

Review

The thalamostriatal systems: Anatomical and functional organization in normal and parkinsonian states

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ABSTRACT

Although we have gained significant knowledge in the anatomy and microcircuitry of the thalamostriatal system over the last decades, the exact function(s) of these complex networks remain(s) poorly understood. It is now clear that the thalamostriatal system is not a unique entity, but consists of multiple neural systems that originate from a wide variety of thalamic nuclei and terminate in functionally segregated striatal territories. The primary source of thalamostriatal projections is the caudal intralaminar nuclear group which, in primates, comprises the centromedian and parafascicular nuclei (CM/Pf). These two nuclei provide massive, functionally organized glutamatergic inputs to the whole striatal complex. There are several anatomical and physiological features that distinguish this system from other thalamostriatal projections. Although all glutamatergic thalamostriatal neurons express vGluT2 and release glutamate as neurotransmitter, CM/Pf neurons target preferentially the dendritic shafts of striatal projection neurons, whereas all other thalamic inputs are almost exclusively confined to the head of dendritic spines. This anatomic arrangement suggests that transmission of input from sources other than CM/Pf to the striatal neurons is likely regulated by dopaminergic afferents in the same manner as cortical inputs, while the CM/Pf axo-dendritic synapses do not display any particular relationships with dopaminergic terminals. A better understanding of the role of these systems in the functional circuitry of the basal ganglia relies on future research of the physiology and pathophysiology of these networks in normal and pathological basal ganglia conditions. Although much remains to be known about the role of these systems, recent electrophysiological studies from awake monkeys have provided convincing evidence that the CM/Pf-striatal system is the entrance for attention-related stimuli to the basal ganglia circuits. However, the processing and transmission of this information likely involves intrinsic GABAergic and cholinergic striatal networks, thereby setting the stage for complex physiological responses of striatal output neurons to CM/Pf activation. Finally, another exciting development that will surely generate significant interest towards the thalamostriatal systems in years to come is the possibility that CM/Pf may be a potential surgical target for movement disorders, most particularly Tourette syndrome and Parkinson's disease. Although the available clinical evidence is encouraging, these procedures remain empirical at this stage because of the limited understanding of the thalamostriatal systems.

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1. Introduction

Vogt and Vogt [105] first suggested the existence of the thalamostriatal system, but the pioneering data of Powell and Cowan [79] showing profuse striatal projections from the whole intralaminar nuclear complex in primates were the true starting point for extensive anatomical studies of this projection in various species. Since then, the anatomical and functional organization of this system and its potential role in regulating neurotransmitter homeostasis in the basal ganglia under normal and pathological conditions has been examined. Studies in our laboratory and others have emphasized the precise topographical arrangement and synaptic organization of these projections in primates. The use of modern and sensitive tracing methods has demonstrated that the thalamostriatal systems have multiple origins that extend beyond the caudal intralaminar thalamic nuclei to include specific and non-specific thalamic nuclear groups, suggesting the existence of multiple thalamostriatal systems (Table 1). The recent cloning of the vesicular glutamate transporters 1 and 2 (vGluT1 and vGluT2) [25], and the insight that these are differentially distributed between thalamic and cortical inputs to the striatum has provided us with unique tools to examine and compare the synaptology and plasticity of the corticostriatal and thalamostriatal systems in normal and pathological conditions. In the following account, we will discuss anatomical and functional characteristics of the thalamostriatal systems and review recent findings on the plasticity of the thalamostriatal projections in the non-human primate model of Parkinson's disease. The implication of these findings on the development of surgical or pharmacological therapies for movement disorders aimed at

targeting the thalamostriatal systems will be discussed. Readers are referred to previous reviews for additional information and a broader coverage of early literature on the thalamostriatal projections [32,33,47,63,65,76,100,102]

2. Origin and anatomical organization of the thalamostriatal systems

The main source(s) of thalamostriatal projections are the intralaminar thalamic nuclei, but substantial inputs from midline and specific relay nuclei have also been described in various species [11,14,18,19,23,32,51,61,62,63,65,76,77,80,84,86,87,99]. The topography of thalamostriatal projections in rats has been studied in detail, and has been summarized in previous reviews [32,100]. In monkeys, tracing studies have mainly focused on the organization of projections from the caudal intralaminar nuclei, the centre median and parafascicular nuclei (CM/Pf). Based on its striatal targets, the CM/Pf complex is divided into five major compartments in primates: (1) the rostral third of Pf projects predominantly to the nucleus accumbens, (2) the caudal two thirds of Pf innervates the caudate nucleus, (3) the dorsolateral extension of Pf (Pfdl) projects to the anterior putamen, (4) the medial two thirds of CM (CMm) projects to the post-commissural putamen and (5) the lateral third of CM (Cml) projects to the primary motor cortex (Fig. 1). Through these topographic and specific projections, the CM/Pf influences widespread striatal regions involved in processing functionally segregated information: The rostral Pf is mainly related to the limbic striatum, the Pf/Pfdl is preferentially connected with associative striatal territories, whereas the CMm is the main source of inputs to sensorimotor striatal regions (Fig. 1) [100].

Thalamostriatal projections also arise from midline and specific thalamic nuclei. In rats, projections from midline thalamic nuclei are mainly confined to the ventral striatum, but they also provide significant inputs to dorsal striatal regions [100]. In primates, it has recently been emphasized that a significant non-intralaminar source of thalamostriatal projections originates from the ventral motor thalamic nuclei [33,61,62]. Interconnected regions of the ventral motor thalamic nuclei and motor cortices send convergent inputs to the sensorimotor striatum suggesting functional interactions between corticostriatal and thalamostriatal projections in motor behaviors [62]. Several other thalamic nuclei have been recognized as potential sources of thalamostriatal projections in non-human primates [99], but details on the topography and intrastriatal arborization of these projections is scarce and will not be discussed further in this review (see ref. 100 for details).

3. Thalamostriatal versus thalamocortical systems: segregated origins or collateralized projections?

There is agreement among retrograde double labeling studies that a substantial proportion of neurons in the rostral intralaminar nuclear group and some specific thalamic nuclei (ventral motor nuclei, mediodorsal nucleus) provide axon collaterals to both the

Table 1
 Summary of key differences between the thalamostriatal systems that originate from CM/Pf versus other thalamic nuclei.

| Multiple thalamostriatal systems | |
|--|---|
| • From CM/Pf | • From other thalamic nuclei |
| • Neurons have reticular dendrites | • Neurons have bushy-like dendrites |
| • Innervate preferentially the striatum with collaterals to cortex | • Innervate preferentially the cortex with collaterals to striatum |
| • Focal highly convergent sites of termination in the striatum | • Diffuse less convergent innervation of the striatum |
| • Form axo-dendritic synapses (75%) | • Form axo-spinous synapses (>95%) |
| • Do not display any relationships with dopaminergic afferents | • Converge with dopaminergic inputs onto common dendritic spines |
| • Discharge single spikes during cortical slow-wave activity | • Discharge low-threshold calcium bursts during cortical slow-wave activity |
| • Sensitive to attention-related multisensory information | • Respond to specific modalities (sensory, motor, limbic, etc.) |
| • Provide the striatum with attention-related information from brainstem? | • Provide the striatum with context-dependent functionally related cortical information |
| • Key components of sub-cortical loops with basal ganglia and brainstem (superior colliculus, PPN, etc.) | • Key components of basal ganglia-thalamocortico-thalamic loops |
| • Partly degenerate in Parkinson's disease | • Do not degenerate in Parkinson's disease |

