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On the relationships between the caudal intralaminar nuclei of the thalamus and the basal ganglia: Implications for the pathophysiology of Parkinson's disease

José L. Lanciego, María Castle, Pedro Barroso-Chinea and María S. Aymerich
Basal Ganglia Neuromorphology Lab, Neurosciences Division, Center for Applied Medical Research (CIMA), University of Navarra Medical College Pamplona, Spain

Abstract

Besides corticostriatal projections, the thalamic intralaminar nuclei are a major source of glutamatergic afferents reaching the basal ganglia input nuclei. Although the thalamostriatal system is already well characterized from the anatomical point of view, the role to be played by

Correspondence/Reprint request: Prof. José L. Lanciego, Basal Ganglia Neuromorphology Lab, Neuroscience Division, Center for Applied Medical Research, University of Navarra, Pio XII Avenue 55, 31008 Pamplona Spain. E-mail: jlanciego@unav.es

this pathway within basal ganglia function (both in normal and pathological conditions) remains poorly understood. On one hand, neurode- generation phenomena restricted to the caudal intralaminar nuclei have been described in several neurodegenerative disorders such as Parkinson's disease, progressive supranuclear palsy and Huntington's disease. On the other hand, after unilateral dopaminergic depletion in rodents the caudal intralaminar nuclei are highly hyperactive. Indeed, the chemical ablation of the caudal intralaminar nuclei prevents the increase of the activity observed in both the basal ganglia output nuclei and the subthalamic nucleus (STN) after unilateral dopaminergic depletion. These findings suggest that the caudal intralaminar nuclei might be responsible (at least partially) for the changes in activity of the STN and basal ganglia output nuclei typically seen under circumstances of dopamine removal. These results paved the way for the implementation of pioneer clinical experiences focused on targeting the caudal intralaminar nuclei with a deep brain stimulation electrode in patients suffering from advanced Parkinson's disease. This approach resulted in the alleviation of cardinal symptoms of the disease such as resting tremor, drug-induced dyskinesias and chronic pain.

Introduction

The basic principles behind basal ganglia function and anatomical organization are summarized in the "classical" basal ganglia model introduced at the beginning of the '90s [1-3]. Since then, the basal ganglia model has became widely accepted by the scientific community and has led to a reappraisal of surgical-based therapies for movement disorders of basal ganglia origin [4]. Although somewhat simplistic, this model represents the main basis for the modern knowledge of the basal ganglia function, both in normal circumstances and under pathological conditions. During the past two decades, an overwhelming number of new physiological and anatomical data have been made available, and therefore the basal ganglia model has been updated by integrating the incoming new experimental evidence [5]. Although the main skeleton of the basal ganglia model remains largely preserved, the updated basal ganglia model has gained increased complexity over the past few years.

Briefly, the model is based on the arrival of dopaminergic afferents arising from the substantia nigra pars compacta (SNc) to the striatum. At the striatal level, dopamine (DA) reaches two different subpopulations of efferent neurons. All the striatofugal neurons are GABAergic neurons and express different types of DA receptors. Striatofugal neurons expressing D1 receptor reach the basal ganglia output nuclei -namely the internal division of the globus pallidus (GPi) and the substantia nigra pars reticulata (SNr)- through a monosynaptic pathway and therefore this pathway has been called the "direct pathway". By contrast, striatofugal neurons expressing D2 receptors innervate

the external division of the globus pallidus (GPe), which in turn project to the subthalamic nucleus (STN). Glutamatergic STN neurons innervate both the GPi and SNr. This polysynaptic pathway linking successively the striatum, GPe, STN and GPi/SNr is named the “indirect pathway”. Both the direct and the indirect pathways converge onto the output nuclei, which in turn project to the thalamus. An appropriate balance between the direct and the indirect pathways results in properly conducted movements, whereas the removal of DA from the system provokes an imbalance between both pathways, which is ultimately responsible for the typical symptoms that characterize movement disorders of basal ganglia origin. The information flow coming from the cortex across the basal ganglia, the thalamus and back again to the cortex is funneled through five separate, segregated loops [6,7].

As stated above, the current model of basal ganglia function is somewhat simplistic and incoming new evidences deserve particular attention, requiring to be further accommodated within the model. Firstly, DA is supposed to exert an excitatory effect onto striatal neurons expressing D1 receptor (the ones giving rise to the direct pathway) and an inhibitory effect towards striatal neurons with D2 receptors (the ones originating the indirect pathway). Such a dual effect of DA on striatofugal neurons is one of the cornerstones of the basal ganglia model. It is hard to conciliate this reasoning with new data showing that most of the striatofugal neurons in fact contain both D1 and D2 receptors [8-11] and therefore instead of inducing a net excitatory or inhibitory effect on the striatofugal neurons, DA is currently seen as a modulator of the interaction between glutamate (GLU) and DA receptors at the striatal level [12]. Secondly, efferent neurons located in almost all the basal ganglia nuclei are characterized by reaching multiple targeted areas through multiple axon collaterals [13] and therefore delineating a complex network connecting different basal ganglia structures. Thirdly, it is hard to maintain a role for the GPe as a simple relay station between the striatum and the STN. In fact, the GPe, GPi and STN could be seen as the vertices of a triangle closely interconnected, and this triangle is a key “inside” network modulating basal ganglia function [14-16]. Fourthly, there is overwhelming evidence showing that the basal ganglia nuclei other than the striatum (such as GPe, GPi and STN) also receive a direct DAergic innervation from the SNc and the ventral tegmental area (VTA). This pathway is known as the nigroextrastriatal projection [17-20]. The net effect of the dopamine on both the nigropallidal and nigrosubthalamic pathways is apparently mediated by D1 and D2 receptors [21-23]. Finally, it is worth noting that transverse circuits directly connecting the thalamus with both the striatum and the STN (thalamostriatal and thalamosubthalamic pathways) have been largely neglected in most of the studies carried out so far in basal ganglia circuitry.

