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Lise Guilhemsang, Nicolas Mallet. Arkypallidal neurons in basal ganglia circuits: Unveiling novel pallidostriatal loops?. *Current Opinion in Neurobiology*, 2024, 84, pp.102814. <10.1016/j.conb.2023.102814>. <hal-04685359>

HAL Id: hal-04685359

<https://hal.science/hal-04685359v1>

Submitted on 3 Sep 2024

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Arkypallidal Neurons in Basal Ganglia Circuits: Unveiling novel pallidostriatal loops?

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Abstract:

Just over a decade ago, a novel GABAergic input originating from a subpopulation of external globus pallidus neurons known as Arkypallidal and projecting exclusively to the striatum was unveiled. At the single-cell level, these pallidostriatal Arkypallidal projections represent one of the largest extrinsic sources of GABA known to innervate the dorsal striatum. This discovery has sparked new questions regarding their role in striatal information processing, the circuit that recruit these neurons, and their influence on behavior, especially in the context of action selection vs. inhibition. In this review, we will present the different anatomo-functional organization of Arkypallidal neurons as compared to classic Prototypic neurons, including their unique molecular properties and what is known about their specific input/output synaptic organization. We will further describe recent findings that demonstrate one mode of action of Arkypallidal neurons, which is to convey feedback inhibition to the striatum, and how this mechanism is differentially modulated by both striatal projection pathways. Lastly, we will delve into speculations on their mechanistic contribution to striatal action execution or inhibition.

Classic functional organization of cortico-basal ganglia circuits:

How motor activity in cortico-basal ganglia (BG) loops translate into motor programs remains unknown and is subject to ongoing research [1]. Nonetheless, a prevalent concept in this field is the action-selection model. Indeed, the anatomical architecture of BG, characterized by parallel and recurrent loops connecting cortical and subcortical areas, has been proposed as a solution in vertebrates for addressing the challenge of action-selection [2,3]. In this model, competing motor plans, arriving in the form of excitatory inputs from cortical and thalamic areas, are processed by the dorsal striatum, a major input stage of the motor BG circuit. Within the dorsal striatum, these putative motor plans are either facilitated or inhibited as they are integrated through segregated striatal pathways (**Figure 1A**). Such striatal integration results in a cascade of firing rate changes that differently impacts on the rodent's BG output nuclei such as the substantia nigra pars reticulata and the entopeduncular nucleus (the homolog of the internal globus pallidus, the GPi in primates). Accordingly, activation of the direct D1-expressing striatal projection neurons (D1-SPNs) directly inhibit BG output nuclei and this signal promotes movement by disinhibiting the motor circuits in the thalamus and the brainstem [4]. In contrast, increased activity in the indirect D2-expressing striatal projection neurons (D2-SPNs), which relay information through the external globus pallidus (GPe) and the subthalamic nuclei (STN), leads to heightened activity in BG output, resulting in increased inhibition of thalamic/brainstem circuit and subsequent movement suppression. Importantly, it is now well-documented that appropriate action execution requires the concurrent activation of D1-SPNs and D2-SPNs [5–7]. Although it may seem paradoxical to simultaneously activate antagonistic pathways, it has been suggested that appropriate action selection also necessitates the inhibition of competing motor plans, a mechanism likely achieved through D2-SPNs activation [5,8].

Another important and unanswered question in the field is what are the mechanisms orchestrating the precise activation of D1-SPNs and D2-SPNs that drive the execution of the intended action? In vivo, SPNs are typically quiescent neurons, and their firing relies on incoming cortical and thalamic excitatory inputs, which are modulated by dopamine transmission. However, effective integration of such excitatory inputs in SPNs is dependent upon GABA transmission. Indeed, it was first proposed that GABAergic lateral inhibition between SPNs initiate the action-selection process via a ‘winner-takes-all’ network [9,10]. Although, the connections formed by the collateral inhibition between D1-SPNs and D2-SPNs are not symmetrical, and the evoked GABAergic currents relatively weak [9], this mechanism might still be important to form functional cell assemblies [11]. Another potential mechanism, known as feedforward inhibition, is mediated by striatal GABAergic interneurons [12]. The GABAergic current generated by these interneurons are significantly larger [12], and potent enough to effectively inhibit or synchronize the activity of SPNs in response to cortical inputs [13]. In conclusion, both these GABAergic mechanisms, lateral inhibition and the feed-forward inhibition, seem to have a pivotal role in locally controlling striatal activity [14]. However, while this canonical model and putative mechanisms provide a useful framework to apprehending how dorsal striatum perform action selection, it unfortunately fails to consider the dense GABAergic projections originating from a subpopulation of GPe neurons: the Arkypallidal neurons (**Figure 1A, B**).

