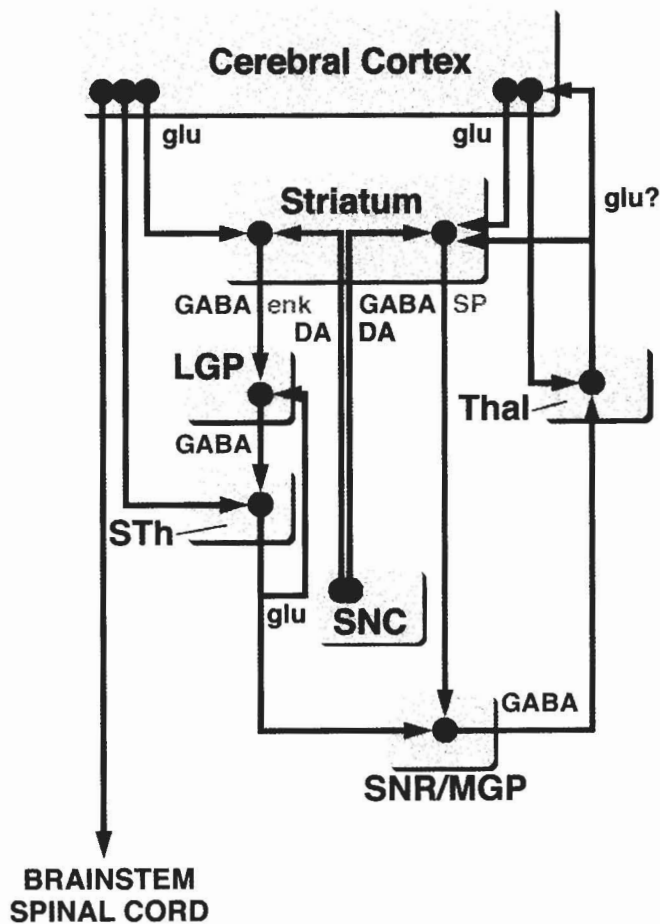
and Graybiel (1991) have found three basic patterns of thalamostriatal projections, namely: (1) a predominant innervation of the striosomes by the paraventricular and rhomboid nuclei; (2) a predominant innervation of the matrix compartment with an even and diffuse distribution by the rostral intralaminar group and portions of the caudal intralaminar nuclei; and (3) a predominant innervation of specific zones within the matrix compartment, by parts of the caudal intralaminar nuclei and the ventral thalamic group.

Monkey

The organization of the thalamostriatal projections in the primate has been described by several authors (Jones and Leavitt, 1974; Kalil, 1978; Parent et al., 1983; Smith and Parent, 1986; Nakano et al., 1990; Sadikot et al., 1990, 1992a,b; Fénelon et al., 1991; François et al., 1991; Smith et al., 1994; Giménez-Amaya et al., 1995). The striatum in primates receives its main thalamic inputs from the rostral nuclei of the ventral group, from rostral intralaminar nuclei such as the central lateral and paracentral nuclei and from the centromedian and parafascicular nuclei in the caudal intralaminar group (Nakano et al., 1990; Heras et al., 1997). Nakano et al. (1990) have postulated that the primate thalamostriatal projections arising from the rostral nuclei of the ventral thalamic group and from the caudal intralaminar nuclei are organized in dorsoventrally and mediolaterally oriented slabs. Moreover, Parent et al. (1983) have demonstrated by means of injections of two different fluorescent tracers that the intralaminar projections to the caudate nucleus and the putamen arise from two distinct neuronal populations. In the rostral intralaminar nuclei, clusters of thalamostriatal cells projecting to the

caudate nucleus are closely intermingled with clusters of cells projecting to the putamen, whereas in the caudal intralaminar nuclei neurons projecting to the putamen and to the caudate nucleus are confined to the centromedian nucleus and to the parafascicular nucleus, respectively (Parent et al., 1983; Parent, 1986). Thalamostriatal projections from the centromedian and parafascicular thalamic nuclei terminate preferentially in the matrix compartment of the sensorimotor and limbic-associative sectors of the striatum where they terminate in a band-like fashion and in a patch-like manner, respectively (Sadikot et al., 1992a,b; Smith et al., 1998a).