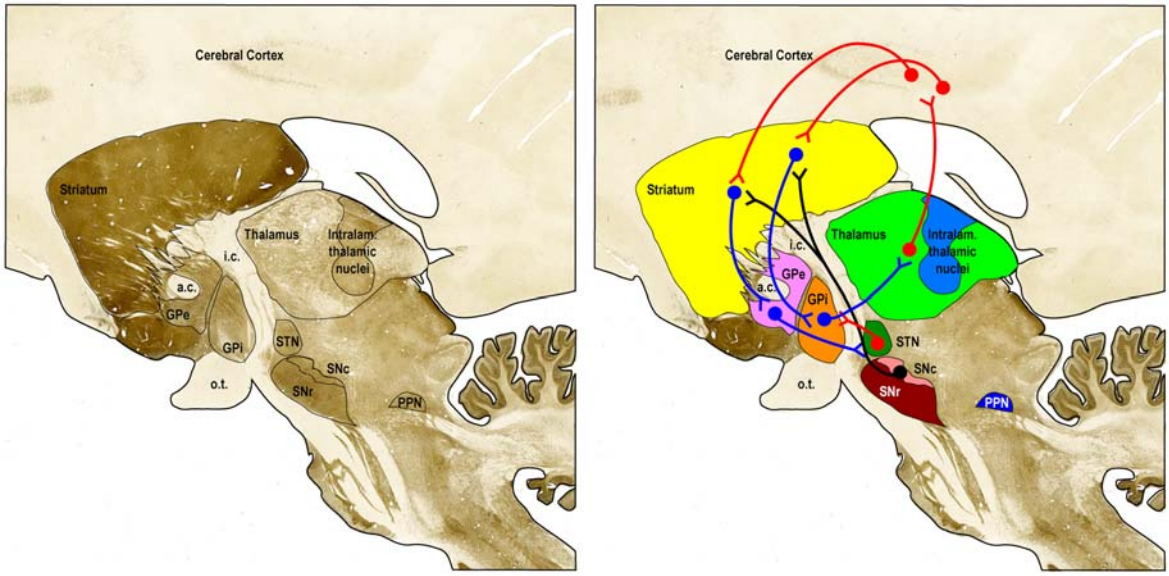

Figure 1. Sagittal sections of the brain of *Macaca fascicularis* stained for acetylcholinesterase showing the localization of the different basal ganglia nuclei (Left). The panel in the right illustrates the different nuclei of the basal ganglia (color-coded) together with the basic circuits linking the basal ganglia, according to the "classic" model of basal ganglia function. Abbreviations: external division of the globus pallidus (GPe), internal division of the globus pallidus (GPi), pedunculopontine nucleus (PPN), substantia nigra pars compacta (SNc), substantia nigra pars reticulata (SNr), subthalamic nucleus (STN), anterior commissure (a.c.), internal capsule (i.c.), optic tract (o.t.).

The present chapter is focused on the position of the caudal intralaminar nuclei within the basal ganglia circuits. This review summarizes the current knowledge on the thalamic modulation of the basal ganglia function both in normal conditions and under circumstances of DA depletion. Emphasis will be made in integrating anatomical and physiological data together with pioneer surgical experiences.

Brain circuits linking the caudal intralaminar nuclei with the basal ganglia

Thalamostriatal projections

Initial data describing the presence of a thalamostriatal pathway were provided by Vogt and Vogt [24] and further confirmed by Powell and Cowan [25]. The caudal intralaminar nuclei of the thalamus are known to be one of the major sources of afferents reaching the striatum [26-39]. Thalamostriatal projections arising from the caudal intralaminar nuclei are known to be excitatory (mediated by GLU) and are characterized by containing the vesicular GLU transporter isoform 2 [40,41]. Both types of striatal efferent neurons are approached by thalamic afferents [42] and therefore these afferents

may exert a widespread excitatory influence on striatofugal neurons [43-46]. Indeed, a closed loop linking successively thalamostriatal afferents reaching striatal neurons, which in turn innervate neurons in the output nuclei and then project back again to the thalamus through the pallidothalamic pathway has been characterized and named as the "Nauta-Mehler loop" [47]. Besides targeting striatofugal neurons, thalamostriatal afferents also innervate different subtypes of striatal interneurons [36,48-54]. Although the intralaminar nuclei are the main sources of glutamatergic thalamic inputs to the striatum [55], other thalamic nuclei including the midline, the principal relay and the association thalamic nuclei are also important contributors to the thalamostriatal pathway [56-63]. Within these nuclei, thalamostriatal projections are most likely to be collaterals of thalamocortical projections. Nevertheless, when considering the caudal intralaminar nuclei, thalamostriatal and thalamocortical projections mainly arise from segregated subpopulations of efferent neurons [29,64,65]. At the striatal level, corticostriatal and thalamostriatal axons innervate different postsynaptic structures. Axons coming from the cortex form asymmetric synapses onto the head of the dendritic spines of the striatal medium-spiny neurons (MSN) whereas thalamostriatal afferents coming from the caudal intralaminar nuclei displayed a marked tendency for making excitatory contacts in the dendritic shafts of MSNs [29,53,55,66]. In primates, MSNs projecting to the GPi are known to be the preferential postsynaptic target for thalamostriatal projections, whereas MSNs originating the indirect pathway became less innervated by glutamatergic axons from thalamic sources [39,53]. By contrast, in the rodent thalamostriatal system both kinds of MSNs neurons are innervated by axons arising from the caudal intralaminar nuclei [37,67-69].

Thalamosubthalamic projections

A substantial thalamic innervation arising from the caudal intralaminar nuclei is directed towards the STN. Thalamosubthalamic projections have been reported in rats, cats and primates [29,37,67,69,70-73]. The thalamosubthalamic projections are topographically organized, since motor-related areas of the STN are innervated by afferents arising from the motor parts of the caudal intralaminar nuclei, whereas the limbic areas of the caudal intralaminar nuclei project to the limbic-related territories of STN [29,67] in both primates and rats. Thalamosubthalamic projections are driven by GLU and are excitatory [74,75]. Neurons originating the thalamostriatal and the thalamosubthalamic projections remain largely segregated within the caudal intralaminar nuclei [32] although there is a subpopulation of thalamostriatal-projecting neurons that also innervates the STN through axon collaterals [34]. Most of the STN efferent neurons innervate both the SNr and GPi [13,76-80]. All kinds of STN efferent neurons are massively innervated by thalamic afferents [69].