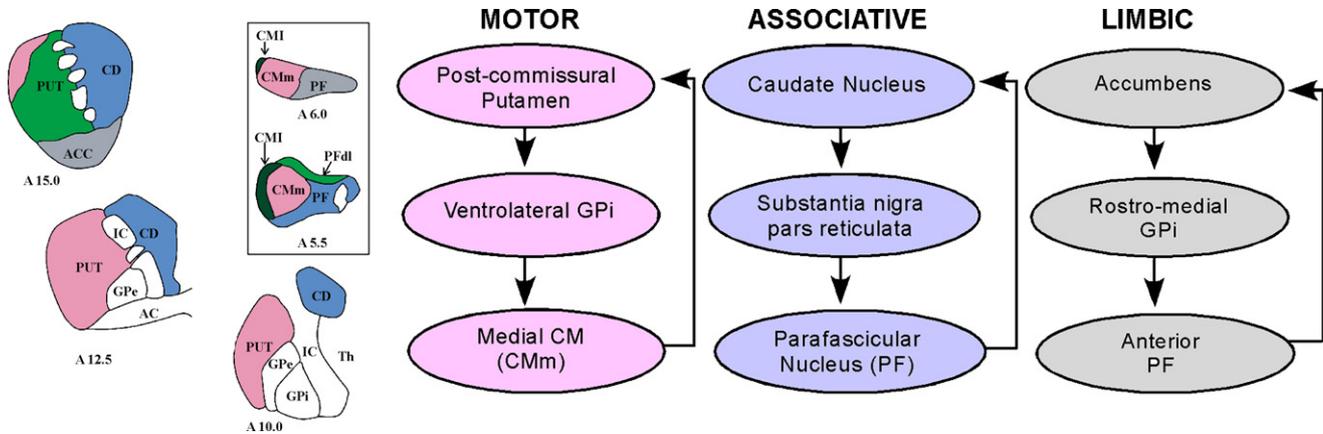


Fig. 1. Color-coded summary of the various sub-compartments of the CM/PF complex with their main striatal-receiving territories in monkeys. The antero-posterior stereotaxic coordinates of the striatal and CM/PF sections are indicated. The lateral part of CM (CMI) projects preferentially to the primary motor cortex, while other areas are connected with specific striatal regions. Via these specific thalamostriatal connections, the information flows through segregated motor, associative and limbic basal ganglia-thalamostriatal loops that involve various regions of the striatum, GPi/SNr and CM/PF. (See Refs. [91,93,100] for more details.) (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

striatum and the cerebral cortex, while thalamostriatal and thalamo-cortical neurons are largely segregated in the caudal intralaminar CM/Pf nuclear complex [32,84,100]. As mentioned above, CM projections to the primary motor cortex in monkeys arise mainly from a neuronal population confined to the lateral part of CM [100], whereas neurons in the medial CM project to the post-commissural putamen (Fig. 1).

However, recent single cell filling data have demonstrated a more complex hodology of CM/Pf neurons, and revealed significant differences in the degree of arborization of thalamostriatal neurons from Pf between rats and monkeys. In rats, most Pf neurons that project to the caudate-putamen complex send sparse collaterals to the cerebral cortex [18]. This projection pattern differs from that of projections from the centrolateral nucleus, which provide scarce loosely organized long varicose processes to the striatum, but form dense patches of terminals in the rat cortex [19]. The projection pattern of individual CM neurons is different and more complex in non-human primates [77]. Three major groups of CM neurons have been identified based on their extent of projections to the striatum and cerebral cortex in monkeys: More than half of all neurons innervate densely and focally the striatum without any significant input to the cerebral cortex, about one third of neurons innervate diffusely the cerebral cortex, without any significant projection to the striatum, and the remaining neurons project to both targets.

In contrast to retrograde labeling studies that revealed a strict regional pattern of localization of CM-striatal vs CM-cortical neurons (Fig. 1), the three main subtypes of CM neurons described in the anterograde single-cell labeling study appear to be randomly distributed in CM [77]. This discrepancy may be explained by the overall scarcity of the diffuse CM-cortical projections compared to the dense and highly focused CM-striatal system (Fig. 2). The small amount of CM terminals in the cerebral cortex may not be enough to take up the minimum amount of tracer needed to retrogradely label most CM-cortical projections, except those that originate from neurons in the lateral part of CM (CMI) (Figs. 1 and 2).

4. Synaptic targets of the thalamostriatal systems

Electron microscopic data from tract-tracing studies in rats and monkeys have provided detailed information on the synaptic microcircuitry of the thalamostriatal system. These studies have mainly focused on the thalamostriatal system originating in CM/Pf. The main characteristic feature of this system is the preponderance

of inputs from CM/Pf neurons to dendritic shafts of striatal projection neurons (Fig. 3) and interneurons [22,80,86,94,100], although a small subset of neurons in the rat Pf appears to preferentially target dendritic spines [51]. Both “direct and indirect” striatofugal neurons are contacted by CM/Pf projections [14,52,94], but electron microscopic studies in monkeys have suggested a preferential innervation of ‘direct pathway’ striatal neurons, projecting to the internal globus pallidus (GPi), compared to ‘indirect pathway’ striatal projecting neurons, projecting to the external globus pallidus (GPe) [94]. However, this does not mean that the intralaminar nuclei do not influence striatal projection neurons that give rise to the ‘indirect pathway’: Pf lesions in rats with prior lesions of the nigrostriatal tract reduce enkephalin mRNA expression in indirect striatofugal neurons, without significantly affecting substance

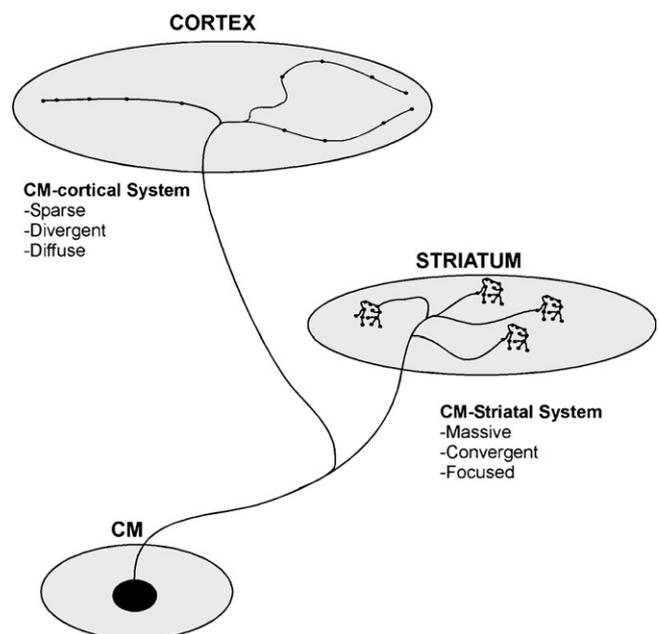


Fig. 2. Summary of the general pattern of CM inputs to the striatum and the cerebral cortex. Although a significant proportion of single CM neurons innervate both regions, CM-striatal projections are more massive and give rise to more profuse and focussed fields of terminals than the sparse CM-cortical axons that innervate motor cortices (See Refs. [77,100] for more details).

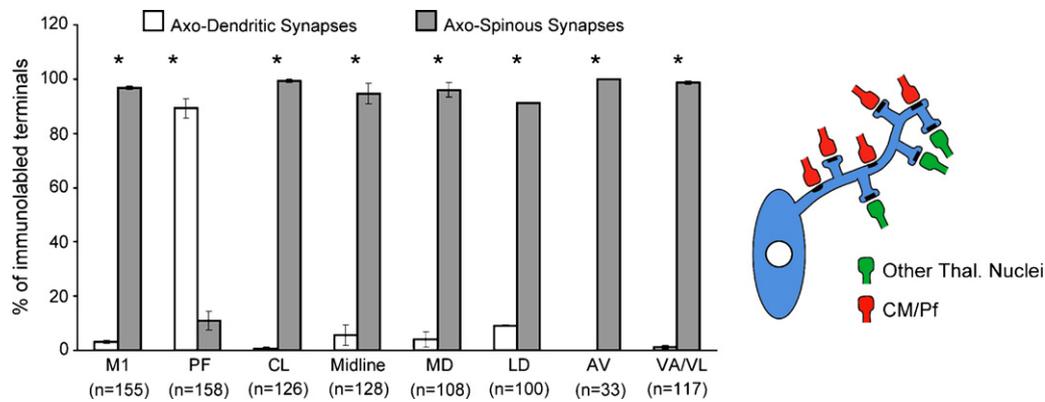


Fig. 3. Summary of results from anterograde tracing studies of thalamic projections to the rat striatum. The histogram illustrates the percentage of labeled boutons from each of the thalamic or cortical (M1) regions injected. Apart from Pf, all other thalamic nuclei and M1 give rise to terminals that contact almost exclusively dendritic spines in the rat striatum. These findings are summarized on the model of striatal medium spiny neuron on the right. Abbreviations: AV: Anteroventral nucleus, CL: Centrolateral nucleus, LD: Laterodorsal nucleus, MD: Mediodorsal nucleus, M1: Primary motor cortex, PF: Parafascicular nucleus, VA/VL: Ventral anterior/ventral lateral nucleus. (See Refs. [80,82] for more details).

