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Yoland Smith, Emory University
Dinesh Raju, Emory University
Biji Nanda, Emory University
Jean-Francois Pare, Emory University
Adriana Galvan, Emory University
Thomas Wichmann, Emory University

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The Thalamostriatal Systems: Anatomical and Functional Organization in Normal and Parkinsonian States

Yoland Smith, Dinesh Raju, Bijli Nanda, Jean-François Pare, Adriana Galvan, and Thomas Wichmann

1Yerkes National Primate Research Center Emory University, Atlanta, GA 30329, USA
2Department of Neurology, Emory University, Atlanta, GA 30329, USA

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.

Keywords

Parkinson's disease; thalamus; striatum; glutamate transporter; synaptic plasticity
INTRODUCTION

Vogt and Vogt [94] first suggested the existence of the thalamostriatal system, but the pioneering data of Powell and Cowan [69] 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) [20a], 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 the nonhuman 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 [25,26,40,58,59,66,88,91].

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 [9,11,16,17,19,25,45,56-59,66,67,70,73-75,87,88]. The topography of thalamostriatal projections in rats has been studied in detail, and has been summarized in previous reviews [25,88]. 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 (CMI) 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) [88].

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 [88]. In primates, it has recently been emphasized that a significant non-intralaminar source of thalamostriatal projections originates from the ventral motor thalamic nuclei [26,56,57,88]. 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 [57]. Several other thalamic nuclei have been recognized as potential sources
of thalamostriatal projections in nonhuman primates [87], but details on the topography and intrastriatal arborization of these projections is scarce and will not be discussed further in this review (see ref. 88 for details).

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 striatum and the cerebral cortex, while thalamostriatal and thalamocortical neurons are largely segregated in the caudal intralaminar CM/Pf nuclear complex [25,73,88]. 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 [88], 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 [16]. 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 [17]. The projection pattern of individual CM neurons is different and more complex in nonhuman primates [67]. 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 [67]. 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 1,2).

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 [18,70,74,82,88], although a small subset of neurons in the rat Pf appears to preferentially target dendritic spines [45]. Both “direct and indirect” striatofugal neurons are contacted by CM/Pf projections [11, 46,82], 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) [82]. 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 P mRNA expression in direct pathway neurons [4],
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
[48,60,83]. In rats, parvalbumin-containing GABAergic interneurons are devoid of Pf inputs
[73a], suggesting a possible species difference in the thalamic regulation of these ‘fast spiking’
interneurons between primates and rats [88]. 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 [64b,98; 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 [86]. 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 [64a,70]. 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
[5,85].

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 [38,65], and
increase striatal dopamine uptake [77] and dopamine D2-receptor density [39]. Infusion of
GABA into the cat CM/Pf reduces dopamine release [72]. 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 [12], while others show increased striatal
dopamine utilization (without changing dopamine levels) in rats [39]. 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 [22,55]. However, since fiber-sparing Pf lesions also
affect striatal dopaminergic functions [37,38], 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 [34,35]. The thalamostriatal projection from CM/Pf may also play roles in
dopamine D1-receptor-mediated stimulation of striatal acetylcholine release [13] and c-fos
gene expression [24]. CM/Pf inputs may also modulate striatal D2-receptor mediated long term
depression [95].

Several studies have also described effects of CM/Pf interventions on striatal serotonergic
transmission [8,77]. As described below, CM/Pf stimulation decreases acetylcholine, but
increases GABA release in rat and monkey striatum [64b,98]. 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 [50,51].
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 [44,70, 71,71a], 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 [6,7,7a]. 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 nonprimates: 70% of the vGluT2-positive boutons contact dendritic spines in rats, whereas only about 50% do so in the monkey striatum [70]. 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 [70]. 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 [21,70]. 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 [74,88]. 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 [44,71]. Although vGluT3 is expressed in the striatum, it is mainly found in non-glutamatergic terminals and post-synaptic dendrites [20,24a], thereby cannot account for the vGluT1-/vGluT2-negative striatal terminals described above.