Sidibé and Smith (1996) have shown combining anterograde and retrograde tracer techniques that a differential synaptic innervation of striatofugal neurons projecting to the internal or external segments of the globus pallidus by thalamic afferents in the squirrel monkey. These authors concluded that their findings demonstrate that thalamic afferents from the centromedian thalamic nucleus innervate preferentially striatopallidal neurons projecting to the internal segment of the globus pallidus upon which they form asymmetric synapses (Sidibé and Smith, 1996).

Sidibé and Smith (1999) have also reported thalamic inputs to striatal interneurons in monkeys. Injections of biotinylated-dextran amine in the centromedian nucleus led to dense bands of anterograde labeling which, in double immunostained sections, largely overlapped with the four populations of interneurons in the post-commissural region of the putamen. Their study concluded showing that striatal interneurons immunoreactive for somatostatin, parvalbumin and choline acetyltransferase, but not those containing calretinin, receive strong inputs from the centromedian nucleus in
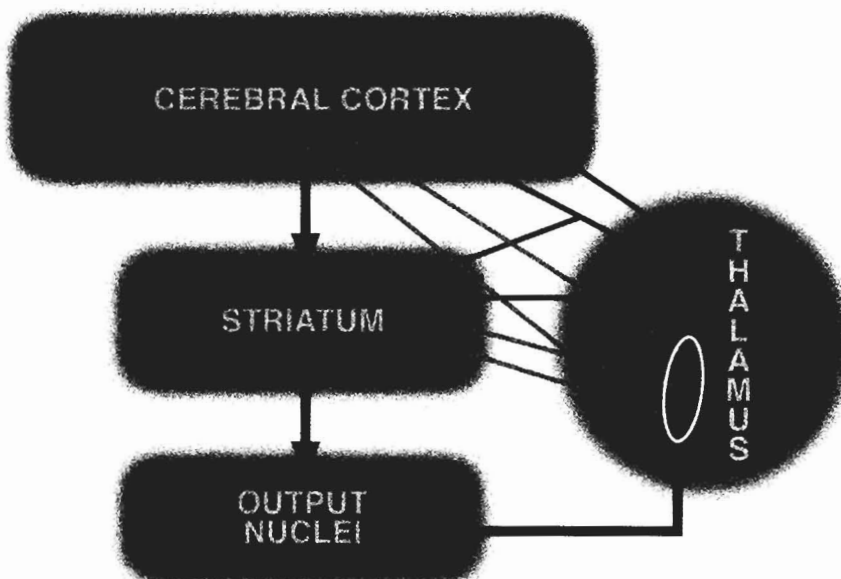

Fig. 3. Schematic diagram illustrating different possibilities of convergence within the thalamus between the output and the input projections of the basal ganglia.

the primate. These results, might implicate that thalamic information may be conveyed to striatal projection neurons and consequently to the output nuclei of the basal ganglia, both directly via excitatory synaptic inputs as well as indirectly via striatal interneurons (Sidibé and Smith, 1999).

The thalamostriatal system and the output of the basal ganglia: functional implications

In the last years many studies have reported the relationships between the output of the basal ganglia and the thalamocortical projections (Schell and Strick, 1984; Ilinsky et al., 1985; Alexander et al., 1986, 1990; Groenewegen, 1988; Hoover and Strick, 1993; Kayahara and Nakano, 1996; Sakai et al., 1998). These contributions were made by means of single- or double-labeling techniques at the light and/or electron microscope levels, as well as using transneuronal techniques. However, the relationships between the output of the basal ganglia and the thalamic input to the striatum, have largely remained unexplored. Only recently, several studies in rats and cats have been carried out in order to clarify the possible relationships between these two projection systems (Heras et al., 1997, 1998a; Erro et al., 1999a; Lanciego et al., 1999; Mengual et al., 1999).