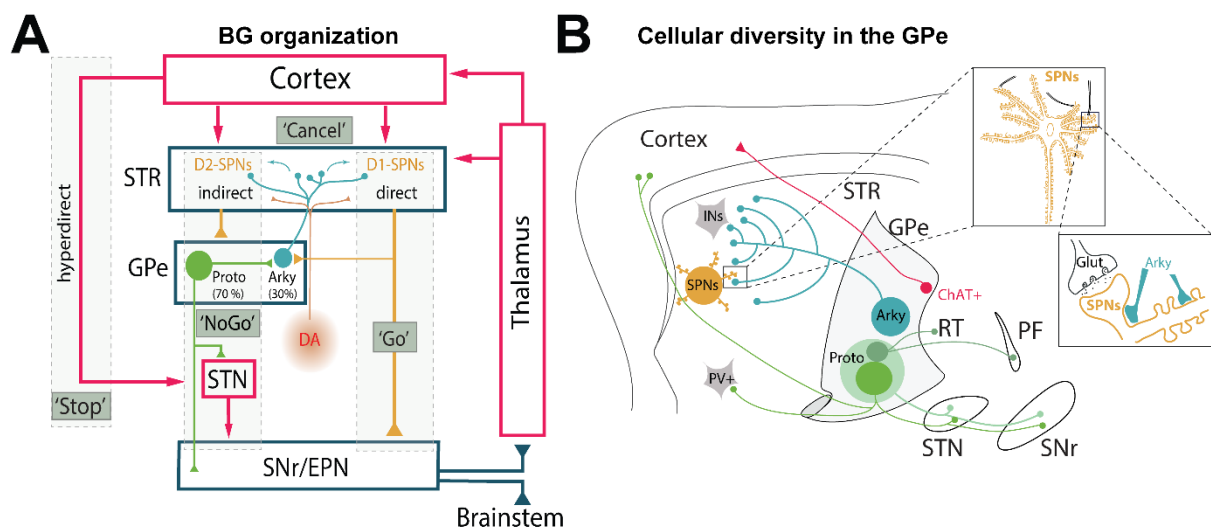


Figure 1. Basal Ganglia anatomo-functional organization. **A**, Schematic representation of the classic ‘direct/indirect’ BG model updated with the GPe Prototypic/Arkypallidal dichotomous organization. Abbreviations: STR: striatum, GPe: external globus pallidus, STN: subthalamic nucleus, SNr: Substantia nigra pars reticulata, EPN: entopeduncular nucleus, D1- or D2-SPNs: Dopamine D1 or D2-expressing striatal projections neurons. **B**, Schematic representation of the GPe cellular diversity and the main output projections from Prototypic and Arkypallidal neurons. Abbreviations: Arky: Arkypallidal GPe neurons, ChAT+: Choline acetyl transferase expressing neurons of the basal nucleus of Meynert, Glut: Glutamatergic inputs, INs: striatal interneurons, Proto: Prototypic GPe neurons, PF: Parafascicular thalamic nucleus, RT: Reticular thalamus, SPNs: striatal projection neurons.

Functional cell diversity in the GPe: Prototypic vs. Arkypallidal neurons

In the traditional organization of BG network, the GPe was typically viewed as a relay nucleus made of one homogenous cell-type integrating inputs from the D2-SPNs and always innervating the STN. However, this perspective has been challenged by recent characterization of the GPe cellular

diversity, which is apparent at various functional levels, including their embryonic origin [15,16], molecular characteristics [17–22●●](see Box 1), structural features [23–25], electrophysiological properties [17,18,26], and behavioural roles [22●●,27,28]. The main GPe neuron population, making up nearly 70–75% of all GPe cells, is referred to as Prototypic neurons. These neurons consistently send long-range axonal projections targeting the STN and all major downstream BG nuclei (**Figure 1B**). Notably, prototypic neurons often establish large and potent synapses directly onto the cell bodies of their target neurons. This strategic synaptic organization allows prototypic neurons to not only regulate the firing activity levels in many target nuclei but also to control synchronization levels and impose phase-firing relationship during oscillatory activity [29]. Importantly, the influence of Prototypic neurons extends beyond BG downstream nuclei. Indeed, a subset of Prototypic neurons also projects axons back to the striatum (**Figure 1B**). Although this projection is relatively sparse, they selectively contact GABAergic interneurons and could thus indirectly affect the firing rate or synchrony level of SPNs networks [30,31]. The specific impact of the Prototypic pallidostriatal GABAergic inputs onto motor behaviours has never been investigated, but these GABA inputs could also contribute to the selection/execution of striatal motor programs [32]. Recently, the classification of Prototypic neurons has been further divided into molecularly defined subclasses [18,19,28]. Notably, these molecular heterogeneity within Prototypic neurons extend into different axonal projection pattern and behavioural specialization, shedding light on novel functional contributions of Prototypic neurons in healthy and parkinsonian state [21,28,33●,34]. In addition, the description of direct projections from GPe neurons to thalamic structures, such as the thalamic reticular nucleus [35] and the parafascicular thalamus [33] ●, opens up the fascinating perspective that the GPe may also serve as a basal ganglia output nucleus.

In contrast, the remaining 25–30% of GPe neurons, so-called Arkypallidal, defy the conventional nature of GPe neurons by exclusively projecting to striatum (**Figure 1B**). These axonal projections are dense—a single neuron can make up more than 10 000 synapses [23]— and they predominantly innervate the dorsolateral ‘motor’ region of the striatum as opposed to the medial ‘associative’ region [36]. These Arkypallidal projections appear to be topographically organized concerning the major striatal domains (i.e. rostral vs. caudal and dorsal vs. ventral). Whether they are also organized with respect to finer striatal functional domains, as defined by somatotopic map [37], remains unknown, although it seems unlikely given the broad striatal extent of these projections. However, it is possible that local presynaptic control mechanisms impart functional specificity to these Arkypallidal inputs. The striatal synaptic targets of Arkypallidal neurons encompass SPNs and all the major types of striatal interneurons (with a preference for cholinergic interneurons). Moreover, the synaptic terminals of Arkypallidal neurons exhibit different localization patterns when targeting SPNs compared to interneurons [23]. Specifically, Arkypallidal terminals established perisomatic contacts with striatal interneurons, whereas they target the distal dendrites of SPNs. Additionally, synapses onto SPNs often target dendritic shafts or the necks of dendritic spines, making these Arkypallidal synapses an effective mechanism for filtering excitatory inputs and controlling which SPNs become activated. In normal animals, Arkypallidal projections equally affect D1-SPNs and D2-SPNs, although the evoked synaptic current appears slightly stronger in D2-SPNs [38]●. As a result, it seems that the inhibitory projections from Arkypallidal neurons lack specificity toward striatal cell type and are instead distributed across extensive striatal territories. This property aligns well with the proposed ‘stop’ signal function that these neurons could potentially perform, particularly when the cancellation of an imminent action is required [39]●. It is worth noting that this GPe functional dichotomy, extensively described in rodent literature over the past decade, is also apparent in the distinct firing

activity patterns observed in GPe neurons during primate recordings [40]•. The hypothesis that this distinction correspond to the Arkypallidal/Prototypic classification is an exciting proposition that future primate studies should explore.