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 [71]. 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 [71]. These findings have been recently confirmed in postmortem human brain tissue showing vGluT1 protein increase in the putamen of patients with Parkinson's disease [36]. At first glance, these observations are at odds with evidence for significant loss of spines in the striatum of MPTP-treated parkinsonian monkeys [92], 6-OHDA-treated rats [32,33] and human PD patients [89]. 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 [71]. 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).

**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 [81]. 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 [25,79,82,88] (Fig. 1). In monkeys, functionally segregated outputs from GPi largely innervate different regions of CM/Pf [79,88], 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 prefrontal nuclei [58], 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 [80,88]. 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 [41].

**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 [40,61,62,88], 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 [41]. Two main functional characteristics of CM/Pf neurons have been identified in monkeys. First, CM/Pf neurons have multimodal properties, i.e., 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 [61,62]. 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 [40,61,62,88]. 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 [62]. For instance, a majority of CM neurons fire when a small-reward action is required, but a large-reward option
is anticipated [62]. 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 [1,13a, 54]. 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 TANs in response to sensorimotor conditioning [40,54,88]. 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 [40,54,88]. 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 [13a,62].

**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 [64b]. All striatal cells tested in this study responded to burst stimulation (100 Hz, 1 sec, 100-175 μA) of the CM with a delay of tens of milliseconds after the onset of the stimulation trains. Phasically 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 [64b].

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 [84, see also 13, 24]. These preliminary observations also suggested interesting differences in short term plasticity and probability of neurotransmitter release between corticostriatal and thalamostriatal projections [17a;84]. 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 [17b].

**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 [27,28,29]. In parkinsonian patients, subpopulations of parvalbumin-containing neurons are mainly affected in Pf, while in CM non-parvalbumin/non-calbindin neurons are specifically targeted [29]. 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 three months after nigrostriatal dopaminergic lesion, another recent study demonstrated more than 50% loss of Pf neurons projecting to the dopamine-depleted striatum.
one month after the lesion [28,29]. Systemic MPTP administration also induces significant loss of midline and intralaminar nuclei in mice [20b]. Recent imaging data reported significant changes in the shape, but not the volume, of thalami between parkinsonian patients and controls [58a].

**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 [64c], while MPTP exposure in monkeys leads to small changes in glucose utilization in CM/Pf [65a]. A significant reduction in GABA level has been measured in postmortem CM/Pf tissue of patients with Parkinson's disease [23]. 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 [2,52].

**NEUROSURGICAL THALAMIC INTERVENTIONS FOR BRAIN DISEASES**

Neurosurgical treatment have long been aimed at the thalamus to treat movement disorders and other diseases. 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.

Hassler and Riechert first reported the use of thalamic lesions as treatment for rigidity and tremor in Parkinson's disease [26a]. 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 1960's. Due to the realization that drug therapy may have significant side effects, these procedures were largely abandoned in the 1970s and 80s, 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 [10,10a]. In older studies, CM/Pf-DBS appears to have specifically anti-dyskinetic effects [42], but more recently [55a], 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 [68].

CM/Pf-DBS is also an effective treatment for Tourette's syndrome [63,93] being effective in reducing the quantity and intensity of tics by 70-90%, and also significantly reduce the psychiatric symptoms of the disease [31,63,78].

**References**


73. Royce GJ. Single thalamic neurons which project to both the rostral cortex and caudate nucleus studied with the fluorescent double labeling method. Exp. Neurol 1983;79:773–784. [PubMed: 6297952]


Brain Res Bull. Author manuscripts; available in PMC 2010 February 16.


92. Villalba, RM.; Lee, H.; Raju, DV.; Smith, Y. Striatal dopaminergic denervation and spine loss in MPTP-treated monkeys. In: Groenewegen, HJ.; Berendse, HJ., editors. The Basal Ganglia IX. Springer; New York: in press


Brain Res Bull. Author manuscript; available in PMC 2010 February 16.
Figure 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 (CMl) 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 gangliathalamostriatal loops that involve various regions of the striatum, GPi/SNr and CM/PF. [See references 79,81,88 for more details]
Figure 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 references 67,88 for more details).
Figure 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 references 70 and 71a for more details].
Figure 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 reference 64b for more details].
## Table 1
Summary of key differences between the thalamostriatal systems that originate from CM/Pf versus other thalamic nuclei.

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

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