In the cat, studies combining retrograde tracer injections into the caudate nucleus and anterograde tracer injections into the pars reticulata of the substantia nigra have demonstrated the existence of overlapping thalamic territories between the thalamostriatal neurons projecting to different areas of the caudate nucleus and the nigrothalamic connections (Heras et al., 1998a; Erro et al., 1999a). The overlapping thalamic territories were observed in the rostral nuclei of the ventral thalamic group (ventral anterior nucleus, ventral anterior-ventral lateral complex and ventral medial nucleus) and, more restricted, in the rostral (rhomboid, paracentral, central lateral, dorsal mediodorsal nuclei) and caudal intralaminar nuclei (centromedian-parafascicular complex).

Similar studies in the rat have confirmed the existence of overlapping thalamic territories between the thalamostriatal projections to the nucleus accumbens and ventral regions of the caudate putamen complex and the nigrothalamic projections in the same section (Lanciego et al., 1998b; Erro et al., 1999a), and also between the thalamostriatal projection system and afferents to the thalamus from the pedunculopontine tegmental nucleus, which is closely related to the basal ganglia circuits (Erro et al., 1999b).

Finally, studies in the monkey also confirm the existence of overlapping thalamic territories between the output of the basal ganglia from the internal segment of the globus pallidus and the input system of the thalamostriatal projections to the caudate nucleus and putamen (Lanciego et al., 1999), so that pallidal fibers seemed to specifically target the thalamic neurons

projecting to the putamen (Lanciego et al., 1998a,b, 1999).

These anatomical data support the hypothesis that the output of the basal ganglia might participate in feedback subcortical circuits through the thalamostriatal projections (Fig. 3). These circuits, however, could be established either directly through the pallidothalamic and nigrothalamic projections, or indirectly through the pallidoreticular projections. The idea that the final outcome of the basal ganglia processing could be conveyed either directly to the cerebral cortex via thalamic relay nuclei, or sent back to the basal ganglia themselves at the striatal level through the thalamostriatal projection system, seems particularly appealing to us (Fig. 3). A third and very suggestive possibility is that this information already processed in the basal ganglia were directed to both the cerebral cortex and the striatum using the thalamic cells which project to these structures by means of collaterals (Fig. 3).

These feedback circuits of the basal ganglia through the thalamus might thus represent the continuation at the subcortical level of the parallel circuits reported by several authors as the way of processing within the basal ganglia, and even the final link closing the cortico-striato-thalamo-striatal/cortical loops. However, a certain interaction among these parallel circuits reaching the thalamus might also take place at the thalamic level, by means of either interneurons or most probably *via* the reticular thalamic nucleus.

With or without interaction at the thalamic level of the output information of the basal ganglia which reaches the thalamus through parallel or convergent ways, these feedback circuits of the basal ganglia through the thalamus might represent another way of intrastriatal communication. In fact, some anatomical data mentioned in this revision support the idea that the output of the basal ganglia reaches thalamic territories occupied by thalamostriatal neurons that, in turn, project to different striatal sectors. Thus, we may hypothesize that the output of the basal ganglia concerning a specific part of the striatum might influence, via the thalamus, additional striatal areas and possibly, amplify the overall response of the basal ganglia to the cerebral cortex and/or the brainstem.

Finally, a third functional consideration is that the reticular thalamic nucleus may also play a crucial role in establishing feedback circuits of the basal ganglia through the thalamus (Gandia et al., 1993). Two possibilities should be taken into account. First, the pallidoreticular and nigroreticular connections could have the global effect of inhibiting or activating different neurons in the reticular thalamic nucleus depending on the corticostriatal excitation. The second possibility is that the reticular thalamic cells might differently influence the thalamocortical and thalamostriatal neurons or even concrete pools of projection cells within these thalamic groups.

References

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

Albin R.L., Young A.B. and Penney J.B. (1995). The functional anatomy of disorders of the basal ganglia. Trends Neurosci. 18, 63-64.

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

Alexander G.E., DeLong M.R. and Strick P.L. (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu. Rev. Neurosci. 9, 357-381.

Alexander G.E., Crutcher M.D. and DeLong M.R. (1990). Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, "prefrontal" and "limbic" functions. Prog. Brain Res. 85, 119-146.