It is also well known that the caudal intralaminar nuclei exert a bilateral modulation of the STN, e.g. the activity of the one STN nucleus is somewhat modulated by afferents coming from the ipsilateral thalamus as well as by crossed projections arising from the contralateral caudal intralaminar nuclei. Electrophysiological recordings obtained after unilateral drug-induced stimulation or inhibition showed opposite changes in the ipsi- and contralateral STNs [75]. The anatomical substrate sustaining this bilateral control of STN by the caudal intralaminar nuclei has been recently demonstrated, by showing that although the ipsilateral thalamic innervation of the STN is by far the most prominent one, several fibers arising from the caudal intralaminar nuclei also reach the contralateral STN [69].

Besides corticosubthalamic projections, thalamic axons reaching the STN are one of the main suppliers of glutamatergic inputs to the STN. Recent studies carried out after unilateral DAergic depletion in rats have demonstrated that neurons in the caudal intralaminar nuclei innervating the STN are highly hyperactive [81,82]. These studies have paved the way for considering the

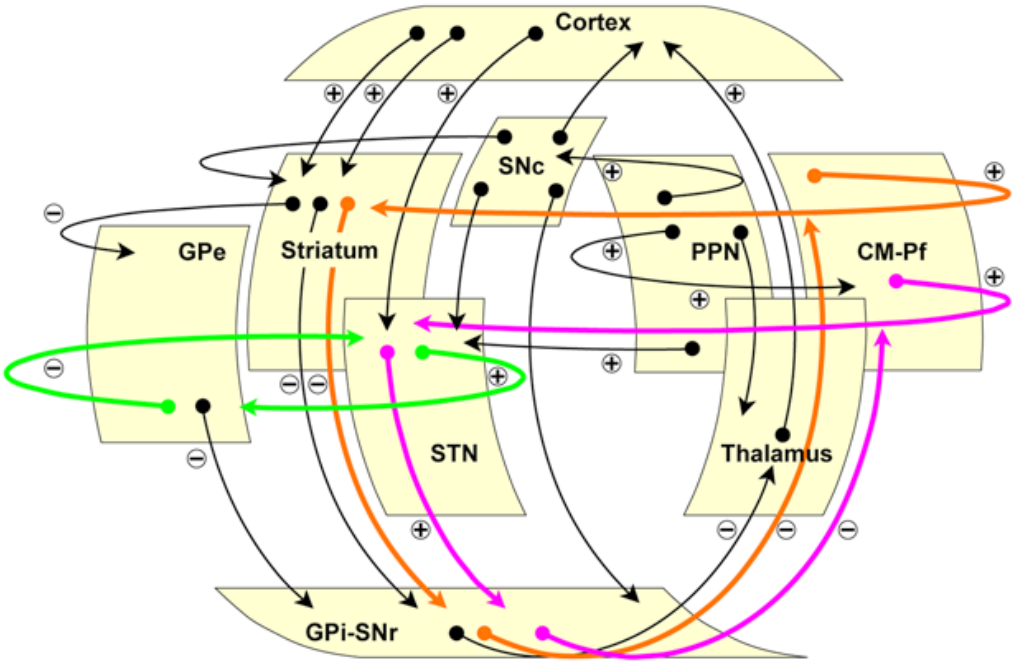

Figure 2. The position of the caudal intralaminar nuclei in basal ganglia circuitry (modified after ref. #85). Two major transverse loops summarize the influence exerted by the caudal intralaminar nuclei on basal ganglia circuits. The "Nauta-Mehler loop" (illustrated in orange color) links successively the caudal intralaminar nuclei (CM-Pf complex), the striatum, the output nuclei and back to the CM-Pf complex. A second loop (drawn in purple) comprises thalamosubthalamic projections linked to subthalamofugal projections reaching the output nuclei and then back to CM-Pf. Another transverse loop (illustrated in green) comprises the circuits linking STN/GPe/STN, although the significance of this loop is beyond the focus of the present review.

caudal intralaminar nuclei as a potential candidate explaining –at least partially- the increases in activity that are typically observed in the STN after DA removal, as will be explained later on in this review.

Thalamopallidal projections

Thalamic axons can also gain access to the globus pallidum and the SNr [38,73,83,84]. Most of the thalamic afferents reaching the globus pallidum are collaterals from the thalamostriatal projection [84]. Finally, it is also worth noting that the thalamopallidal projection exhibits a clear topographic pattern of distribution parallel to thalamostriatal projections [84].

Increased activity of the caudal intralaminar nuclei after dopamine depletion

The well-known hyperactivity of the STN after DA depletion is one of the main cornerstones of the basal ganglia model. The model explains the STN increased activity as a consequence of decreased inhibition received from GPe neurons, the latter due to an increased GABAergic striatopallidal outflow as a result of the removal of DA reaching striatofugal neurons originating the indirect pathway [1-3]. Despite this reasoning, there is a growing body of evidence suggesting that STN hyperactivity might depend on mechanisms other than reduced inhibition coming from GPe. For example, model predictions are challenged by studies measuring the metabolic activity of GPe in both rats and primates by using the messenger encoding for the subunit I of cytochrome oxidase (CO-I) as a marker for activity. These studies have found increased activity –instead of decreased- in GPe after DA depletion [86]. Electrophysiological recordings within the STN and GPe in MPTP-treated primates have shown an increased activity of the STN –as expected- together with no variations in the GPe activity [87]. Additional data difficult to accommodate within the model are the lack of induction of dyskinesias in control animals after a GPe blockade [88] as well as the failure to abolish levodopa-induced dyskinesias in MPTP-treated monkeys after performing a GPe lesion [89]. Furthermore, STN hyperactivity is an early phenomenon within the cascade of events taking place after dopamine depletion [90,91]. Overall, these data suggested that the reduced GABA levels coming from GPe could not be the only explanation for STN hyperactivity.

At this point, it is worth noting that the caudal intralaminar nuclei –together with the pedunculopontine nucleus- could be seen as an attractive candidate for explaining the increased STN activity after dopaminergic removal. With regard to this, recent studies carried out in rodents have demonstrated that the neurons within the caudal intralaminar nuclei innervating the STN displayed a clear increase in their activity under circumstances of DAergic depletion [81,82].