Box 1: Molecular profiles of Arkypallidal neurons. In the brain, the molecular profile of a cell is intricately linked to its fate and future function [41]. This principle also holds true for GPe neurons, where cellular diversity emerges early in the development. During embryogenesis, different progenitor domains contribute to the specification of various classes of GABAergic projection neurons [16,42]. Specifically, Prototypic neurons derive from the medial ganglionic eminence, while Arkypallidal neurons originate from the lateral/caudal ganglionic eminence [22••]. This distinct developmental origin of GPe neurons extends into their complex molecular architecture. Many Prototypic neurons express markers such as parvalbumin (PV) or transcription factors like NK2 homeobox 1 (Nkx2.1) and LIM homeobox 6 (Lhx6) [17–19,21,22••]. However, the reported numbers and overlap of each population vary across studies and may depend on factors such as antibodies, age, strains, and species of the animals (rats/mice) used. This variability makes it challenging to provide a precise quantification of these markers in prototypic neurons. Nevertheless, the Nkx2.1 cell lineage appears to consistently label most Prototypic neurons [22••]. In contrast, Arkypallidal neurons can be defined by the expression of specific molecular makers. These markers include the opioid precursor preproenkephalin (PPE) and the transcription factors Forkhead box protein 2 (FoxP2) and meis homeobox 2 protein (Meis2), which are almost exclusively expressed by Arkypallidal neurons [17,18,22••,23]. Additionally, the transcription factor neuronal PAS domain protein 1 (Npas1) is expressed in Arkypallidal neurons (defined as FoxP2+ neurons), albeit to varying degrees depending on studies: ranging from 80% [20] to 100% [17]. It is important to note that Npas1 is not expressed in adjacent GPe regions, in contrast to FoxP2, which shows strong expression throughout the striatum [43]. Therefore, Npas1-Cre mice have been employed as a tool for optogenetic experiments to target a substantial portion of Arkypallidal neurons while avoiding the risk of virus leakage beyond the boundaries of GPe. However, it is essential to recognize that Npas1 is also expressed by a significant fraction of Prototypic Lhx6+ neurons (up to 30-35%) [17–19]. This population correspond to the 30% of Prototypic neurons sending an axon to striatum [30]. In essence, utilizing Npas1-Cre mice to target neuronal population will inclusively capture all pallidostriatal GPe neurons, regardless of whether they are Arkypallidal or Prototypic in nature. This limitation highlights the challenge of employing Npas1-Cre mice to investigate the specific function of unique GPe cell population. Improving the circuit-specificity of Npas1-Cre mice by combining it with intersectional optogenetic tools [44] could represent a promising approach.

Marker	Population	Percentage
Nkx2.1+	Prototypic	70 - 98%
Lhx6+	Prototypic	~ 70%
PV+	Prototypic	50 - 60%
ChAT+	Other	~ 5%
FoxP2+/PPE+	Arkypallidal	15 - 28%
Npas1+	Arkypallidal	~ 40%
Prototypic only	Prototypic	8%
Prototypic & Arkypallidal	Overlap	13%
Arkypallidal only	Arkypallidal	15%

Circuit connectivity and functional impact of Arkypallidal neurons

Previous *in vivo* electrophysiological recordings conducted in parkinsonian animals with 6-OHDA lesions, have revealed that Prototypic and Arkypallidal neurons exhibit opposing phase firing during synchronized oscillatory activity events [23]. Furthermore, optogenetic excitation of STN neurons had contrasting effects on both GPe neurons: it induced rapid excitation in Prototypic neurons but a corresponding inhibitory response in Arkypallidal cells [29]. Collectively, these findings raise the intriguing possibility that the functional dichotomy between Prototypic and Arkypallidal neurons extends to disparities in their input organization. This hypothesis was recently examined for D2-SPNs and STN inputs using optogenetic stimulation in D2-Cre and Vglut2-Cre animals, respectively [45●●,46]. The outcomes of these experiments can be summarized as follows: both D2-SPNs and STN inputs elicited stronger and more numerous synaptic responses in Prototypic neurons as compared to Arkypallidal. This differential synaptic organization consistently translate into opposing firing patterns between Prototypic and Arkypallidal neurons during *in vivo* extracellular recordings [46]. For instance, D2-SPNs stimulation led to inhibition of Prototypic neurons but excitation in Arkypallidal neurons (**Figure 2A**). Conversely, STN stimulation triggered excitation in Prototypic neurons but inhibition in Arkypallidal activity (**Figure 2B**). This opposition of response was attributed to the potent inhibitory impact of Prototypic local axon collaterals onto Arkypallidal neurons. In addition to these two primary GPe inputs, the axons of D1-SPNs neurons form ‘bridging’ collaterals into the GPe [47]. Interestingly, optogenetic excitation of D1-SPNs in D1-Cre mice triggered a strong biased response towards Arkypallidal neurons [45]●●, but see [34]. These synaptic organization are further supported by *in vitro* studies showing that D1-SPNs preferentially influence Npas1+ GPe neurons (half of which are Arkypallidal)[27], while STN inputs evoke stronger synaptic currents into PV+ neurons (many of which are Prototypic) than in Npas1+ cells [19]. Similar conclusions regarding GPe inputs organization were reached when dissecting the responses elicited by *in vivo* sensory stimulation, rather than bulk optogenetic excitation of specific inputs [48].