Alheid G.F., Heimer L. and Switzer III R.C. (1990). Basal ganglia. In: The human nervous system. Paxinos G. (ed). Academic Press. San Diego. pp 483-583.

Beckstead R.M. (1984a). The thalamostriatal projection in the cat. J. Comp. Neurol. 223, 313-346.

Beckstead R.M. (1984b). A projection to the striatum from the medial subdivision of the posterior group of the thalamus in the cat. Brain Res. 300, 351-356.

Berendse H.W. and Groenewegen H.J. (1990). Organization of the thalamostriatal projections in the rat, whit special emphasis on the ventral striatum. J. Comp. Neurol. 299, 187-228.

Berendse H.W., Voorn P., te Kortschot A. and Groenewegen H.J. (1988). Nuclear origin of thalamic afferents of the ventral striatum determines their relation to patch/matrix configurations in enkephalin-immunoreactivity in the rat. J. Chem. Neuroanat. 1, 3-10.

Bernard V., Legay C., Massoulie J. and Bloch B. (1995). Anatomical analysis of the neurons expressing the acetylcholinesterase gene in the rat brain, with special reference to the striatum. Neuroscience 64, 995-1005.

DeLong M.R. (1990). Primate models of movement disorders of basal ganglia origin. Trends Neurosci. 13, 281-285.

Deschênes M., Bourassa J. and Parent A. (1995). Two different types of thalamic fibers innervate the rat striatum. Brain Res. 701, 288-292.

Deschênes M., Bourassa J., Doan V.D. and Parent A. (1996). A single-cell study of the axonal projections arising from the posterior intralaminar thalamic nuclei in the rat. Eur. J. Neurosci. 8, 329-343.

Dubé L., Smith A.D. and Bolam J.P. (1988). Identification of synaptic terminals of thalamic or cortical origin in contact with distinct medium-size spiny neurons in the rat neostriatum. J. Comp. Neurol. 267, 455-471.

Erro E., Lanciego J.L., Heras S. de las and Giménez-Amaya J.M. (1998). A comprehensive retrograde tracer study of the thalamostriatal projections in the rat. Soc. Neurosci. Abstr. 24, 662.

Erro E., Lanciego J.L. and Giménez-Amaya J.M. (1999a). Relationships between thalamostriatal neurons and pedunculopontine projections to the thalamus: a neuroanatomical tract-tracing study in the rat. Exp. Brain Res. 127, 162-170.

Erro E., Lanciego J.L., Arribas J. and Giménez-Amaya J.M. (1999b).

Striatal inputs from the ventrobasal complex of the rat thalamus. Soc. Neurosci. Abstr. 25, 1924.

Féger J., Bevan M. and Crossman A.R. (1994). The projections from the parafascicular thalamic nucleus to the subthalamic nucleus and the striatum arise from separate neuronal populations: a comparison with the corticostriatal and corticosubthalamic efferents in a retrograde fluorescent double-labeling study. Neuroscience 60, 125-132.

Fénelon G., François C., Percheron G. and Yelnik J. (1991). Topographic of the neurons of the central complex (centre-median-parafascicular complex) and of other thalamic neurons projecting to the striatum in macaques. Neuroscience 45, 495-510.

François C., Percheron G., Parent A., Sadikot A.F., Fenelon G. and Yelnik J. (1991). Topography of the projection from the central complex of the thalamus to the sensorimotor striatal territory in monkeys. J. Comp. Neurol. 305, 17-34.

Funaki S., Meguro R., Abe H. and Norita M. (1998). The organization of the thalamostrtiatal projection from the lateral posterior thalamic nuclear complex (LP) in the pigmented rat. Neurobiology 6, 273-294.

Gandia J.A., Heras S. de las, García M. and Giménez-Amaya J.M. (1993). Afferent projections to the reticular thalamic nucleus from the globus pallidus and the substantia nigra in the rat. Brain Res. Bull. 32, 351-358.

Giménez-Amaya J.M. and Scarnati E. (1999). The thalamus as a place for interaction between the input and the output systems of the basal ganglia: a commentary. J. Chem. Neuroanat. 16, 149-152.