P mRNA expression in direct pathway neurons [5,88], suggesting that Pf inputs to the striatum may influence striatal activity in a complex, perhaps multisynaptic manner that is not immediately predicted by anatomical studies.

In monkeys, most striatal interneurons, except those that express calretinin, receive direct CM inputs, but the cholinergic interneurons seem to be preferential target of these projections [54,66,95]. In rats, parvalbumin-containing GABAergic interneurons are devoid of Pf inputs [85], suggesting a possible species difference in the thalamic regulation of these ‘fast spiking’ interneurons between primates and rats [100]. Despite strong monosynaptic innervation from the caudal intralaminar nuclei, CM stimulation results predominantly in reduced firing of tonically active neurons (TANs; likely corresponding to cholinergic interneurons) and decreased acetylcholine release in the rat and monkey striatum [72,108; see below].

As mentioned before, thalamostriatal projections from CM/Pf and from other thalamic areas differ with regard to their synaptic targets in the striatum, and, related to this, with regard to their relationship with dopaminergic inputs. In contrast to cortical terminals that frequently form convergent axo-spinous synapses with dopaminergic terminals, CM axo-dendritic synapses do not display specific synaptic relationships with dopaminergic afferents on striatal neurons [98]. On the other hand, striatal inputs from relay, associative and rostral intralaminar thalamic nuclei form almost exclusively axo-spinous synapses (Fig. 3) that often converge with dopaminergic inputs onto individual spines in the rat caudate-putamen [71,80]. Therefore, except for CM/Pf axo-dendritic afferents, dopaminergic inputs are located to provide tight regulation of other thalamic and cortical axo-spinous glutamatergic afferents in the striatum [6,97].

5. Thalamic regulation of striatal release of neuromodulators

Considerable attention has been paid at the role of CM/Pf effects on dopamine functions in the striatum. In anesthetized rats and cats, Pf lesions reduce dopamine utilization [45,74], and increase striatal dopamine uptake [89] and dopamine D2-receptor density [46]. Infusion of GABA into the cat CM/Pf reduces dopamine release [83]. There is some controversy regarding the effects of electrical Pf stimulation on striatal dopamine release, some studies demonstrating a reduction of striatal dopamine release in cats [15], while others show increased striatal dopamine utilization (without

changing dopamine levels) in rats [46]. Some of the modulation of dopamine levels with electrical stimulation of Pf may be due to inadvertent involvement of the fasciculus retroflexus that contains descending inhibitory projections from the lateral habenula to dopaminergic SNc neurons [28,59]. However, since fiber-sparing Pf lesions also affect striatal dopaminergic functions [44,45], it is likely that CM/Pf neurons *per se* mediate some of these effects. Because there is no direct axo-axonic synapses between thalamic and dopaminergic terminals in the striatum, these effects are probably mediated through complex polysynaptic routes that may involve transcortical systems and/or intrinsic striatal microcircuits [41,42]. The thalamostriatal projection from CM/Pf may also play roles in dopamine D1-receptor-mediated stimulation of striatal acetylcholine release [16] and c-fos gene expression [30]. CM/Pf inputs may also modulate striatal D2-receptor mediated long term depression [106].

Several studies have also described effects of CM/Pf interventions on striatal serotonergic transmission [10,89]. As described below, CM/Pf stimulation decreases acetylcholine, but increases GABA release in rat and monkey striatum [72,108]. There is a significantly increased expression of the astrocytic glutamate transporter, GLT-1, combined with a corresponding reduction of extracellular glutamate levels in the rat striatum after cortical, but not thalamic, deafferentation [55,56].

6. Vesicular glutamate transporters 1 and 2—selective markers of corticostriatal and thalamostriatal systems

In recent years, there has been increasing evidence that the vesicular glutamate transporters vGluT1 and vGluT2 can be used as selective markers for the corticostriatal and thalamostriatal systems, respectively. The selective labeling has helped us to further understand the synaptic organization of the two major glutamatergic projection systems in the rat and monkey striatum under normal and parkinsonian conditions. Despite strong evidence for complete segregation of vGluT1 and vGluT2 proteins at the terminal level in the rat and monkey striatum [50,80–82], the mRNA and protein for these markers partly co-localize in neuronal cell bodies of thalamostriatal neurons in the rat ventral thalamus, but not in intralaminar and midline thalamic nuclei [7–9]. The significance of this partial co-expression of the two vGluTs at the cell body level on the relative distribution of vGluT1 and vGluT2 immunoreactivity in thalamostriatal terminals remains to be determined.

In monkeys and rats, more than 95% vGluT1-immunoreactive (presumably corticostriatal) terminals target dendritic spines, while vGluT2-containing thalamostriatal terminals display a more heterogeneous pattern of synaptic connectivity that differs between primates and non-primates: 70% of the vGluT2-positive boutons contact dendritic spines in rats, whereas only about 50% do so in the monkey striatum [80]. Terminals positive for vGluT2 can be further divided by their nucleus of origin. It has been shown that vGluT2-positive CM/Pf terminals form predominantly axo-dendritic synapses, while vGluT2-containing thalamostriatal terminals from rostral intralaminar, relay and associative thalamic nuclei target almost exclusively dendritic spines [80]. In rats, the relative abundance and pattern of synaptic connectivity of vGluT2 terminals varies significantly between the patch and matrix compartments; almost 90% vGluT2 terminals form axo-spinous synapses in patches, but only about 50–70% do so in the matrix suggesting a strikingly different synaptology of the thalamostriatal system between these two striatal compartments [27,80]. This difference is accounted for by the large proportion of vGluT2 terminals from Pf that form axo-dendritic synapses in the matrix compartment, while avoiding patches [86,100]. In both rats and monkeys, about 20% of the putative glutamatergic terminals that form asymmetric synapses do not express vGluT1 or vGluT2 suggesting that another, as yet undetermined vGluT may exist [50,81]. Although vGluT3 is expressed in the striatum, it is mainly found in non-glutamatergic terminals and post-synaptic dendrites [24,31], thereby cannot account for the vGluT1-/vGluT2-negative striatal terminals described above.

7. Synaptic reorganization of thalamostriatal and corticostriatal glutamatergic systems in Parkinson's disease

vGluT1 and vGluT2 were recently used to examine changes in the synaptic organization of the corticostriatal and thalamostriatal systems in MPTP-treated parkinsonian monkeys [81]. No significant change in the overall pattern of synaptic connectivity and relative prevalence of vGluT2 thalamostriatal terminals were found in the caudate nucleus and putamen of dopamine-depleted monkeys, while there was a significant increase in the relative abundance of vGluT1 immunoreactivity [81]. These findings have been recently confirmed in postmortem human brain tissue showing vGluT1 protein increase in the putamen of patients with Parkinson's disease [43]. At first glance, these observations are at odds with evidence for significant loss of spines in the striatum of MPTP-treated parkinsonian monkeys [103], 6-OHDA-treated rats [39,40] and human PD patients [101]. However, unbiased stereological studies are needed to demonstrate a genuine increase in the total number vGluT1-immunoreactive terminals and characterize potential remodeling of the synaptology of vGluT1-immunoreactive boutons in the striatum of parkinsonian monkeys. Although no clear change in the abundance of vGluT2 terminals was found in various striatal territories of MPTP-treated monkeys, the ratio of axo-spinous to axo-dendritic synapses was substantially increased in the post-commissural putamen of these animals [81]. This change in the synaptic connectivity of vGluT2 terminals may be the result of cell loss in CM which, as discussed below, has been found to degenerate in Parkinson's disease and in some rodent models of parkinsonism (see below).