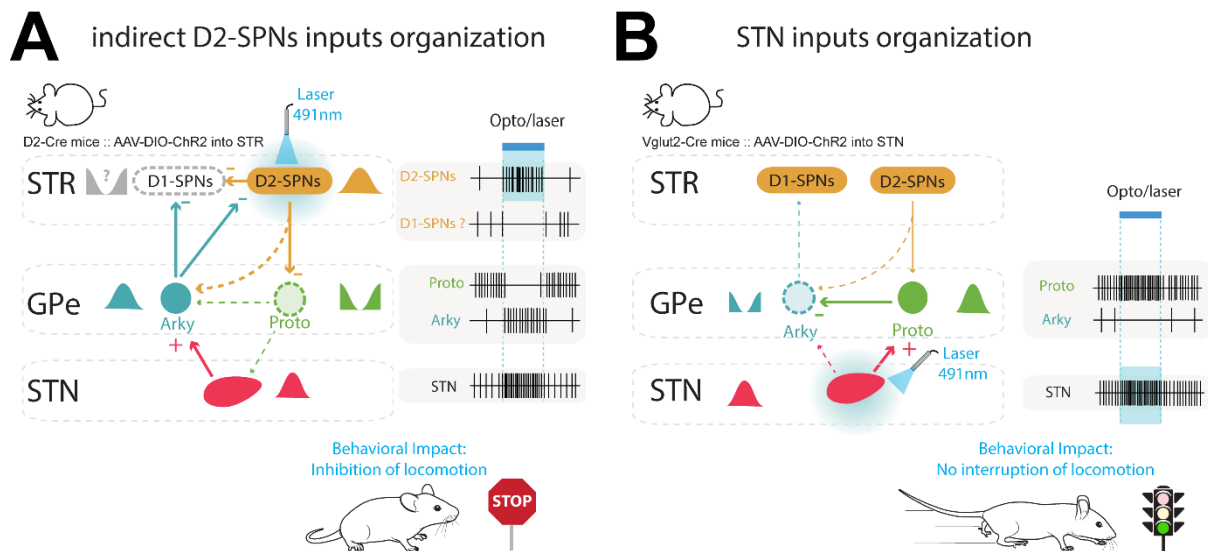


Figure 2. Optogenetic dissection of GPe input organization and motor impact. A, Schematic illustrating the STR-GPe-STN activity dynamics and motor impact induced by D2-SPNs optogenetic stimulation in D2-Cre mice. In this condition, D2-SPNs stimulation induced a di-synaptic excitation in Arkypallidal neurons, which could directly mediate locomotion inhibition by suppressing motor-related striatal activity. B, Schematic illustrating the GPe activity and motor impact induced by STN

optogenetic stimulation using Vglut2-Cre mice. In this condition, treadmill locomotion was not impaired by STN excitation. This behavioural output was associated with an inhibition of Arkypallidal neurons (leaving motor-related striatal unperturbed) and co-activation of Prototypic and STN neurons, which might counteract each other at the BG output level.

Investigation into how the activity change in Prototypic and Arkypallidal neurons, induced by optogenetic stimulation of D2-SPNs or STN, influenced locomotion behaviour revealed interesting findings. While both inputs are traditionally considered as motor-suppressing pathways, locomotion inhibition was exclusively observed following optogenetic stimulation of D2-SPNs neurons, not STN neurons [46]. This disparity in behavioural outcomes could be attributed to the distinct influences these stimulations exert on BG output activity. Indeed, the prevailing idea in the field is that movement inhibition induced by both pathways depends solely on their net effect on BG output. However, this conventional view is challenged by a recent study showing that locomotion inhibition following D2-SPNs stimulation is achieved through the local influence of D2-SPNs axon collaterals [49]●●. Similarly, Arkypallidal opto-excitation reproduced the locomotor inhibitory effect observed with D2-SPNs stimulation, but without disturbing Prototypic neurons, thus leaving the remaining indirect pathway unperturbed [46]. This last work demonstrates that Arkypallidal neurons effectively form a pallidostriatal feedback loop capable of modulating action inhibition at the BG input stage: the striatum. Importantly, this Arkypallidal feedback might be directly controlled by D1-SPNs inputs [45]●● or indirectly recruited by D2-SPNs through the inhibition of Prototypic neurons [46]. Beyond such striato-pallidostriatal feedback loop, it is plausible that unconventional GPe inputs might directly target Arkypallidal neurons, independently regulating the execution or cancellation of movement-related striatal activity. For instance, direct projections from the motor cortex onto Arkypallidal neurons [50]● and Npas1+ GPe neurons [19] have been reported. Furthermore, additional inputs from the limbic system might directly impact motor information processing by Arkypallidal neurons [51]. Nevertheless, the precise identity of all such direct inputs, as well as their functional contributions to motor control, remain unknown.

Speculation on the mechanistic contribution of Arkypallidal neurons to action selection/inhibition

Striatal information processing is crucial for generating neuronal network activity that is properly organized in space and time to implement what actions to perform [52●●,53] and how fast to do them [54]. In this last section, we will speculate on the mechanistic contribution of the Arkypallidal GABAergic feedback to striatal microcircuits. We will consider two conditions depending on whether the feedback projections operate in an 'open loop' or a 'closed loop' mode. This distinction is based on whether the Arkypallidal feedback inhibition functionally impact onto D2-SPNs that trigger the feedback (close loop) or not (open loop mode).

In the open loop mode, our first hypothesis is that Arkypallidal neurons may participate to a 'centre select/surround inhibition' mechanism, reinforcing the selective activation of striatal neurons (**Figure 3A**). In this scenario, activation of D1-SPNs carrying motor-related information will, through their GPe bridging collaterals, selectively suppress the feedback inhibition from a subset of Arkypallidal neurons. This effect on Arkypallidal neurons could synergize with the direct effect of D1-SPNs on BG outputs, ensuring proper movement initiation at both the input and output stages of BG circuits. Concurrent activation of the D2-SPNs will result in widespread inhibition of Prototypic neurons and, consequently, a disinaptic disinhibition of Arkypallidal neurons. Inhibiting Prototypic neurons will lead to increased BG output activity and inhibition of competing motor programs. This mechanism may