Giménez-Amaya J.M., McFarland N.R., Heras S. de las and Haber S.N. (1995). Organization or thalamic projections to the ventral striatum in the primate. J. Comp. Neurol. 354, 127-149.

Graybiel A.M. (1990). Neurotransmitters and neuromodulators in the basal ganglia. Trends Neurosci. 13, 244-254.

Graybiel A.M. (1995). The basal ganglia. Trends Neurosci. 18, 60-62.

Graybiel A.M. and Ragsdale C.W. Jr. (1978). Histochemically distinct compartments in the striatum of human, monkey, and cat demonstrated by acetylthiolcholinesterase staining. Proc. Natl. Acad. Sci. USA 75, 5723-5726.

Groenewegen H.J. (1988). Organization of the afferent connections of the mediodorsal thalamic nucleus in the rat, related to the mediodorsal-prefrontal topography. Neuroscience 24, 379-431.

Heras S. de las, Mengual E., Velayos J.L. and Giménez-Amaya J.M. (1997). New data on the anatomical organization of the thalamostriatal projections. Adv. Neurol. 74, 69-81.

Heras S. de las, Mengual E. and Giménez-Amaya J.M. (1998a). Overlapping territories between the thalamostriatal and nigrothalamic projections in cats. NeuroReport 9, 1913-1916.

Heras S. de las, Mengual E., Velayos J.L. and Giménez-Amaya J.M. (1998b). Re-examination of topographic distribution of thalamic neurons projecting to the caudate nucleus. A retrograde labeling study in the cat. Neurosci. Res. 31, 283-293.

Heras S. de las, Mengual E. and Giménez-Amaya J.M. (1999). Double retrograde tracer study of the thalamostriatal projections to the cat caudate nucleus. Synapse 32, 80-92.

Herkenham M. and Pert C.B. (1981). Mosaic distribution of opiate receptors, parafascicular projections and acetylcholinesterase in rat striatum. Nature 291, 415-418.

Hoover J.E. and Strick P.L. (1993). Multiple output channels in the basal ganglia. Science 259, 819-821.

Ilinsky I.A., Jouandet M.L. and Goldman-Rakic P.S. (1985). Organization of the nigrothalamocortical system in the Rhesus

monkey. J. Comp. Neurol. 236, 315-330.

Jayaraman A. (1985). Organization of thalamic projections in the nucleus accumbens and in the caudate nucleus in cats and its relation with hippocampal and other subcortical afferents. J. Comp. Neurol. 231, 396-420.

Jones E.G. and Leavitt R.Y. (1974). Retrograde axonal transport and the demonstration of non-specific projections to the cerebral cortex and striatum from thalamic intralaminar nuclei in the rat, cat and monkey. J. Comp. Neurol. 154, 349-378.

Kalil K. (1978). Patch-like termination of thalamic fibers in the putamen of the rhesus monkey: an autoradiographic study. Brain Res. 140, 333-339.

Kayahara T. and Nakano N. (1996). Pallido-thalamo-cortical connections: an electron microscopic study in the macaque monkey. Brain Res. 706, 337-342.

Lanciego J.L., Luquin M.R., Guillén J. and Giménez-Amaya J.M. (1998a). Multiple neuroanatomical tracing in primates. Brain Res. Prot. 2, 323-332.

Lanciego J.L., Wouterlood F.G., Erro E. and Giménez-Amaya J.M. (1998b). Multiple axonal tracing: simultaneous detection of three tracers in the same section. Histochem. Cell Biol. 110, 509-515.

Lanciego J.L., Erro E., Arribas J. and Giménez-Amaya J.M. (1999). Output and input circuits of the primate basal ganglia: the relationship between the pallidothalamic projection and identified thalamostriatal neurons. Soc. Neurosci. Abtr. 25, 1924.

Lang E.A. and Lozano A.M. (1998). Parkinson's disease. Second of two parts. N. Engl. J. Med. 339, 1130-1143.

Lapper S.R. and Bolam J.P. (1992). Input from the frontal cortex and the parafascicular nucleus to cholinergic interneurones in the dorsal striatum of the rat. Neuroscience 51, 533-545.