8. Afferents to thalamostriatal neurons

The main inputs to thalamostriatal neurons originate from the basal ganglia output nuclei, the GPi and the substantia nigra pars reticulata (SNr), and from the brainstem. In monkeys, GPi and SNr provide massive and topographic projections to the caudal

intralaminar complex that form direct synaptic contacts with thalamostriatal neurons [93]. This projection system originates from axon collaterals of the basal ganglia-thalamocortical system that terminate mainly in the ventrobasal nuclear group. In turn, both nuclei send highly topographic and specific inputs to different functional territories of the striatum [32,91,94,100] (Fig. 1). In monkeys, functionally segregated outputs from GPi largely innervate different regions of CM/Pf [91,100], while projections from SNr are confined to the Pf. Together, these anatomical data provide a substrate for the formation of functionally segregated basal ganglia-thalamostriatal loops in primates (Fig. 1). The anterior intralaminar nuclei also receive subcortical inputs from various brainstem, cerebellar, and spinal cord nuclei, as well as inputs from the amygdala, superior colliculus, and pretectal nuclei [63], but direct evidence for synaptic innervation of thalamostriatal neurons is lacking. Brainstem cholinergic and monoaminergic inputs from the pedunculopontine nucleus, raphe nuclei, and locus coeruleus have also been established. Projections from the pedunculopontine nucleus are mainly directed toward Pf and display a high degree of chemical heterogeneity using acetylcholine, GABA, and glutamate as co-existing neurotransmitters [92,100]. The reticular formation (RF) also provides massive inputs to anterior and posterior intralaminar nuclei. By virtue of these strong associations with the RF, the intralaminar nuclei are traditionally seen as part of the "reticular activating system" that regulates the mechanisms of cortical arousal and attention [48].

9. Functional properties of CM/Pf thalamostriatal neurons

The exact functional role of the thalamostriatal system remains poorly understood. Kimura and his colleagues have proposed that CM and Pf supply striatal neurons with information that have attentional values, thus acting as detectors of behaviorally significant events occurring on the contralateral side [47,67,68,100], which is consistent with positron emission tomographic data in humans showing activation of the CM/Pf complex when participants switch from a relaxed awake state to an attention-demanding reaction-time task [48]. Two main functional characteristics of CM/Pf neurons have been identified in monkeys. First, CM/Pf neurons have multimodal properties, ie they respond to a large variety of sensory stimuli (auditory, visual, somatosensory) presented either in or outside sensorimotor conditioning tasks. Second, CM/Pf neurons are temporally tuned, i.e., they can generate in a timely fashioned manner discrete responses to a wide variety of sensory stimuli [67,68]. On the basis of their latency and pattern of responses to sensory stimuli, CM/Pf neurons have been categorized into two main populations, namely those that display short-latency facilitatory responses (SLF neurons) or long-latency facilitatory responses (LLF) to sensory events. These two populations are largely segregated in the CM/Pf complex, SLF neurons being mainly found in Pf, whereas LLF are particularly abundant in CM [47,67,68,100]. Responses of both types of neurons are not associated with reward. On the contrary, the magnitude of CM/Pf neuronal responses is larger when the stimulus is unpredictable and different from expectations [68]. For instance, a majority of CM neurons fire when a small-reward action is required, but a large-reward option is anticipated [68]. This contrasts them from the tonically active neurons (TANs; putative striatal cholinergic interneurons); one of their main targets in the striatum (see above), which under the same experimental conditions, respond preferentially to rewarding stimuli [2,17,58]. However, CM/Pf inputs are required for the expression of the sensory responses of TANs acquired through sensorimotor learning. Inactivation of CM/Pf decreases the characteristic pause and subsequent rebound facilitation, but does not affect the early short latency facilitation, of

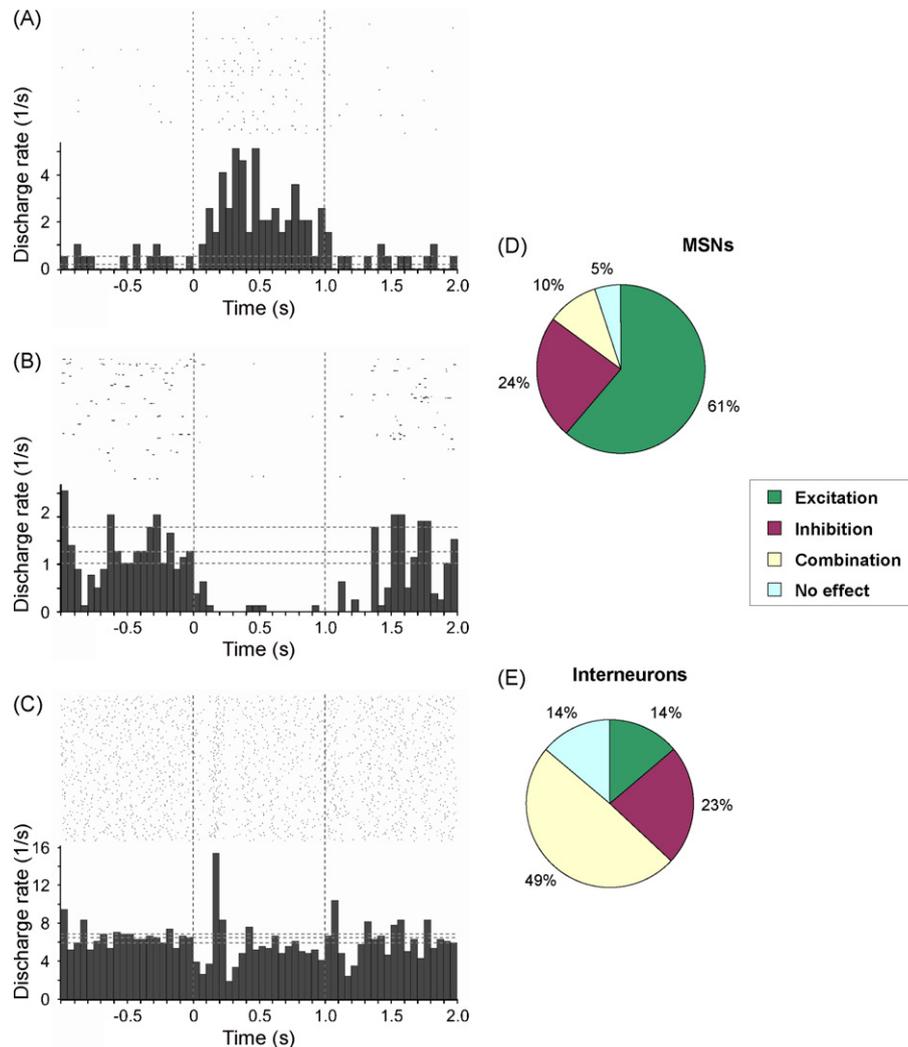


Fig. 4. Responses of striatal neurons to CM stimulation. (A–C) Peri-stimulus raster and rate diagrams of two MSNs (called PANs, A, B) and one interneuron (called TANs, C), in response to CM stimulation. Stimuli were applied at 100 Hz, during the shaded period. Stimulation trains were aligned to the onset of the first pulse (time = 0). In the rate diagrams, the dashed horizontal lines show the median and the 22nd and 78th percentiles. (D–E) Distribution of responses of striatal MSNs (D; $n = 22$) and interneurons (E; $n = 21$) to CM nucleus stimulation. (See Ref. [72] for more details).

TANs in response to sensorimotor conditioning [47,58,100]. Taken into consideration the importance of the dopaminergic system in modulating striatal activity through TANs, one may suggest that the behaviorally sensory events transmitted along the thalamostriatal projection from CM/Pf, in coordination with the motivational value of the dopamine inputs, provide a strong basis for proper selection of actions through the basal ganglia thalamocortical/striatal circuitry [47,58,100]. Therefore, based on their strong physiological responses to unanticipated small-reward action, CM/Pf neurons may complement decision and action bias through the thalamostriatal system and basal ganglia-thalamocortical functional loops [17,68].

10. Effects of CM stimulation upon striatal activity

The paucity of functional studies of the thalamostriatal systems limits considerably our understanding of these projections in the functional circuitry of the basal ganglia. Our recent primate in vivo recordings of changes in the activity of striatal neurons induced by electrical stimulation of CM addressed this issue [72]. All striatal cells tested in this study responded to burst stimulation (100 Hz, 1 s, 100–175 μ A) of the CM with a delay of tens of milliseconds

after the onset of the stimulation trains. Physically active neurons (PANs-likely medium spiny projection neurons) responded mainly with early increases in firing, while most tonically active neurons (TANs; likely cholinergic interneurons), displayed combinations of increases and decreases in firing (Fig. 4). These changes in neuronal activity were accompanied by a GABA-mediated decrease in striatal acetylcholine. Based on these studies, it appears that striatal responses to CM stimulation are not due to monosynaptic excitation, but mediated via striatal or cortical routes. Through these routes, CM stimulation with small currents may eventually engage large portions of the striatum, and trigger complex response patterns of striatal neurons [72].