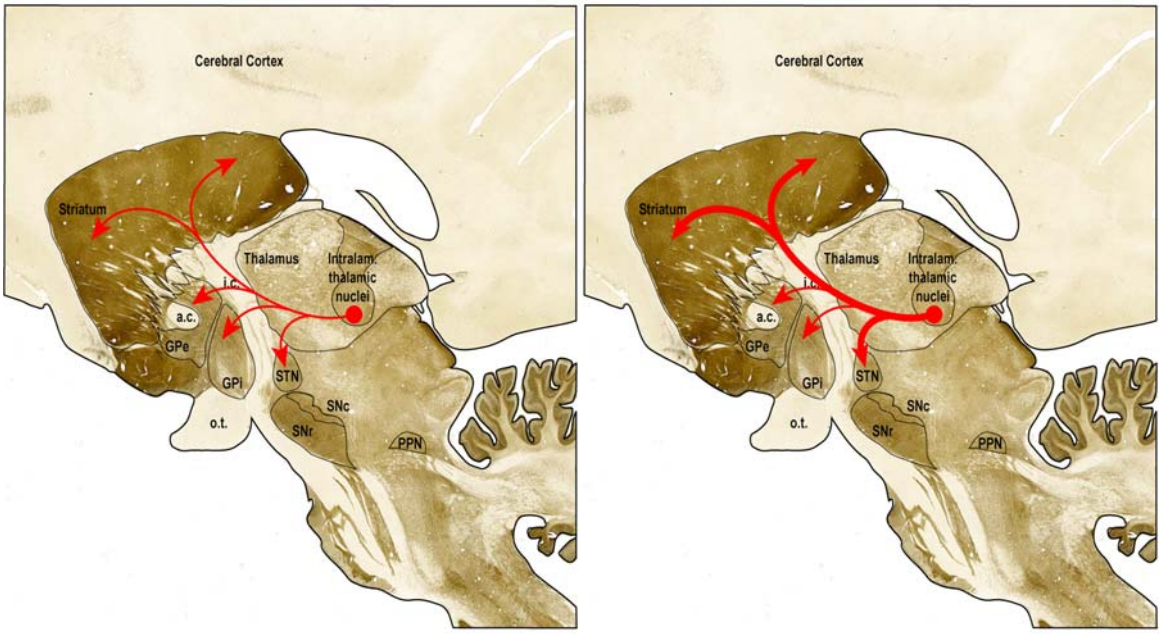

Figure 3. Sagittal sections of the brain of *Macaca fascicularis* stained for acetylcholinesterase showing a summary of the main pathways linking the CM-Pf complex of the thalamus with the basal ganglia nuclei, both in normal conditions (Left) as well as under circumstances of dopaminergic depletion (Right). Both the thalamostriatal and the thalamosubthalamic projections are highly hyperactive in Parkinson's disease (see refs. #41 and #81, respectively). The activity of the brain circuits linking CM-Pf with both segments of the globus pallidus after dopamine removal has not been elucidated. Abbreviations: external division of the globus pallidus (GPe), internal division of the globus pallidus (GPi), pedunculopontine nucleus (PPN), substantia nigra pars compacta (SNc), substantia nigra pars reticulata (SNr), subthalamic nucleus (STN), anterior commissure (a.c.), internal capsule (i.c.), optic tract (o.t.).

These findings led to the design of pioneer surgical experiments lesioning the caudal intralaminar nuclei. Lesions performed in control rats with normal DA levels showed a deep impact on the activity of almost all basal ganglia nuclei [92]. Observed changes are in agreement with the removal of direct glutamatergic innervation. When considering rats with a unilateral depletion of DA, the lesion of the caudal intralaminar nuclei is highly effective in preventing the increase on the activity typically observed in both the STN and the output nuclei of the basal ganglia [68].

Besides the increased activity of the thalamosubthalamic projections after DA depletion, our group has recently demonstrated that this might also be the case for the thalamostriatal pathway [40,41]. Using the mRNA expression of vGlut2 and CO-I as measured by real-time PCR as markers for activity, we have found a marked increase on the expression for both mRNAs within thalamostriatal-projecting neurons in the caudal intralaminar nuclei on the side of the brain depleted with DA when compared to the contralateral side

(a three-fold increase on the expression for vGlut2 mRNA and a two-fold increase on the expression for CO-I mRNA). In summary, both the thalamostriatal and the thalamosubthalamic pathways are highly hyperactive after DAergic depletion. Since both pathways are glutamatergic, there is a situation of GLU overflow arising from the caudal intralaminar nuclei and reaching most of the key structures of the basal ganglia under circumstances of DA removal.

Degeneration of the caudal intralaminar nuclei in neurodegenerative diseases

The existence of a primary, non-DAergic neurodegeneration restricted to the caudal intralaminar nuclei (CM-Pf complex) in Parkinson's disease has been recently demonstrated by a group of neuropathologists from Sydney University [93,94]. A marked degeneration estimated at an average of 50% of cell loss has been found in the CM-Pf complex in brains coming from necropsies of patients suffering from Parkinson's disease when compared with age-matched controls. This was the first time in which degeneration phenomena in Parkinson's disease has been documented outside the DAergic cells in the mesencephalon. Similar degeneration phenomena in the CM-Pf complex have also been reported in other neurodegenerative disorders of the basal ganglia such as the progressive supranuclear palsy [94] and Huntington's disease [95,96]. When considering animal models of Parkinson's disease, a marked degeneration within the intralaminar nuclei was found both in MPTP-treated mice [97] and after the delivery of MPP+ in the striatum of 6-OHDA-treated rats [98]. The observed degeneration is apparently selective for thalamostriatal-projecting neurons within the caudal intralaminar nuclei [41], while the thalamosubthalamic-projecting neurons appeared to be less vulnerable [81]. Overall, cell loss is estimated at an average of 70% within thalamostriatal-projecting neurons in rats [41].