Levy R., Hazrati L.-N., Herrero M.-T., Vila M., Hassani O.-K., Mouroux M., Ruberg M., Asensi H., Agid Y., Féger J., Obeso J.A., Parent A. and Hirsch E.C. (1997). Re-evaluation of the functional anatomy of the basal ganglia in normal and parkinsonian states. Neuroscience 76, 335-343.

Lozano A.M., Lang A.E., Hutchison W.D. and Dostrovsky J.O. (1998). New developments in understanding the etiology of Parkinson's disease and in its treatment. Curr. Opin. Neurobiol. 8, 783-790.

Macchi G., Bentivoglio M., Molinari M. and Minciacchi D. (1984). The thalamo-caudate versus thalamo-cortical projections as studied in the cat with fluorescent retrograde double labeling. Exp. Brain Res. 54, 225-239.

Marín O., Smeets W.J.A.J. and González A. (1998). Evolution of the basal ganglia in tetrapods: a new perspective based on recent studies in amphibians. Trends Neurosci. 21, 487-494.

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

Mengual E., Heras S. de las, Erro E., Lanciego J.L. and Giménez-Amaya J.M. (1999). Thalamic interaction between the input and the output systems of the basal ganglia. J. Chem. Neuroanat. 16, 187-200.

Meredith G.E. and Wouterlood F.G. (1990). Hippocampal and midline thalamic fibers and terminals in relation to the cholineacetyl-transferase-immunoreactive neurons in nucleus accumbens of the rat: a light and electron microscopic study. J. Comp. Neurol. 296, 204-221.

Mink J.W. (1999). Basal ganglia. In: Fundamental neuroscience. Zigmond M.J., Bloom F.E., Landis S.C., Roberts J.L. and Squire L.R. (eds). Academic Press, San Diego. pp 951-972.

Nakano K., Hasegawa Y., Tokushige A., Nakagawa S., Kayahara T. and Mizuno N. (1990). Topographical projections from the thalamus, subthalamic in the Japanese monkey, *Macaca fuscata*. Brain Res. 537, 54-68.

Nauta H.J.W., Pritz M.B. and Lasek R.J. (1974). Afferents to the rat caudoputamen studied with horseradish peroxidase: an evaluation of a retrograde neuroanatomical research method. Brain Res. 67, 219-238.

Parent A. (1986). Comparative neurobiology of the basal ganglia. John Wiley & Sons. New York.

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

Penney J.B. and Young A.B. (1983). Speculations on the functional anatomy of basal ganglia disorders. Annu. Rev. Neurosci. 6, 73-94.

Philipson O.T. and Griffiths A.C. (1985). The topographic order of inputs to nucleus accumbens in the rat. Neuroscience 16, 275-296.

Ragsdale C.W. Jr. and Graybiel A.M. (1991). Compartmental organization of the thalamostriatal connection in the cat. J. Comp. Neurol. 311, 134-167.

Royce G.J. (1978a). Autoradiographic evidence for a discontinous projection to the caudate nucleus from the centromedian nucleus in the cat. Brain Res. 146, 145-150.

Royce G.J. (1978b). Cells of origin of subcortical afferents to the caudate nucleus: a horseradish peroxidase study in the cat. Brain Res. 153, 465-475.

Royce G.J. and Mourey R.J. (1985). Efferent connections of the centromedian and parafascicular thalamic nuclei: an autoradiographic investigation in the cat. J. Comp. Neurol. 235, 277-300.

Rudkin T.M. and Sadikot A.F. (1999). Thalamic input to parvalbumin-immunoreactive GABAergic interneurons: organization in normal striatum and effect of neonatal decortication. Neuroscience 88, 1165-1175.

Sadikot A.F., Parent A. and François C. (1990). The centre médian and parafascicular thalamic nuclei project respectively to the sensorimotor and associative-limbic striatal territories in the squirrel monkey. Brain Res. 510, 161-165.

Sadikot A.F., Parent A. and François C. (1992a). Efferent connections of the centromedian and parafascicular thalamic nuclei in the squirrel moneky: a PHA-L study of subcortical projections. J. Comp. Neurol. 315, 137-159.