In vitro data from sagittal slices of young rat brains that partly preserve the integrity of the Pf-striatal projections showed that both NMDA and non-NMDA receptors mediate thalamic and cortical excitatory effects in more than half of the striatal projection neurons [96, see also 16,30]. These observations also suggested interesting differences in short term plasticity and probability of neurotransmitter release between corticostriatal and thalamostriatal projections [20,96]. In this in vitro preparation, thalamic stimulation, but not cortical stimulation, can generate burst-pause pattern of activity in cholinergic interneurons, which differentially

gates corticostriatal signaling through striatopallidal and striatonigral pathways [21].

11. CM/Pf neuronal loss in neurodegenerative diseases

Significant neuronal loss has been found in the CM/Pf of patients with progressive supranuclear palsy, Huntington's disease or Parkinson's disease [34–36]. In parkinsonian patients, subpopulations of parvalbumin-containing neurons are mainly affected in Pf, while in CM non-parvalbumin/non-calbindin neurons are specifically targeted [36]. In rodents, there is controversy as to whether unilateral 6-OHDA lesion of the dopaminergic nigrostriatal pathway induces Pf neurodegeneration; while some authors could not find evidence for neuronal loss in the ipsilateral Pf 3 months after nigrostriatal dopaminergic lesion, another recent study demonstrated more than 50% loss of Pf neurons projecting to the dopamine-depleted striatum 1 month after the lesion [4,37]. Systemic MPTP administration also induces significant loss of midline and intralaminar nuclei in mice [26]. Recent imaging data reported significant changes in the shape, but not the volume, of thalami between parkinsonian patients and controls [64].

12. CM/Pf neuronal activity in Parkinson's disease

There is limited information available on changes of neuronal activity in CM/Pf of dopamine-depleted parkinsonians. Pf firing rates are transiently decreased in anesthetized dopamine-depleted rats [73], while MPTP exposure in monkeys leads to small changes in glucose utilization in CM/Pf [75]. A significant reduction in GABA level has been measured in postmortem CM/Pf tissue of patients with Parkinson's disease [29]. The CM/Pf neuronal activity is locked to rest tremor or voluntary movements in parkinsonian patients, consistent with strong ascending proprioceptive influences reaching CM/Pf from brainstem and spinal cord [3,57].

13. Neurosurgical thalamic interventions for brain diseases

Neurosurgical treatment have long been aimed at the thalamus to treat movement disorders and other diseases [1]. The first stereotaxic thalamotomies in humans targeted the mediodorsal nucleus for the treatment of psychiatric diseases. The ventral anterior and centre median nuclei were later found to be suitable lesion sites for the treatment of psychosis or compulsive and aggressive behavior, respectively. The CM/Pf and adjacent thalamic nuclei also became targets of choice for the alleviation of pain syndromes [107]. Left thalamic infarction that involves part of CM/Pf results in verbal memory disturbances in humans [70].

Hassler and Riechert first reported the use of thalamic lesions as treatment for rigidity and tremor in Parkinson's disease. These influential studies made thalamic surgeries the treatment of choice for Parkinson's diseases and other brain diseases, until the introduction of novel and highly effective pharmacotherapies for these disorders in the late 1960s. Due to the realization that drug therapy may have significant side effects, these procedures were largely abandoned in the 1970s and 1980s, but were then re-introduced with safer neurosurgical techniques stereotaxic functional surgeries after it had become clear that pharmacotherapies often have substantial long-time side effects. Development of electrical macro-stimulation (deep brain stimulation, DBS) as a potentially reversible and adjustable form of surgical treatment of movement disorders, such as Parkinson's disease, dystonia and tremor and other conditions, has also had a major impact.

The primary application of DBS in parkinsonian patients is the treatment of disabling tremor. DBS at the border of the Vop and Vim

results in significant reduction of both parkinsonian and essential tremors, with few side effects. Several studies have also described benefits of DBS of CM/Pf in Parkinson's disease [12,13]. In older studies, CM/Pf-DBS appears to have specifically anti-dyskinetic effects [49], but more recently [60], CM/Pf-DBS was found to be also effective against freezing of gait, a symptom that is poorly responsive to DBS at other targets. Tremor also seems to be significantly alleviated with CM DBS in advanced PD patients [78]. Unilateral CM lesion has transitory antiparkinsonian effects in MPTP-treated monkeys [53].

CM/Pf-DBS is also an effective treatment for Tourette's syndrome [69,104] being effective in reducing the quantity and intensity of tics by 70–90%, and also significantly reduce the psychiatric symptoms of the disease [38,69,90].

References

- [1] J.E. Adams, B.B. Rutkin, Lesions of the centrum medianum in the treatment of movement disorders, *Confin. Neurol.* 26 (1965) 231–245.
- [2] T. Aosaki, A.M. Graybiel, M. Kimura, Effect of the nigrostriatal dopamine system on acquired neural responses in the striatum of behaving monkeys, *Science* 265 (1994) 412–415.
- [3] A.V. Apkarian, C.J. Hodge, Primate spinothalamic pathways. II. The cells of origin of the dorsolateral and ventral spinothalamic pathways, *J. Comp. Neurol.* 288 (1989) 474–492.
- [4] M.S. Aymerich, P. Barroso-Chinea, M. Perez-Manso, A.M. Munoz-Patino, M. Moreno-Igoa, T. Gonzalez-Hernandez, J.L. Lanciego, Consequences of unilateral nigrostriatal denervation on the thalamostriatal pathway in rats, *Eur. J. Neurosci.* 23 (2006) 2099–2108.
- [5] J.-J. Bacci, P. Kachidian, L. Kerkerian-LeGoff, P. Salin, Intralaminar thalamic nuclei lesions: widespread impact on dopamine denervation-mediated cellular defects in the rat basal ganglia, *J. Neuropathol. Exp. Ther.* 63 (2004) 20–31.
- [6] N.S. Bamford, H. Zhang, Y. Schmitz, N.P. Wu, C. Cepeda, M.S. Levine, C. Schmauss, S.S. Zakharenko, L. Zablow, D. Sulzer, Heterosynaptic dopamine neurotransmission selects sets of corticostriatal terminals, *Neuron* 42 (2004) 653–663.
- [7] P. Barroso-Chinea, M.S. Aymerich, M.M. Castle, M. Perez-Manso, T. Tunon, E. Erro, J.L. Lanciego, Detection of two different mRNAs in a single section by dual in situ hybridization: a comparison between colorimetric and fluorescent detection, *J. Neurosci. Methods* 162 (2007) 119–128.
- [8] P. Barroso-Chinea, M. Castle, M.S. Aymerich, M. Perez-Manso, E. Erro, T. Tunon, J.L. Lanciego, Expression of the mRNAs encoding for the vesicular glutamate transporters 1 and 2 in the rat thalamus, *J. Comp. Neurol.* 501 (2007) 703–715.
- [9] P. Barroso-Chinea, M. Castle, M.S. Aymerich, J.L. Lanciego, Expression of vesicular glutamate transporters 1 and 2 in the cells of origin of the rat thalamostriatal pathway, *J. Chem. Neuroanat.* 35 (2008) 101–107.
- [10] D. Becquet, M. Faudon, F. Hery, Effects of thalamic lesion on the bilateral regulation of serotonergic transmission in rat basal ganglia, *J. Neural Transm.* 74 (1988) 117–128.
- [11] H.W. Berendse, H.J. Groenewegen, Organization of the thalamostriatal projections in the rat, with special emphasis on the ventral striatum, *J. Comp. Neurol.* 299 (1990) 187–228.
- [12] D. Caparros-Lefebvre, S. Blond, M.P. Feltin, P. Pollak, A.L. Benabid, Improvement of levodopa induced dyskinesias by thalamic deep brain stimulation is related to slight variation in electrode placement: possible involvement of the centre median and parafascicularis complex, *J. Neurol. Neurosurg. Psychiatry* 67 (1999) 308–314.
- [13] D. Caparros-Lefebvre, P. Pollak, M.P. Feltin, S. Blond, A.L. Benabid, The effect of thalamic stimulation on levodopa induced dyskinesias—evaluation of a new target: the center parafascicular median, *Revue Neurologique* 155 (1999) 543–550.
- [14] M. Castle, M.S. Aymerich, C. Sanchez-Escobar, N. Gonzalo, J.A. Obeso, J.L. Lanciego, Thalamic innervation of the direct and indirect basal ganglia pathways in the rat: ipsi- and contralateral projections, *J. Comp. Neurol.* 483 (2005) 143–153.
- [15] A. Cheramy, M.F. Chesselet, R. Romo, V. Leviel, J. Glowinski, Effects of unilateral electrical stimulation of various thalamic nuclei on the release of dopamine from dendrites and nerve terminals of neurons of the two nigrostriatal dopaminergic pathways, *Neuroscience* 8 (1983) 767–780.
- [16] S. Consolo, G. Baldi, S. Giorgi, L. Nannini, The cerebral cortex and parafascicular thalamic nucleus facilitate in vivo acetylcholine release in the rat striatum through distinct glutamate receptor subtypes, *Eur. J. Neurosci.* 8 (1996) 2702–2710.
- [17] S.J. Cragg, Meaningful silences: how dopamine listens to the Ach pause, *Trends Neurosci.* 29 (2006) 125–131.
- [18] M. Deschênes, J. Bourassa, V.D. Doan, A. Parent, A single-cell study of the axonal projections arising from the posterior intralaminar thalamic nuclei in the rat, *Eur. J. Neurosci.* 8 (1996) 329–343.