One of the most important issues here is to ascertain whether thalamic degeneration is a phenomenon appearing before or after the degeneration of the SNc, as well as to analyze the relationships between both kinds of cell loss, if such exists. Thalamic degeneration in CM-Pf is a phenomenon already present in the earlier stages of Parkinson's disease (Hoehn and Yahr's stages 2-3) and remains without apparent changes until stage 5 and therefore the cell loss observed in CM-Pf complex cannot be taken as an end-stage phenomenon [99]. Indeed, data coming from behavioral studies carried out after chemical lesion of the caudal intralaminar nuclei in rats treated with 6-OHDA did not support the idea that thalamic degeneration is a retrograde change to DAergic depletion [99]. Data available suggest that both thalamic and nigral degeneration are different phenomena co-existing with each other and without

apparent relationship. Nevertheless, there may be another way of explaining thalamic degeneration, such as the one suggested by a group of British researchers indicating that thalamic nerve cell loss in neurodegenerative disorders such as Parkinson or Alzheimer is likely to be an age-related phenomenon instead of disease-related [100].

The caudal intralaminar nuclei as a potential surgical target for movement disorders of basal ganglia orgin

The increased activity of the STN under circumstances of dopaminergic depletion is one of the main cornerstones of the basal ganglia model and has led to the reappraisal of functional neurosurgical therapies approaching the STN as the best target to alleviate most of the motor symptoms that typically characterize Parkinson's disease [4]. Several experimental evidences have suggested that the caudal intralaminar nuclei are likely to play a key role sustaining STN hyperactivity. Firstly, the thalamosubthalamic projection is highly hyperactive in 6-OHDA-depleted rats [81,82]. Secondly, the hyperactivity of the STN that typically appears in 6-OHDA-treated rats is reverted to baseline levels after performing a chemical ablation of the caudal intralaminar nuclei [68]. In summary, the increased activity of the STN is currently seen as the result of reduced levels of GABA received from GPe together with an increased glutamatergic outflow from the caudal intralaminar nuclei. These results pave the way for reconsidering CM-Pf as a potential surgical target in Parkinson's disease, in an attempt to decrease the glutamatergic overflow reaching the STN after DAergic removal.

Pioneer clinical experiences were initially carried out by Benabid's group in France in a series of parkinsonian patients subjected to deep brain stimulation (DBS) targeting the ventral intermediodorsal thalamic nuclei (Vim). The best results were obtained in those patients in which the electrode was placed in CM-Pf instead of Vim [101-103]. Later on, a group of German neurosurgeons demonstrated that DBS in CM-Pf is highly successful in alleviating cardinal symptoms of Parkinson's disease such as resting tremor and levodopa-induced dyskinesias [104-105]. This approach (DBS in CM-Pf) also has beneficial effects for the treatment of severe forms of Tourette's syndrome [106] as well as in patients suffering from chronic pain [104,105]. Nevertheless, it is important to keep in mind that we are dealing with a brain target that is undergoing severe degeneration phenomena. In regards to this, a case report showed a clear deterioration of the contralateral bradykinesia and rigidity in one patient treated with DBS in CM-Pf [107].

Although we consider that there is a clear rationale supporting the CM-Pf as a promising target for surgical therapies of movement disorders, pioneer clinical experiences exhibited differential outcomes, ranging from a clear benefit to a marked worsening of parkinsonian symptoms. Different clinical results probably reflect variations in electrode placement within different territories of CM-PF. At this point we conclude that although initially very promising data were obtained, more research efforts in relevant animal models of Parkinson's disease such as the MPTP primate model are needed in order to better address the usefulness of this target for the treatment of movement disorders of basal ganglia origin.

Looking for a role to be played by the caudal intralaminar nuclei on the plasticity of striatal microcircuits

During the past few years, the study of DA-GLU interactions at the level of the MSNs has gained increased attention. The repetitive stimulation of the corticostriatal fibers resulted in a massive release of GLU and DA in the striatum, inducing either long-term potentiation (LTP) or long-term depression (LTD) of the excitatory synaptic transmission depending on the involvement of different subtypes of GLU receptors [108]. The corticostriatal synaptic plasticity is seriously compromised after DAergic depletion, requiring the stimulation of DARPP-32 (a small protein presented in high levels in MSNs in dyskinetic rats) [109]. In conclusion, the appearance of levodopa-induced dyskinesias is related to the abnormal synaptic functioning of the corticostriatal transmission [109-112].

At the anatomical level, corticostriatal afferents synapse onto the head of the spines of the MSNs, whereas thalamostriatal afferents exhibit a marked preference for contacting dendritic shafts of MSNs [55,113]. DAergic nigrostriatal afferents make synapses with either the head or the neck of the spines of the MSNs, or with the dendritic shaft of MSNs. This microcircuitry was revisited later on, and the current knowledge accepts that both thalamostriatal and corticostriatal afferents make synapses with the head of the spines of the MSNs, whereas the thalamostriatal afferents coming from the caudal intralaminar nuclei are the only ones contacting the dendritic shafts of MSNs. Regarding the DAergic nigrostriatal innervation, the preferred postsynaptic target for these afferents is the neck of the spines of the MSNs [39,114].

The appearance of plastic changes on the spines of the neuronal dendrites is widely documented in the basal ganglia and in Parkinson's disease. Increases of up to 30% in spine density have been reported in MSNs at the striatal level in rats housed over time in a stimulus-rich environment [115]. Normal aging resulted in a marked decrease on spine density in cats and mice

[116,117]. After DAergic depletion, a clear decrease in the number of dendritic spines, together with an atrophy of the dendrites themselves was initially reported in 1988 [118] and confirmed later on by a British group [119-122]. Similar phenomena have been nicely documented in postmortem tissue from parkinsonian patients [123]. Indeed, the loss of dendritic spines induced a breakdown in the number of glutamatergic synapses –presumed corticostriatal-innervating the striatal MSNs (20% reduction in the number of glutamatergic synapses after DA depletion), therefore suggesting that DA is somewhat necessary for the maintenance of glutamatergic transmission at the striatal level. Very recently, it has been demonstrated both in rats and mice that the breakdown in the glutamatergic innervation of the MSNs under circumstances of DAergic depletion is more focused on striatal neurons projecting to the GPe, whereas the glutamatergic innervation of the striatal neurons giving rise to the direct pathway remains better preserved [124].