also work in concert with a parallel recruitment of Arkypallidal directly impacting the striatum. Indeed, the heightened activity of Arkypallidal neurons will likely broadcast inhibitory feedback to large striatal territories, providing additional inhibition to competing motor programs, thereby contributing to an increased signal-to-noise ratio mechanism. This scenario aligns with *in vivo* electrophysiological recordings, which show that a large proportion of Prototypic GPe neurons are inhibited during movement execution [22●●,55] while Arkypallidal neurons are excited [22]●●. Now, let's consider a situation in which, due to changes in the external environment, an animal needs to quickly cancel the ongoing motor plan. Such a condition can be experimentally reproduced using a 'Stop-signal' task in rodents [56]. Interestingly, in such condition, it has been demonstrated that a subpopulation of Arkypallidal neurons can rapidly convey this stop signal sensory response to directly cancel motor-related striatal information [39]●. It is possible that these 'stop-signal' responding Arkypallidal neurons functionally represent the 'centre select' cluster otherwise inhibited by the D1-SPNs initiating the action. Specific sensorimotor inputs to Arkypallidal neurons might directly drive this fast 'cancel' response (Figure 3A).

Our second hypothesis relies on a close loop mode of functioning of Arkypallidal feedback projections (**Figure 3B**). This hypothesis could have implications in two different aspects of striatal motor function. The first aspect is related to the role of striatum in controlling motor vigor [54]. To efficiently adjust and control vigor during a movement, it might be crucial for the striatum to receive a closed-loop signal that regulates its activity as workloads increase over time. In this context, the Arkypallidal feedback projection could represent a beneficiary mechanism to properly scale striatal response according to the demands. It is noteworthy that, despite the direct inhibitory effect on locomotion caused by Arkypallidal opto-excitation, the stimulation also significantly reduces the maximal velocity of locomotion that the animal can achieve during such optogenetic Arkypallidal excitation [46]. Dissecting more precisely the causal impact that Arkypallidal neurons have on the velocity of fine movements will be important in future studies.

The second aspect, potentially important for striatal motor control, is related to recent evidences indicating that during naturalistic behaviour, striatal networks dynamics are temporally organized into sequences of motor syllables [52]●●. Likewise, during locomotion, striatal activity is spatially organized into cluster of activities that are relevant to encode locomotion [57]. In both these scenarios, it is possible that the feedback projections from Arkypallidal neurons contribute to organizing, in space and time, the dynamical state-transitions observed between SPNs cell assemblies. Whether and how Arkypallidal neurons activity impact on switching between striatal states associated to different motor syllables should also be assessed by future studies. Additionally, it is crucial to determine if the anatomical substrate of Arkypallidal axonal projections, specifically their spatial specificity towards active D1- and D2-SPNs, is compatible with this hypothesis. However, even a global and non-selective inhibitory signal to striatal neurons would be effective in switching striatal states if such feedbacks were appropriately timed.

In conclusion, we have shown that Arkypallidal neurons represent yet another source of striatal GABAergic inputs, strategically positioned to contribute to the computation of action selection/inhibition, especially given their projections to the dorsal part of the striatum [36]. This significant physiological contribution also raises the intriguing possibility of their involvement in the pathophysiological aspect of movement disorders, a topic ripe for future investigations. Furthermore, it is conceivable that the function of Arkypallidal neurons extend beyond the motor domain through their projections to other regions of the striatum [58]. Recent research has even suggested the

existence of Arkypallidal neurons in the ventral pallidum, which could play a crucial role in regulating the functions of ventral BG loops, such as those related to reward- or stress-related processing [59,60]. In summary, the multifaceted roles of Arkypallidal neurons in orchestrating various aspects of BG function underscore the complexity and richness of these neural circuits, offering exciting avenues for further exploration and characterization of these circuit both in function and dysfunction.