- [19] M. Deschenes, J. Bourassa, A. Parent, Striatal and cortical projections of single neurons from the central lateral thalamic nucleus in the rat, *Neuroscience* 72 (1996) 679–687.
- [20] J. Ding, J.D. Pejerson, D.J. Surmeier, Corticostriatal and thalamostriatal synapses have distinctive properties, *J. Neurosci.* 28 (2008) 6483–6492.
- [21] J. Ding, D.J. Surmeier, Thalamic gating of corticostriatal signaling mediated by cholinergic interneurons, Program no. 514.7/SS21, Neuroscience Meeting Planner, Society of Neuroscience, San Diego, CA, 2007.
- [22] L. Dube, A.D. Smith, J.P. Bolam, 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 (1988) 455–471.
- [23] C. Francois, G. Percheron, A. Parent, A.F. Sadikot, G. Fenelon, J. Yelnik, Topography of the projection from the central complex of the thalamus to the sensorimotor striatal territory in monkeys, *J. Comp. Neurol.* 305 (1991) 17–34.
- [24] R.T. Fremeau Jr., J. Burman, T. Qureshi, C.H. Tran, J. Proctor, J. Johnson, H. Zhang, D. Sulzer, D.R. Copenhagen, J. Storm-Mathisen, R.J. Reimer, F.A. Chaudhry, R.H. Edwards, The identification of vesicular glutamate transporter 3 suggests novel modes of signaling by glutamate, *Proc. Natl. Acad. Sci. U.S.A.* 99 (2002) 14488–14493.
- [25] R.T. Fremeau Jr., S. Voglmaier, R.P. Seal, R.H. Edwards, VGLUTs define subsets of excitatory neurons and suggest novel roles for glutamate, *Trends Neurosci.* 27 (2004) 98–103.
- [26] T.E. Freyaldenhoven, S.F. Ali, L.C. Schmued, Systemic administration of MPTP induces thalamic neuronal degeneration in mice, *Brain Res.* 759 (1997) 9–17.
- [27] F. Fujiyama, T. Unzai, K. Nakamura, S. Nomura, T. Kaneko, Difference in organization of corticostriatal and thalamostriatal synapses between patch and matrix compartments of rat neostriatum, *Eur. J. Neurosci.* 24 (2006) 2813–2824.
- [28] D.M. Gao, L. Jeaugey, P. Pollak, A.L. Benabid, Intensity-dependent nociceptive responses from presumed dopaminergic neurons of the substantia nigra, pars compacta in the rat and their modification by lateral habenula inputs, *Brain Res.* 529 (1990) 315–319.
- [29] M. Gerlach, W. Gsell, J. Kornhuber, K. Jellinger, V. Krieger, F. Pantucek, R. Vock, P. Riederer, A post mortem study on neurochemical markers of dopaminergic, GABA-ergic and glutamatergic neurons in basal ganglia-thalamocortical circuits in Parkinson syndrome, *Brain Res.* 741 (1996) 142–152.
- [30] S. Giorgi, M. Rimoldi, S. Consolo, Parafascicular thalamic nucleus deafferentation reduces c-fos expression induced by dopamine D-1 receptor stimulation in rat striatum, *Neuroscience* 103 (2001) 653–661.
- [31] C. Gras, E. Herzog, G.C.V. Belenchi, V. Bernard, P. Ravassard, M. Pohl, B. Gasnier, S. El Mestikawy, A third vesicular glutamate transporter expressed by cholinergic and serotonergic neurons, *J. Neurosci.* 22 (2002) 5442–5451.
- [32] H.J. Groenewegen, H.W. Berendse, The specificity of the nonspecific midline and intralaminar thalamic nuclei, *Trends Neurosci.* 17 (1994) 52–57.
- [33] S. Haber, N.R. McFarland, The place of the thalamus in frontal cortical-basal ganglia circuits, *Neuroscientist* 7 (2001) 315–324.
- [34] H. Heinsen, U. Rub, D. Gangnus, G. Jungkunz, M. Bauer, G. Ulmar, B. Bethke, M. Schuler, I. Bocker, W. Eisenmenger, M. Gotz, M. Strik, Nerve cell loss in thalamic centromedian-parafascicular complex in patients with Huntington's disease, *Acta Neuropathol.* 91 (1996) 161–168.
- [35] J.M. Henderson, K. Carpenter, H. Cartwright, G.M. Halliday, Loss of thalamic intralaminar nuclei in progressive supranuclear palsy and Parkinson's disease: clinical and therapeutic implications, *Brain* 123 (Pt 7) (2000) 1410–1421.
- [36] J.M. Henderson, K. Carpenter, H. Cartwright, G.M. Halliday, Degeneration of the centre median-parafascicular complex in Parkinson's disease, *Ann. Neurol.* 47 (2000) 345–352.
- [37] J.M. Henderson, S.B. Schleimer, H. Allbutt, V. Dabholkar, D. Abela, J. Jovic, M. Quinlivan, Behavioural effects of parafascicular thalamic lesions in an animal model of parkinsonism, *Behav. Brain Res.* 162 (2005) 222–232.
- [38] J.L. Houeto, C. Karachi, L. Mallet, B. Pillon, J. Yelnik, V. Mesnage, M.L. Welter, S. Navarro, A. Pelissolo, P. Damier, B. Pidoux, D. Dormont, P. Cornu, Y. Agid, Tourette's syndrome and deep brain stimulation, *J. Neurol. Neurosurg. Psychiatry* 76 (2005) 992–995.
- [39] C.A. Ingham, S.H. Hood, G.W. Arbuthnot, Spine density on neostriatal neurones changes with 6-hydroxydopamine lesions and with age, *Brain Res.* 503 (1989) 334–338.
- [40] C.A. Ingham, S.H. Hood, P. Taggart, G.W. Arbuthnot, Plasticity of synapses in the rat neostriatum after unilateral lesion of the nigrostriatal dopaminergic pathway, *J. Neurosci.* 18 (1998) 4732–4743.
- [41] M.W. Jones, I.C. Kilpatrick, O.T. Phillipson, Regulation of dopamine function in the prefrontal cortex of the rat by the thalamic mediodorsal nucleus, *Brain Res. Bull.* 19 (1987) 9–17.
- [42] M.W. Jones, I.C. Kilpatrick, O.T. Phillipson, Thalamic control of subcortical dopamine function in the rat and the effects of lesions applied to the medial prefrontal cortex, *Brain Res.* 475 (1988) 8–20.
- [43] A. Kashani, C. Betancur, B. Giros, E. Hirsch, S. El Mestikawy, Altered expression of vesicular glutamate transporters VGLUT1 and VGLUT2 in Parkinson disease, *Neurobiol. Aging* 28 (2007) 568–578.
- [44] I.C. Kilpatrick, O.T. Phillipson, Thalamic control of dopaminergic functions in the caudate-putamen of the rat. I. The influence of electrical stimulation of the parafascicular nucleus on dopamine utilization, *Neuroscience* 19 (1986) 965–978.
- [45] I.C. Kilpatrick, M.W. Jones, B.J. Johnson, J. Cornwall, O.T. Phillipson, Thalamic control of dopaminergic functions in the caudate-putamen of the rat. II. Studies using ibotenic acid injection of the parafascicular-intralaminar nuclei, *Neuroscience* 19 (1986) 979–990.