During the past few years, our research efforts have been focused on analyzing the influences driven by thalamic glutamatergic projections onto striatofugal neurons. Striatal projecting neurons giving rise to both the direct and indirect pathways are massively innervated by excitatory afferents arising from the caudal intralaminar nuclei [37,67,69]. Very recently, we have demonstrated the existence of severe degeneration phenomena involving up to 70% of the thalamostriatal-projecting neurons located in the caudal intralaminar nuclei [41]. These results are in agreement with earlier data showing similar degeneration phenomena in CM-Pf during Parkinson's disease [93,94]. When trying to analyze the relationships between DA loss and thalamic degeneration, a feasible explanation is based on the plastic changes occurring at the striatal level, as stated previously. We consider that the loss of synaptic spines might have some important impact on the arrival of glutamatergic axons from thalamic source, e.g., we can hypothesize that thalamic degeneration might be a phenomenon retrograde to the remodeling of striatal microcircuits after dopaminergic depletion.

Overall, the existence of a marked plasticity within the striatal microcircuits after DA removal calls for a reappraisal of the current view of Parkinson's disease, in the sense that this disease cannot be seen as simply nigrostriatal damage, since the changes in glutamatergic transmission might also play a key role in the pathophysiology of this neurodegenerative disorder.

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References

1. Crossman, A.R. 1987, Neuroscience, 21, 1.
2. Albin, R.L., Young, A.B., and Penney, J.B. 1989, Trends Neurosci., 12, 366.
3. DeLong, M.R. 1990, Trends Neurosci., 13, 281.
4. Hamani, C., Saint-Cyr, J.A., Fraser, J., Kaplitt, M., and Lozano, A.M. 2003, Brain, 127, 4.
5. Bar-Gad, I., and Bergman, H. 2001, Curr. Opin. Neurobiol., 11, 689.
6. Alexander, G.E., DeLong, M.R., and Strick, P.L. 1986, Ann. Rev. Neurosci., 9, 357.
7. Alexander, G.E., and Crutcher, M.D. 1990, J. Neurophysiol., 64, 164.
8. Yung, K.K., Bolam, J.P., Smith, A.D., Herch, S.M., Ciliax, B.J., and Levey, A.I. 1995, Neuroscience, 65, 709.
9. Surmeier, D.J., Song, W.J., and Yan, Z. 1996, J. Neurosci., 16, 6579.
10. Aizman, O., Brismar, H., Uhlen, P., Zettergren, E., Levyia, A.I., Forssberg, H., Greengard, P., and Aper, A. 2000, Nature Neurosci., 3, 226.
11. Smith Y., and Kieval, J.Z. 2000, Trends Neurosci., 23, S28.
12. Zheng, P., Zhang, X.X., Bunney, B.S., and Shi, W.X. 1999, Neuroscience, 91, 527.
13. Parent, A., Sato, F., Wu, Y., Gauthier, J., Lévesque, M., and Parent, M. 2000, Trends Neurosci., 23, S20.
14. Shink, E., Bevan, M.D., Bolam, J.P., and Smith, Y. 1996, Neuroscience, 73, 335.
15. Joel, D., and Weiner, I. 1997, Neuroscience, 63, 363.
16. Nambu, A. 2004, Progr. Brain Res., 143, 461.
17. Smith, Y., Lavoie, B., Dumas, J., and Parent, A. 1989, Brain Res., 482, 381.
18. Hanley, J.J., and Bolam, J.P. 1997, Neuroscience, 81, 353.
19. Hassani, O.K., François, C., Yelnik, J., and Féger, J. 1997, Brain Res., 749, 88.
20. Gauthier, J., Parent, M., Levesque, M., and Parent, A. 1999, Brain Res., 834, 228.
21. Ruskin, D.N., and Marshall, J.F. 1995, Brain Res., 703, 156.
22. Kreiss, D.S., Anderson, L.A., and Walters, J.R. 1996, Neuroscience, 72, 863.
23. Hassani, O.K., and Féger, J. 1999, Neuroscience, 92, 533.
24. Vogt, C., and Vogt, O. 1941, J. Physiol. Neurol., 50, 32.
25. Powell, T.P.S., and Cowan, W.M. 1956, Brain, 79, 364.
26. Parent A., Mackey, A., and De Bellefeuille, L. 1983, Neuroscience, 10, 1137.
27. Nakano, K., Hasegawa, Y., Tokushige, A., Nakagawa, S., Kayahara, T., Mizuno, N. 1990, Brain Res., 537, 54.
28. Sadikot, A.F., Parent, A., and François, C. 1990, Brain Res., 510, 161.
29. Sadikot, A.F., Parent, A., and François, C. 1992, J. Comp. Neurol., 315, 137.
30. Sadikot, A.F., Parent, A., Smith, Y., and Bolam, J.P. 1992, J. Comp. Neurol., 320, 228.
31. Fenelon, G., François, C., Percheron, G., and Yelnik, J. 1991, Neuroscience, 45, 495.
32. Féger, J., Bevan, M.D., and Crossman, A.R. 1994, Neuroscience, 60, 125.
33. Deschênes, M., Bourassa, J., and Parent, A. 1995, Brain Res., 701, 288.
34. Deschênes, M., Bourassa, J., Doan, V.D., and Parent, A. 1996, Eur. J. Neurosci., 8, 329.