Sadikot A.F., Parent A., Smith Y. and Bolam J.P. (1992b). Efferent connections of the centromedian and parafascicular thalamic nuclei in the squirrel monkey: a light and electron microscopic study of the thalamostriatal projection in relation to striatal heterogeneity. J. Comp. Neurol. 320, 228-242.

Sakai S.T., Grofova I. and Bruce K. (1998). Nigrothalamic projections and nigrothalamocortical pathway to the medial agranular cortex in the rat: single- and double-labeling light and electron microscopic studies. J. Comp. Neurol. 391, 506-525.

Sato M., Itoh K. and Mizuno N. (1979). Distribution of thalamo-caudate neurons in the cat as demonstrated by horseradish peroxidase. Exp. Brain Res. 34, 143-153.

Schell G.R. and Strick P.L. (1984). The origin of thalamic inputs to the arcuate premotor and supplementary motor areas. J. Neurosci. 4, 539-560.

Schneider J.S. and Rothblat D.S. (1996). Alterations in intralaminar and motor thalamic physiology following nigrostriatal dopamine depletion. Brain Res. 742, 25-33.

Schultz W. (1997). Dopamine neurons and their role in reward mechanisms. Curr. Opin. Neurobiol. 7, 191-197.

Sidibé M. and Smith Y. (1996). Differential synaptic innervation of striatofugal neurones projecting to the internal and external segments of the globus pallidus by thalamic afferents in the squirrel monkey. J. Comp. Neurol. 365, 445-465.

Sidibé M. and Smith Y. (1999). Thalamic inputs to striatal interneurons in monkeys: synaptic organization and co-localization of calcium binding proteins. Neuroscience 89, 1189-1208.

Smith Y. and Parent A. (1986). Differential connections of caudate nucleus and putamen in the squirrel monkey (*Saimiri sciureus*). Neuroscience 18, 347-371.

Smith Y., Bennett B.D., Bolam J.P., Parent A. and Sadikot A.F. (1994). Synaptic relationships between dopaminergic afferents and cortical or thalamic input in the sensorimotor territory of the striatum in monkey. J. Comp. Neurol. 344, 1-19.

Smith Y., Shink E. and Sidibé M. (1998a). Neuronal circuitry and synaptic connectivity of the basal ganglia. Neurosurg. Clin. North Am. 9, 203-222.

Smith Y., Bevan M.D., Shink E. and Bolam J.P. (1998b). Microcircuitry of the direct and indirect pathways of the basal ganglia. Neuroscience 86, 353-387.

Sugimoto T., Takada M., Kaneko T. and Mizuno N. (1984). Substance P-positive thalamocaudate neurons in the centre median-parafascicular complex in the cat. Brain Res. 323, 181-184.

Takada M., Itoh K., Sugimoto T. and Mizuno N. (1985). Topographical projections from the thalamus to the putamen in the cat. Neurosci. Lett. 54, 207-212.

Tanaka D. Jr., Isaacson L.G. and Trosko B.K. (1986). Thalamostriatal projections from the ventral anterior nucleus in the dog. J. Comp. Neurol. 247, 56-68.

van der Kooy D. (1979). The organization of the thalamic, nigral and raphe cells projecting to the medial vs. lateral caudate-putamen in rat: a fluorescent retrograde double labeling study. Brain Res. 169, 381-387.

Veening J.G., Cornelissen F.M. and Lieven P.A.J.M. (1980). The topical organization of the afferents to the caudatoputamen of the rat. A horseradish peroxidase study. Neuroscience 5, 1253-1268.

Vogt C. and Vogt O. (1941). Thalamusstudien I-III. I. Zur Einfürung. II Homogenität und Grenzgestaldung der Grisea des Thalamus. III. Das Griseum centrale (centrum medianum Luys). J. Psychol. Neurol. (Leipzig) 50, 31-154.

Wichmann T. and DeLong M.R. (1996). Functional and pathophysiological models of the basal ganglia. Curr. Opin. Neurobiol. 6, 751-758.