- [46] I.C. Kilpatrick, M.W. Jones, C.J. Pycocock, I. Riches, O.T. Phillipson, Thalamic control of dopaminergic functions in the caudate-putamen of the rat. III. The effects of lesions in the parafascicular-intralaminar nuclei on D2 dopamine receptors and high affinity dopamine uptake, *Neuroscience* 19 (1986) 991–1005.
- [47] M. Kimura, T. Minamimoto, N. Matsumoto, Y. Hori, Monitoring and switching of cortico-basal ganglia loop functions by the thalamo-striatal system, *Neurosci. Res.* 48 (2004) 355–360.
- [48] S. Kinomura, J. Larsson, B. Gulyas, P.E. Roland, Activation by attention of the human reticular formation and thalamic intralaminar nuclei, *Science* 271 (1996) 512–515.
- [49] J.K. Krauss, T. Pohle, R. Weigel, J.M. Burgunder, Deep brain stimulation of the centre median-parafascicular complex in patients with movement disorders, *J. Neurol. Neurosurg. Psychiatry* 72 (1996) 546–548.
- [50] C.J. Lacey, J. Boyes, O. Gerlach, L. Chen, P.J. Magill, J.P. Bolam, GABA(B) receptors at glutamatergic synapses in the rat striatum, *Neuroscience* 136 (2005) 1083–1095.
- [51] C.J. Lacey, J.P. Bolam, P.J. Magill, Novel and distinct operational principles of intralaminar thalamic neurons and their striatal projections, *J. Neurosci.* 27 (2007) 4374–4384.
- [52] J.L. Lanciego, N. Gonzalo, M. Castle, C. Sanchez-Escobar, M.S. Aymerich, J.A. Obeso, Thalamic innervation of striatal and subthalamic neurons projecting to the entopeduncular nucleus, *Eur. J. Neurosci.* 19 (2004) 1267–1277.
- [53] J.L. Lanciego, M.C. Rodriguez-Oroz, F.J. Blesa, L. Alvarez-Erviti, J. Guridi, P. Barroso-Chinea, Y. Smith, J.A. Obeso, Lesion of the centromedian thalamic nucleus in MPTP-treated monkeys, *Mov. Disord.* 23 (2008) 708–715.
- [54] S.R. Lapper, J.P. Bolam, Input from the frontal cortex and the parafascicular nucleus to cholinergic interneurons in the dorsal striatum of the rat, *Neuroscience* 51 (1992) 533–545.
- [55] J.C. Lievens, F. Bernal, C. Forni, N. Mahy, L. Kerkerian-Le Goff, Characterization of striatal lesions produced by glutamate uptake alteration: cell death, reactive gliosis, and changes in GLT1 and GADD45 mRNA expression, *Glia* 29 (2000) 222–232.
- [56] J.C. Lievens, P. Salin, L. Had-Aissouni, N. Mahy, L. Kerkerian-Le Goff, Differential effects of corticostriatal and thalamostriatal deafferentation on expression of the glutamate transporter GLT1 in the rat striatum, *J. Neurochem.* 74 (2000) 909–919.
- [57] M. Magnin, A. Morel, D. Jeanmonod, Single-unit analysis of the pallidum, thalamus and subthalamic nucleus in parkinsonian patients, *Neuroscience* 96 (2000) 549–564.
- [58] N. Matsumoto, T. Minamimoto, A.M. Graybiel, M. Kimura, Neurons in the thalamic CM-Pf complex supply striatal neurons with information about behaviorally significant sensory events, *J. Neurophysiol.* 85 (2001) 960–976.
- [59] M. Matsumoto, O. Hikosaka, Lateral habenula as a source of negative reward signals in dopamine neurons, *Nature* 447 (2007) 1111–1115.
- [60] P. Mazzone, F. Stocchi, S. Galati, A. Insola, M.G. Altibrandi, N. Modugno, D. Tropepi, L. Brusa, A. Stefani, Bilateral implantation of centromedian-parafascicular complex and GPi: a new combination of unconventional targets for deep brain stimulation in severe Parkinson disease, *Neuromodulation* 9 (2006) 221–228.
- [61] N.R. McFarland, S.N. Haber, Organization of thalamostriatal terminals from the ventral motor nuclei in the macaque, *J. Comp. Neurol.* 429 (2001) 321–336.
- [62] N.R. McFarland, S.N. Haber, Convergent inputs from thalamic motor nuclei and frontal cortical areas to the dorsal striatum in the primate, *J. Neurosci.* 2 (2000) 3798–3813.
- [63] J.G. McHaffie, T.R. Stanford, B.E. Stein, V. Coizet, P. Redgrave, Subcortical loops through the basal ganglia, *Trends Neurosci.* 28 (2005) 401–407.
- [64] M.J. McKeown, A. Uthama, R. Abugharbieh, S. Palmer, M. Lewis, X. Huang, Shape (but not volume) changes in the thalami in Parkinson's disease, *BMC Neurol.* 8 (2008) 8.
- [65] E. Mengual, S. de las Heras, E. Erro, J.L. Lanciego, J.M. Gimenez-Amaya, Thalamic interaction between the input and the output systems of the basal ganglia, *J. Chem. Neuroanat.* 16 (1999) 187–200.
- [66] G.E. Meredith, F.G. Wouterlood, Hippocampal and midline thalamic fibers and terminals in relation to the choline acetyltransferase-containing neurons in the nucleus accumbens of the rat: a light and electron microscopic study, *J. Comp. Neurol.* 296 (1990) 204–221.
- [67] T. Minamimoto, M. Kimura, Participation of the thalamic CM-Pf complex in attentional orienting, *J. Neurophysiol.* 87 (2002) 3090–3101.
- [68] T. Minamimoto, Y. Hori, M. Kimura, Complementary process to response bias in the centromedian nucleus of the thalamus, *Science* 308 (2005) 1798–1801.
- [69] J.W. Mink, J. Walkup, K.A. Frey, P. Como, D. Cath, M.R. Delong, G. Erenberg, J. Jankovic, J. Juncos, J.F. Leckman, N. Swerdlow, V. Visser-Vandewalle, J.L. Vitek, Patient selection and assessment recommendations for deep brain stimulation in Tourette syndrome, *Mov. Disord.* 21 (2006) 1831–1838.
- [70] E. Mori, A. Yamadori, Y. Mitani, Left thalamic infarction and disturbance of verbal memory: a clinicoanatomical study with a new method of computed tomographic stereotaxic lesion localization, *Ann. Neurol.* 20 (1986) 671–676.
- [71] J. Moss, J.P. Bolam, The relationship between cortical, thalamic and nigral terminals in the striatum, in: Proceedings of the Ninth International Meeting of the International Basal Ganglia Society, 2007, p. 76, Abstract P-025.
- [72] B.N. Nanda, A. Galvan, Y. Smith, T. Wichmann, Effects of high frequency stimulation of the centromedian nucleus of thalamus on neuronal activity in the