35. Sidibé, M., and Smith, Y. 1996, J. Comp. Neurol., 365, 445.
36. Rudkin, T.M., and Sadikot, A.F. 1999, Neuroscience, 88, 1165.
37. Gonzalo, N., Lanciego, J.L., Castle, M., Vázquez, A., Erro, E., and Obeso, J.A. 2002, Thal. Rel. Sys., 1, 341.
38. Vercelli, A., Marini, G., and Tredici, G. 2003, Eur. J. Neurosci., 18, 275.
39. Smith, Y., Raju, D.V., Paré, J.F., and Sidibé, M. 2004, Trends Neurosci., 27, 520.
40. Pérez-Manso, M., Barroso-Chinea, P., Aymerich, M.S., and Lanciego, J.L. 2006, Brain Res., 1072, 91.
41. Aymerich, M.S., Barroso-Chinea, P., Pérez-Manso, M., Muñoz-Patiño, A.M., Moreno-Igoa, M., González-Hernández, T., and Lanciego, J.L. 2006, Eur. J. Neurosci., 23, 2099-2108.
42. Dubé, L., Smith, A.D., and Bolam, J.P. 1988, J. Comp. Neurol., 267, 455.
43. Buchwald, N.A., Price, D.D., Vernon, L., and Hull, C.D. 1973, Exp. Neurol., 38, 311.
44. Kitai, S.T., Kocsis, J.D., Preston, R.J., Sugimori, M. 1976, Brain Res., 109, 601.
45. Kocsis, J.D., Sugimori, M., Kitai, S.T. 1977, Brain Res., 124, 403.
46. Wilson, C.J., Chang, H.T., and Kitai, S.T. 1983, Exp. Brain Res., 51, 217.
47. Nauta, W.J.H., and Mehler, W.R. 1966, Brain Res., 1, 3.
48. Meredith, G.E., and Wouterlood, F.G. 1990, J. Comp. Neurol., 296, 204-221.
49. Lapper, S.R., and Bolam, J.P. 1992, Neuroscience, 51, 533.
50. Lapper, S.R., Smith, Y., Sadikot, A.F., Parent, A., and Bolam, J.P. 1992, Brain Res., 580, 215.
51. Bennet, B.D., and Bolam, J.P. 1994, Neuroscience, 62, 707.
52. Consolo, S., Baldi, G., Giorgi, S., Nannini, L. 1996, Eur. J. Neurosci., 8, 2702.
53. Sidibé, M., and Smith, Y. 1999, Neuroscience, 89, 1189.
54. Thomas, T.M., Smith, Y., Levey, A.I., and Hersch, S.M. 2000, Synapse, 37, 252.
55. Smith Y., Bennet, B.D., Bolam, J.P., Parent, A., and Sadikot, A.F. 1994, J. Comp. Neurol., 344, 1.
56. Beckstead, R.M. 1984a, J. Comp. Neurol., 223, 313.
57. Beckstead, R.M., 1984b, Brain Res., 300, 351.
58. Smith, Y., and Parent, A. 1986, Neuroscience, 18, 347.
59. Berendse, H.W., and Groenewegen, H.J. 1990, J. Comp. Neurol., 299, 187.
60. Erro, M.E., Lanciego, J.L., Arribas, J., and Giménez-Amaya, J.M. 2001, Histochem. Cell Biol., 115, 447.
61. Erro, M.E., Lanciego, J.L., and Giménez-Amaya, J.M. 2002, Neurosci. Res., 42, 45.
62. McFarland, N.R., and Haber, S.N. 2001, J. Comp. Neurol., 429, 321.
63. Van der Werf, Y.D., Witter, M.P., and Groenewegen, H.J. 2002, Brain Res. Rev., 39, 107.
64. Royce, G.J. 1983, Exp. Neurol., 79, 773.
65. Parent, A., and Hazrati, L.N. 1995, Brain Res. Rev., 20, 128.
66. Smith, Y., and Bolam, J.P. 1990, Trends Neurosci., 13, 259.
67. Lanciego, J.L., Gonzalo, N., Castle, M., Sánchez-Escobar, C., Aymerich, M.S., and Obeso, J.A. 2004, Eur. J. Neurosci., 19, 1267.
68. Bacci, J.J., Kachidian, P., Kerkerian-Le Goff, L., and Salin, P. 2004, J. Neuropathol. Exp. Neurol., 63, 20.
69. Castle, M., Aymerich, M.S., Sánchez-Escobar, C., Gonzalo, N., Obeso, J.A., and Lanciego, J.L. 2005, J. Comp. Neurol., 483, 143.
70. Sugimoto, T., and Hattori, T. 1983, Brain Res., 267, 335.

71. Sugimoto, T., Hattori, T., Mizuno, N., Itoh, K., and Sato, M. 1983, J. Comp. Neurol., 214, 209.
72. Royce, G.J., and Mourey, R.J. 1985, J. Comp. Neurol., 235, 277.
73. Marini, G., Pianca, L., and Tredici, G. 1999, Somatosens. Motor Res., 16, 207.
74. Mouroux, M., and Féger, J. 1993, NeuroReport, 4, 613.
75. Mouroux, M., Hassani, O.K., and Féger, J. 1995, Neuroscience, 67, 399.
76. Van der Kooy, D., and Hattori, T. 1980, J. Comp. Neurol., 192, 751.
77. Kita, H., Chang, H.T., and Kitai, S.T. 1983, J. Comp. Neurol., 215, 245.
78. Kita, H., and Kitai, S.T. 1987, J. Comp. Neurol., 260, 435.
79. Plenz, D., and Kitai, S.T. 1999, Nature, 400, 677.
80. Sato, F., Parent, M., Levesque, M., and Parent, A. 2000, J. Comp. Neurol., 424, 142.
81. Orieux, G., François, C., Féger, J., Yelnik, J., Vila, M., Ruberg, M., Agid, Y., and Hirsch, E.C. 2000, Neuroscience, 97, 79.
82. Hirsch, E.C., Périer, C., Orieux, G., François, C., Féger, J., Yelnik, J., Vila, M., Levy, R., Tolosa, E.S., Marín, C., Herrero, M.T., Obeso, J.A., and Agid, Y. 2000, Trends Neurosci., 10, S78.
83. Kincaid, A.E., Penney Jr, J.B., Young, A.B., and Newman, S.W. 1991, Brain Res., 553, 18.
84. Yasukawa, T., Kita, T., Xue, Y., and Kita, H. 2004, J. Comp. Neurol., 471, 153.
85. Obeso, J.A., Rodríguez-Oroz, M.C., Rodríguez, M., Lanciego, J.L., Artieda, J., Gonzalo, N., and Olanow, C.W. 2000, Trends Neurosci., 23, S8.
86. Vila, M., Levy, R., Herrero, M.T., Ruberg, M., Faucheux, B., Obeso, J.A., Agid, Y., and Hirsch, E.C. 1997, J. Neurosci., 17, 765.
87. Bezard, E., Boraud, T., Bioulac, B., and Gross, C.E. 1999, Eur. J. Neurosci., 11, 2167.
88. Robertson, R.G., Farmery, S.M., Sambrook, M.A., and Crossman, A.R. 1989, Brain Res., 476, 317.
89. Blanchet, P.J., Boucher, R., and Bédard, P.J. 1994, Brain Res., 650, 32.
90. Vila, M., Périer, C., Féger, J., Yelnik, J., Faucheux, B., Ruberg, M., Raisman-Vozari, R., Agid, Y., and Hirsch, E.C. 2000, Eur. J. Neurosci., 12, 337.
91. Obeso, J.A., Rodríguez-Oroz, M.C., Lanciego, J.L., and Rodríguez-Díaz, M. 2004, Trends Neurosci., 26, 215.
92. Bacci, J.J., Kerkerian-Le Goff, L., and Salin, P. 2002, Eur. J. Neurosci., 15, 1918.
93. Henderson, J.M., Carpenter, K., Cartwright, H., and Halliday, G.M. 2000, Ann. Neurol., 47, 345.
94. Henderson, J.M., Carpenter, K., Cartwright, H., and Halliday, G.M. 2000, Brain, 123, 1410.
95. Heinsen, H., Rub, U., Gangnus, D., Jungkunz, G., Bauer, M., Ulmar, G., Bethke, B., Schuler, M., Bocker, F., Eisenmenger, W., Gotz, M., and Strik, M. 1996, Acta Neuropathol., 91, 161.
96. Kassubek, J., Juengling, F.D., Ecker, D., and Landwehrmeyer, G.B. 2005, Cereb. Cortex., 15, 846.
97. Freyaldenhoven, T.E., Ali, S.F., and Schmued, L.C. 1997, Brain Res., 759, 9.
98. Ghorayeb, I., Fernagut, P.O., Hervier, L., Labattu, B., Bioulac, B., and Tison, F. 2002, Neuroscience, 115, 533.