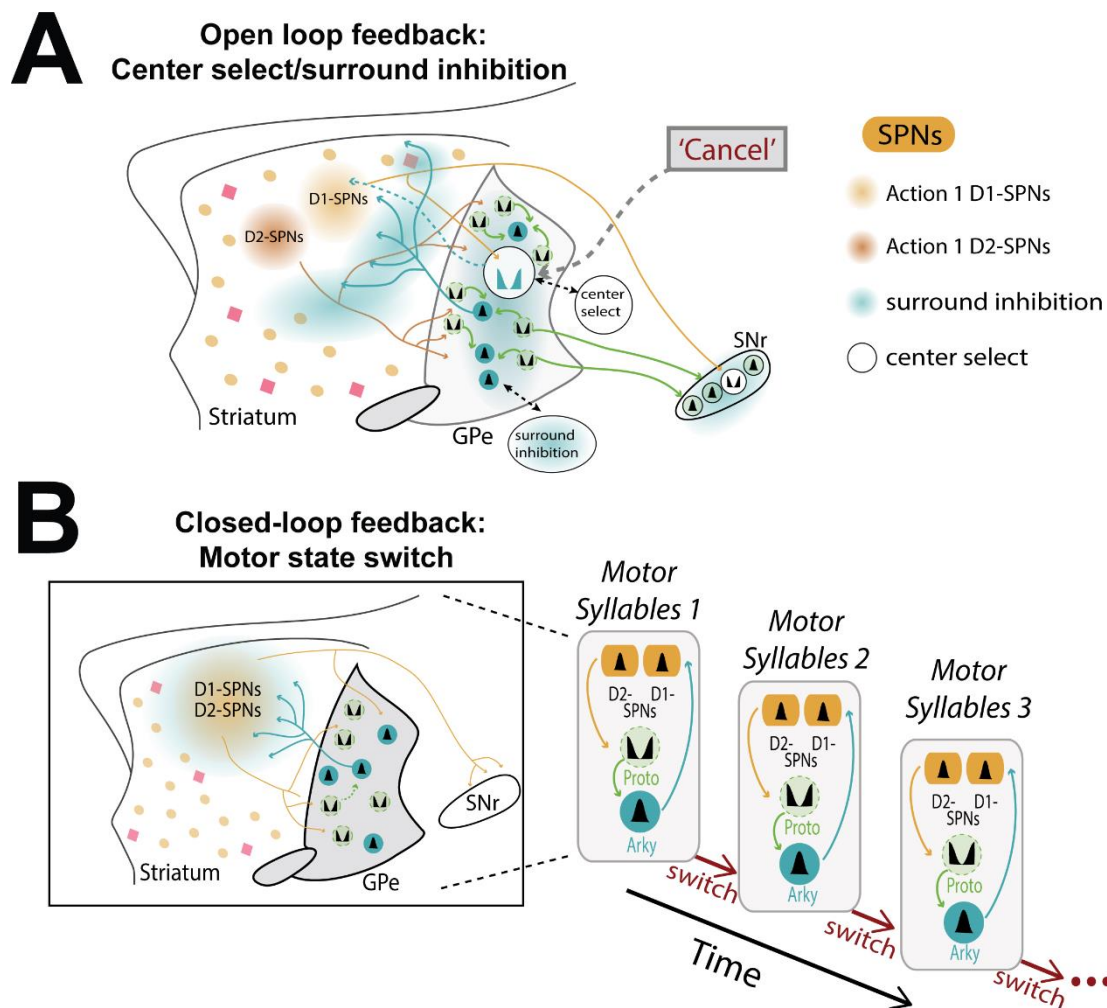


Figure 3. Speculations on the mechanistic impact of the Arkypallidal pallidostriatal feedback loop. **A**, Simplified BG schematic illustrating the potential impact of Arkypallidal feedback projections when functioning in an ‘open loop’ mode. In this scenario, a mechanism known as ‘center select/surround inhibition’ may come into play, strengthening both action selection and competition inhibition directly within the striatum. **B**, Schematic illustrating another potential functional mode of Arkypallidal projections relying on closed-loop feedback mechanism. In this scenario, Arkypallidal projections could facilitate the dynamical transitions observed between functional SPNs clusters. While motor syllables are represented here as non-overlapping neuronal ensemble (for visualization purposes), it has been shown that different actions are continuously represented within the neural activity space by overlapping SPS ensembles [53].

Acknowledgements: This work was supported by grants from the French Agence Nationale de la Recherche (ANR-21-CE16-0025-01 and ANR-22-CE16-0014-02), the Fondation pour la Recherche Médicale (Equipe FRM EQU202203014688), the French government in the framework of the University of Bordeaux's IdEx (Investments for the Future – France 2030 program / GPR BRAIN_2030). This work was also conducted in the scope of the Transborder Joint Laboratory (LTC CoMorPD). We are grateful to J. Baufreton, M. Deffains, A. Dubreuil, F. Georges, A. Leblois for insightful scientific discussions and comments on the manuscript.

Declaration of Interests: The authors declare no competing interests.

References:

Papers of particular interest, recently published have been highlighted as:

- of special interest
- of outstanding interest

1. Arber S, Costa RM: **Networking brainstem and basal ganglia circuits for movement.** *Nat Rev Neurosci* 2022, **0123456789**.
2. Redgrave P, Vautrelle N, Reynolds JNJ: **Functional properties of the basal ganglia's re-entrant loop architecture: Selection and reinforcement.** *Neuroscience* 2011, **198**:138–151.
3. Grillner S, Robertson B: **The Basal Ganglia Over 500 Million Years.** *Curr Biol* 2016, **26**:R1088–R1100.
4. McElvain LE, Chen Y, Moore JD, Lim BK, Costa RM: **Specific populations of basal ganglia output neurons target functionally distinct brainstem areas while collateralizing throughout the diencephalon.** *Neuron* 2019, **400**:1–18.
5. Tecuapetla F, Jin X, Lima SQ, Costa RM: **Complementary Contributions of Striatal Projection Pathways to Action Initiation and Execution.** *Cell* 2016, **166**:1–13.
6. Cui G, Jun SB, Jin X, Pham MD, Vogel SS, Lovinger DM, Costa RM: **Concurrent activation of striatal direct and indirect pathways during action initiation.** *Nature* 2013, **494**:238–42.
7. Weglage M, Wärnberg E, Lazaridis I, Calvigioni D, Tzortzi O, Meletis K: **Complete representation of action space and value in all dorsal striatal pathways.** *Cell Rep* 2021, **36**.
8. Sheng M jun, Lu D, Shen Z ming, Poo M ming: **Emergence of stable striatal D1R and D2R neuronal ensembles with distinct firing sequence during motor learning.** *Proc Natl Acad Sci U S A* 2019, **166**:11038–11047.
9. Tunstall MJ, Oorschot DE, Kean A, Wickens JR: **Inhibitory interactions between spiny projection neurons in the rat striatum.** *J Neurophysiol* 2002, **88**:1263–1269.
10. Plenz D: **When inhibition goes incognito: Feedback interaction between spiny projection neurons in striatal function.** *Trends Neurosci* 2003, **26**:436–443.
11. Burke DA, Rotstein HG, Alvarez VA: **Striatal Local Circuitry: A New Framework for Lateral Inhibition.** *Neuron* 2017, **96**:267–284.
12. Tepper JM, Koós T, Wilson CJ: **GABAergic microcircuits in the neostriatum.** *Trends Neurosci* 2004, **27**:662–669.
13. Mallet N, Ballion B, Le Moine C, Gonon F: **Cortical inputs and GABA interneurons imbalance projection neurons in the striatum of parkinsonian rats.** *J Neurosci* 2006, **26**:3875–3884.
14. Tepper JM, Wilson CJ, Koós T: **Feedforward and feedback inhibition in neostriatal GABAergic spiny neurons.** *Brain Res Rev* 2008, **58**:272–281.
15. Flandin P, Kimura S, Rubenstein JLR: **The progenitor zone of the ventral medial ganglionic eminence requires Nkx2-1 to generate most of the globus pallidus but few neocortical**