- monkey striatum, in: Proceedings of the Ninth International Meeting of the International Basal Ganglia Society, 2007, p. 134, Abstract P-129.
- [73] Z.G. Ni, D.M. Gao, A.L. Benabid, A. Benazzouz, Unilateral lesion of the nigrostriatal pathway induces a transient decrease of firing rate with no change in the firing pattern of neurons of the parafascicular nucleus in the rat, *Neuroscience* 101 (2000) 993–999.
- [74] A. Nieoullon, E. Scarfone, L. Kerkerian, M. Errami, N. Dusticier, Changes in choline acetyltransferase, glutamic acid decarboxylase, high-affinity glutamate uptake and dopaminergic activity induced by kainic acid lesion of the thalamostriatal neurons, *Neurosci. Lett.* 58 (1985) 299–304.
- [75] E. Palombo, L.J. Porrino, K.S. Bankiewicz, A.M. Crane, L. Sokoloff, I.J. Kopin, Local cerebral glucose utilization in monkeys with hemiparkinsonism induced by intracarotid infusion of the neurotoxin MPTP, *J. Neurosci.* 10 (1990) 860–869.
- [76] A. Parent, L.N. Hazrati, Functional anatomy of the basal ganglia. I. The cortico-basal-thalamo-cortical loop, *Brain Res. Rev.* 20 (1995) 91–127.
- [77] M. Parent, A. Parent, Single-axon tracing and three-dimensional reconstruction of centre median-parafascicular thalamic neurons in primates, *J. Comp. Neurol.* 481 (2005) 127–144.
- [78] A. Peppe, A. Gasbarra, A. Stefani, C. Chiavalon, M. Pierantozz, E. Ferri, P. Stanzione, C. Caltagirone, P. Mazzone, Deep brain stimulation of CM/PF of thalamus could be the new elective target for tremor in advanced Parkinson's disease? *Parkinsonism Relat. Disord.* (2008).
- [79] T.P.S. Powell, W.M. Cowan, A study of thalamo-striate relations in the monkey, *Brain* 79 (1956) 364–390.
- [80] D.V. Raju, D.J. Shah, T.M. Wright, R.A. Hall, Y. Smith, Differential synaptology of vGluT2-containing thalamostriatal afferents between the patch and matrix compartments in rats, *J. Comp. Neurol.* 499 (2006) 231–243.
- [81] D.V. Raju, T.H. Ahern, D.J. Shah, T.M. Wright, D.G. Standaert, R.A. Hall, Y. Smith, Differential synaptic plasticity of the corticostriatal and thalamostriatal systems in an MPTP-treated monkey model of parkinsonism, *Eur. J. Neurosci.* 27 (2008) 1647–1658.
- [82] D.V. Raju, Y. Smith, Differential localization of vesicular glutamate transporters 1 and 2 in the rat striatum, in J.P. Bolam, C.A. Ingham, P.J. Magill (Eds.), *The Basal Ganglia VIII*, Springer, New York, pp. 601–610.
- [83] R. Romo, A. Cheramy, M. Desban, G. Godeheu, J. Glowinski, GABA in the intralaminar thalamic nuclei modulates dopamine release from the two dopaminergic nigro-striatal pathways in the cat, *Brain Res. Bull.* 11 (1983) 671–680.
- [84] G.J. Royce, Single thalamic neurons which project to both the rostral cortex and caudate nucleus studied with the fluorescent double labeling method, *Exp. Neurol.* 79 (1983) 773–784.
- [85] T.M. Rudskin, A.F. Sadikot, Thalamic input to parvalbumin-immunoreactive GABAergic interneurons: organization in normal striatum and effect of neonatal decortication, *Neuroscience* 88 (1999) 1165–1175.
- [86] A.F. Sadikot, A. Parent, Y. Smith, J.P. Bolam, 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 (1992) 228–242.
- [87] A.F. Sadikot, A. Parent, C. Francois, Efferent connections of the centromedian and parafascicular thalamic nuclei in the squirrel monkey: a PHA-L study of subcortical projections, *J. Comp. Neurol.* 315 (1992) 137–159.
- [88] P. Salin, P. Kachidian, Thalamo-striatal deafferentation affects preproenkephalin but not preprotachykinin gene expression in the rat striatum, *Mol. Brain Res.* 57 (1998) 257–265.
- [89] D. Samuel, L. Kerkerian-Le Goff, U. Kumar, M. Errami, E. Scarfone, A. Nieoullon, Changes in striatal cholinergic, gabaergic, dopaminergic and serotonergic biochemical markers after kainic acid-induced thalamic lesions in the rat, *J. Neural Transm. Parkinsonian Dis. Dement. Sect. 2* (1990) 193–203.
- [90] D. Servello, M. Porta, M. Sassi, A. Brambilla, M.M. Robertson, Deep brain stimulation in 18 patients with severe Gilles de la Tourette syndrome refractory to treatment: the surgery and stimulation, *J. Neurol. Neurosurg. Psychiatry* 79 (2008) (2008) 136–142.
- [91] M. Sidibé, M.D. Bevan, J.P. Bolam, Y. Smith, Efferent connections of the internal globus pallidus in the squirrel monkey. I. Topography and synaptic organization of the pallidothalamic projection, *J. Comp. Neurol.* 382 (1997) 323–347.
- [92] M. Sidibe, J.F. Pare, D.V. Raju, Y. Smith, Anatomical and functional relationships between intralaminar thalamic nuclei and basal ganglia in monkeys, in: L.F.B. Nicholson, R.L.M. Faull (Eds.), *The Basal Ganglia VII*, Kluwer Academic/Plenum, New York, 2002, pp. 409–420.
- [93] M. Sidibe, J.F. Pare, Y. Smith, Nigral and pallidal inputs to functionally segregated thalamostriatal neurons in the centromedian/parafascicular intralaminar nuclear complex in monkey, *J. Comp. Neurol.* 447 (2002) 286–299.
- [94] M. Sidibe, Y. Smith, Differential synaptic innervation of striatofugal neurones projecting to the internal or external segments of the globus pallidus by thalamic afferents in the squirrel monkey, *J. Comp. Neurol.* 365 (1996) 445–465.
- [95] M. Sidibé, Y. Smith, Thalamic inputs to striatal interneurons in monkeys: synaptic organization and co-localization of calcium binding proteins, *Neuroscience* 89 (1999) 1189–1208.
- [96] R.M. Smeal, R.C. Gaspar, K.A. Keefe, K.S. Wilcox, A rat brain slice preparation for characterizing both thalamostriatal and corticostriatal afferents, *J. Neurosci. Methods* 159 (2007) 224–235.
- [97] A.D. Smith, J.P. Bolam, The neural network of the basal ganglia as revealed by the study of synaptic connections of identified neurons, *Trends Neurosci.* 13 (1990) 259–265.
- [98] Y. Smith, B.D. Bennett, J.P. Bolam, A. Parent, A.F. Sadikot, Synaptic relationships between dopaminergic afferents and cortical or thalamic input at the single cell level in the sensorimotor territory of the striatum in monkey, *J. Comp. Neurol.* 344 (1994) 1–19.
- [99] Y. Smith, A. Parent, Differential connections of caudate nucleus and putamen in the squirrel monkey (*Saimiri sciureus*), *Neuroscience* 18 (1986) 347–371.
- [100] Y. Smith, D.V. Raju, J.F. Pare, M. Sidibe, The thalamostriatal system: a highly specific network of the basal ganglia circuitry, *Trends Neurosci.* 27 (2004) 520–527.
- [101] B. Stephens, A.J. Mueller, A.F. Shering, S.H. Hood, P. Taggart, G.W. Arbuthnott, J.E. Bell, L. Kilford, A.E. Kingsbury, S.E. Daniel, C.A. Ingham, Evidence of a breakdown of corticostriatal connections in Parkinson's disease, *Neuroscience* 132 (2005) 741–754.
- [102] Y.D. Van der Werf, M.P. Witter, H.J. Groenewegen, The intralaminar and midline nuclei of the thalamus. Anatomical and functional evidence for participation in processes of arousal and awareness, *Brain Res. Rev.* 39 (2002) 107–140.
- [103] R.M. Villalba, H. Lee, D.V. Raju, Y. Smith, Striatal dopaminergic denervation and spine loss in MPTP-treated monkeys, in H.J. Groenewegen, H.J. Berendse (Eds.), *The Basal Ganglia IX*, Springer, New York, in press.
- [104] V. Visser-Vandewalle, Y. Temel, P. Boon, F. Vreeling, H. Colle, G. Hoogland, H.J. Groenewegen, C. van der Linden, Chronic bilateral thalamic stimulation: a new therapeutic approach in intractable Tourette syndrome. Report of three cases, *J. Neurosurg.* 99 (2003) 1094–1100.
- [105] C. Vogt, O. Vogt, Thalamusstudien I–III. I. Zur Einföhrung, II. Homogenität und Grenzgestaltung der Grisea des Thalamus, III. Griseum centrale (centrum medianum Luys), *J. Physiol. Neurol. Lpz.* 50 (1941) 31–154.
- [106] Z. Wang, L. Kai, M. Day, J. Ronesi, H.H. Yin, J. Ding, T. Tkatch, D.M. Lovinger, D.J. Surmeier, Dopaminergic control of corticostriatal long-term synaptic depression in medium spiny neurons is mediated by cholinergic interneurons, *Neuron* 50 (2006) 443–452.
- [107] R. Weigel, J.K. Krauss, Center median-parafascicular complex and pain control. Review from a neurosurgical perspective, *Stereotact. Funct. Neurosurg.* 82 (2004) 115–126.
- [108] J. Zackheim, E.D. Abercrombie, Thalamic regulation of striatal acetylcholine efflux is both direct and indirect and qualitatively altered in the dopamine-depleted striatum, *Neuroscience* 131 (2005) 423–436.