99. Henderson, J.M., Schleimer, S.B., Allbutt, H., Dabholkar, V., Abela, D., Jovic, J., and Quinlivan, M. 2005, Behav. Brain Res., 162, 222.
100. Xuereb, J.H., Perry, R.H., Candy, J.M., Perry, E.K., Marshall, E., and Bonham, J.R. 1991, Brain, 114, 1363.
101. Caparros-Lefebvre, D., Ruchoux, M.M., Blond, S., Petit, H., and Percheron, G. 1994, Neurology, 44, 1856.
102. Caparros-Lefebvre, D., Pollak, P., Feltin, M.P., Blond, S., and Benabid, A.L. 1999, Rev. Neurol., 155, 543.
103. Caparros-Lefebvre, D., Blond, S., Feltin, M.P., Pollak, P., and Benabid, A.L. 1999, J. Neurol. Neurosurg. Psychiatr., 67, 308.
104. Krauss, J.K., Pohle, T., Weigel, R., and Burgunder, J.M. 2002, J. Neurol. Neurosurg. Psychiatr., 72, 546.
105. Weigel, R., and Krauss, J.K. 2004, Stereotact. Funct. Neurosurg., 82, 115.
106. Houeto, J.L., Karachi, C., Mallet, L., Pilon, B., Yelnik, J., Mesnage, V., Welter, M.L., Navarro, S., Pelissolo, A., Darmier, P., Pidoux, B., Dormont, D., Cornu, P., and Agid, Y. 2005, J. Neurol. Neurosurg. Psychiatr., 76, 992.
107. Henderson, J.M., O'Sullivan, D.J., Fung, V.S., Hely, M.A., Morris, J.G., and Halliday, G.M. 2001, Neurology, 56, 1576.
108. Centonze, D., Picconi, B., Gubellini, P., Bernardi, G., and Calabresi, P. 2001, Eur. J. Neurosci., 13, 1071.
109. Picconi, B., Centonze, D., Hakansson, K., Bernardi, G., Greengard, P., Fisone, G., Cenci, M.A., and Calabresi, P. 2003, Nat. Neurosci., 6, 437.
110. Calabresi, P., Giacomini, P., Centonze, D., and Bernardi, G. 2000, Ann. Neurol., 47, S60.
111. Calabresi, P., Centonze, D., Gubellini, P., Marfia, G.A., Pisani, A., Sancesario, G., Bernardi, G. 2000, Progr. Neurobiol., 61, 231.
112. Picconi, B., Pisani, A., Barone, I., Bonsi, P., Centonze, D., Bernardi, G., and Calabresi, P. 2005, Neurotoxicology, 26, 779-.
113. Freund, T.F., Powell, J.F., and Smith, A.D. 1984, Neuroscience, 13, 1189-1215.
114. Raju, D.V., and Smith, Y. 2005, The Basal Ganglia VIII J.P. Bolam, C.A. Ingham, P.J. Magill, (Eds.), New York, Springer Science, 601.
115. Comery, T.A., Shah, R., and Greenough, W.T. 1995, Neurobiol. Learn. Mem., 63, 217.
116. Levine, M.S., Adinolfi., A.M., Fisher, R.S., Hull, C.D., Buchwald, N.A., and McAllister, J.P. 1986, Neurobiol. Aging, 7, 277.
117. Rafols, J.A., Cheng, H.W., and McNeill, T.H. 1989, J. Comp. Neurol., 279, 212.
118. McNeill, T.H., Brown, S.A., Rafols, J.A., and Shoulson, I. 1988, Brain Res., 455, 148.
119. Ingham, C.A., Hood, S.H., and Arbuthnott, G.W. 1989, Brain Res., 503, 334.
120. Ingham, C.A., Hood, S.H., van Maldegem, B., Weenink, A., and Arbuthnott, G.A. 1993, Exp. Brain Res., 93, 17.
121. Ingham, C.A., Hood, S.H., Taggart, P., and Arbuthnott, G.W. 1998, J. Neurosci., 18, 4732.
122. Arbuthnott, G.W., Ingham, C.A., and Wickens, J.B. 2000, J. Anat., 196, 587.
123. Stephens, B., Mueller, A.J., Shering, A.F., Hood, S.H., Taggart, P., Arbuthnott, G.W., Bell, J.E., Kilford, L., Kingsbury, A.E., Daniel, S.E., and Ingham, C.A. 2005, Neuroscience, 132, 741.

124. Day, M., Wang, Z., Ding, J., An, X., Ingham, C.A., Shering, A.F., Wokosin, D., Ilijic, E., Sun, Z., Sampson, A.R., Mugnaini, E., Deutch, A.Y., Sesack, S.R., Arbuthnott, G.W., and Surmeier, D.J. 2006, Nat. Neurosci., 9, 251.