- interneurons.** *J Neurosci* 2010, **30**:2812–23.
16. Nóbrega-Pereira S, Gelman D, Bartolini G, Pla R, Pierani A, Marín O: **Origin and molecular specification of globus pallidus neurons.** *J Neurosci* 2010, **30**:2824–34.
 17. Abdi A, Mallet N, Mohamed FY, Sharott A, Dodson PD, Nakamura KC, Suri S, Avery S V., Larvin JT, Garas FN, et al.: **Prototypic and Arkypallidal Neurons in the Dopamine-Intact External Globus Pallidus.** *J Neurosci* 2015, **35**:6667–6688.
 18. Abrahao KP, Lovinger DM: **Classification of GABAergic neuron subtypes from the globus pallidus using wild-type and transgenic mice.** *J Physiol* 2018, **596**:4219–4235.
 19. Abecassis ZA, Berceau BL, Win PH, García D, Xenias HS, Cui Q, Pamukcu A, Cherian S, Hernández VM, Chon U, et al.: **Npas1 + -Nkx2.1 + Neurons Are an Integral Part of the Cortico-pallido-cortical Loop.** *J Neurosci* 2020, **40**:743–768.
 20. Hernandez VM, Hegeman DJ, Cui Q, Kelver D a, Fiske MP, Glajch KE, Pitt JE, Huang TY, Justice NJ, Chan CS: **Parvalbumin+ Neurons and Npas1+ Neurons Are Distinct Neuron Classes in the Mouse External Globus Pallidus.** *J Neurosci* 2015, **35**:11830–11847.
 21. Mastro KJ, Bouchard RS, Holt HAK, Gittis AH: **Transgenic Mouse Lines Subdivide External Segment of the Globus Pallidus (GPe) Neurons and Reveal Distinct GPe Output Pathways.** *J Neurosci* 2014, **34**:2087–2099.
 22. Dodson PDD, Larvin JTT, Duffell JMM, Garas FNN, Doig NMM, Kessar N, Duguid ICC, Bogacz R, Butt SJB, Magill PJJ: **Distinct developmental origins manifest in the specialized encoding of movement by adult neurons of the external globus pallidus.** *Neuron* 2015, **86**:501–513.
- In this study, the authors conducted fate mapping experiments to trace the developmental origin of GPe neurons. They also combined *in vivo* electrophysiological recordings in head-fixed mice spontaneously performing brief movements with post hoc immunological identification of the recorded GPe neurons. Altogether, this work elegantly demonstrates that both Arkypallidal and Prototypic neurons have different developmental origins, molecular architecture, and contribution to motor behavior.
23. Mallet N, Micklem BR, Henny P, Brown MT, Williams C, Bolam JP, Nakamura KC, Magill PJ: **Dichotomous organization of the external globus pallidus.** *Neuron* 2012, **74**:1075–86.
 24. Fujiyama F, Nakano T, Matsuda W, Furuta T, Udagawa J, Kaneko T: **A single-neuron tracing study of arkypallidal and prototypic neurons in healthy rats.** *Brain Struct Funct* 2016, **221**:4733–4740.
 25. Saunders A, Oldenburg IA, Berezovskii VK, Johnson CA, Kingery ND, Elliott HL, Xie T, Gerfen CR, Sabatini BL: **A direct GABAergic output from the basal ganglia to frontal cortex.** *Nature* 2015, **521**:85–89.
 26. Mallet N, Pogosyan A, Sharott A, Csicsvari J, Bolam JP, Brown P, Magill PJ: **Disrupted dopamine transmission and the emergence of exaggerated beta oscillations in subthalamic nucleus and cerebral cortex.** *J Neurosci* 2008, **28**:4795–4806.
 27. Cui Q, Pamukcu A, Cherian S, Chang IYM, Berceau BL, Xenias HS, Higgs MH, Rajamanickam S, Chen Y, Du X, et al.: **Dissociable Roles of Pallidal Neuron Subtypes in Regulating Motor Patterns.** *J Neurosci* 2021, **41**:JN-RM-2210-20.
 28. Mastro KJ, Zitelli KT, Willard AM, Leblanc KH, Kravitz A V, Gittis AH: **Cell-specific pallidal intervention induces long-lasting motor recovery in dopamine-depleted mice.** *Nat Neurosci* 2017, **20**:815–823.
 29. Crompe B de la, Aristieta A, Leblois A, Elsherbiny S, Boraud T, Mallet NP: **The globus pallidus orchestrates abnormal network dynamics in a model of Parkinsonism.** *Nat Commun* 2020, **11**:1–14.
 30. Bevan MD, Booth PAC, Eaton SA, Bolam JP: **Selective Innervation of Neostriatal Interneurons by a Subclass of Neuron in the Globus Pallidus of the Rat.** *J Neurosci* 1998, **18**:9438–9452.
 31. Saunders A, Huang KW, Sabatini BL: **Globus Pallidus Externus Neurons Expressing parvalbumin Interconnect the Subthalamic Nucleus and Striatal Interneurons.** *PLoS One*

- 2016, **11**:1–20.
32. Gage GJ, Stoetzner CR, Wiltschko AB, Berke JD: **Selective Activation of Striatal Fast-Spiking Interneurons during Choice Execution.** *Neuron* 2010, **67**:466–479.
 33. Lilascharoen V, Wang EH-J, Do N, Pate SC, Tran AN, Yoon CD, Choi J-H, Wang X-Y, Pribram H, Park Y-G, et al.: **Divergent pallidal pathways underlying distinct Parkinsonian behavioral deficits.** *Nat Neurosci* 2021, doi:10.1038/s41593-021-00810-y.
 - In this work, the authors nicely demonstrate that PV-expressing Prototypic GPe neurons can be further subdivided into two populations depending on their projection sites to the SNr vs. the parafascicular thalamus (PF). Interestingly, GPe-PV neurons projecting to the SNr are associated to locomotion function, whereas the GPe-PV neurons projecting to the PF control reversal learning. Manipulating these specific pathways can also rescue the locomotor and learning deficits present in a mouse model of Parkinson's disease. From a broader perspective, this study also demonstrates that GPe neurons can transmit information directly to thalamic nuclei independently from their classic projections to basal ganglia output nuclei.
 34. Spix TA, Nanivadekar S, Toong N, Kaplow IM, Isett BR, Goksen Y, Pfenning AR, Gittis AH: **Population-specific neuromodulation prolongs therapeutic benefits of deep brain stimulation.** *Science (80-)* 2021, **374**:201–206.
 35. Nakajima M, Schmitt LI, Halassa MM: **Prefrontal Cortex Regulates Sensory Filtering through a Basal Ganglia-to-Thalamus Pathway.** *Neuron* 2019, **103**:445–458.e10.
 36. Baker M, Kang S, Hong S-I, Song M, Yang MA, Peyton L, Essa H, Lee SW, Choi D: **External globus pallidus input to the dorsal striatum regulates habitual seeking behavior in male mice.** *Nat Commun* 2023, **14**:4085.
 37. Foster NN, Barry J, Korobkova L, Garcia L, Gao L, Becerra M, Sherafat Y, Peng B, Li X, Choi J, et al.: **The mouse cortico–basal ganglia–thalamic network.** *Nature* 2021, **598**:188–194.
 38. Glajch KE, Kolver XDA, Hegeman DJ, Cui Q, Xenias XHS, Augustine EC, Herna VM, Verma N, Huang TY, Luo XM, et al.: **Npas1+ Pallidal Neurons Target Striatal Projection Neurons.** *J Neurosci* 2016, **36**:5472–5488.
 - This paper described the input and output organization of Npas1+ GPe neurons and how this pathway is remodelled in parkinsonian mice. In particular, the authors show that Npas1+ neurons establish synaptic contact with both D1- and D2-SPNs, but the GABAergic currents are slightly stronger in D2-SPNs. Given that 60% of Npas1+ neurons are Arkypallidal FoxP2+ neurons, this work is the best evidences we have so far to suggest that Arkypallidal neurons project onto both striatal output pathways.
 39. Mallet N, Schmidt R, Leventhal D, Chen F, Amer N, Boraud T, Berke JD: **Arkypallidal Cells Send a Stop Signal to Striatum.** *Neuron* 2016, **89**:308–316.
 - This paper describes for the first time a functional role of Arkypallidal neurons in action inhibition using a stop-signal task in rats. It also describes that Arkypallidal and Prototypic neurons have very distinct electrical activity during natural sleep and that these properties can be used as electrophysiological signatures to identify both population in awake freely-moving animals.
 40. Katabi S, Adler A, Deffains M, Bergman H: **Dichotomous activity and function of neurons with low- and high-frequency discharge in the external globus pallidus of non-human primates.** *Cell Rep* 2023, doi:10.1016/j.celrep.2022.111898.
 - This interesting paper investigates the functional heterogeneity of GPe neurons in non-human primates engaged in classical conditioning task. The authors demonstrate that GPe low-frequency discharge (LFD) and high-frequency discharge (HFD) neurons exhibit distinct discharge features and different task-related activities. They also propose the intriguing hypothesis that LFD neurons might be homologous to the rodent Arkypallidal neurons.
 41. Fishell G, Kepecs A: **Interneuron Types as Attractors and Controllers.** *Annu Rev Neurosci* 2020, **43**:1–30.
 42. Sandberg M, Flandin P, Silberberg S, Su-Feher L, Price JD, Hu JS, Kim C, Visel A, Nord AS, Rubenstein JLR: **Transcriptional Networks Controlled by NKX2-1 in the Development of**

- Forebrain GABAergic Neurons.** *Neuron* 2016, **91**:1260–1275.
43. Fong WL, Kuo HY, Wu HL, Chen SY, Liu FC: **Differential and Overlapping Pattern of Foxp1 and Foxp2 Expression in the Striatum of Adult Mouse Brain.** *Neuroscience* 2018, **388**:214–223.
 44. Fenno LE, Ramakrishnan C, Kim YS, Evans KE, Lo M, Vesuna S, Inoue M, Cheung KYM, Yuen E, Pichamoorthy N, et al.: **Comprehensive Dual- and Triple-Feature Intersectional Single-Vector Delivery of Diverse Functional Payloads to Cells of Behaving Mammals.** *Neuron* 2020, **107**:836–853.e11.
 45. Ketzef M, Silberberg G: **Differential Synaptic Input to External Globus Pallidus Neuronal Subpopulations In Vivo.** *Neuron* 2020, doi:10.1101/2020.02.27.967869.
 - This insightful study employed *in vivo* whole-cell patch-clamp recordings and optogenetic stimulations to demonstrate that Prototypic and Arkypallidal neurons receive distinct synaptic inputs from the direct, indirect and hyperdirect BG pathways. Specifically, Arkypallidal cells receive stronger inputs from D1-SPNs neurons, while they receive fewer inputs from the D2-SPNs and STN compared to prototypic neurons.
 46. Aristieta A, Barresi M, Azizpour Lindi S, Barrière G, Courtand G, de la Crompe B, Guilhemsang L, Gauthier S, Fioramonti S, Baufreton J, et al.: **A Disynaptic Circuit in the Globus Pallidus Controls Locomotion Inhibition.** *Curr Biol* 2021, **31**:707–721.e7.
 47. Cazorla M, de Carvalho FD, Chohan MO, Shegda M, Chuhma N, Rayport S, Ahmari SE, Moore H, Kellendonk C: **Dopamine D2 receptors regulate the anatomical and functional balance of basal ganglia circuitry.** *Neuron* 2014, **81**:153–164.
 48. Johansson Y, Ketzef M: **Sensory processing in external globus pallidus neurons.** *Cell Rep* 2023, **42**:111952.
 49. Isett BR, Nguyen KP, Schwenk JC, Yurek JR, Snyder CN, Vounatsos M V, Adegbesan KA, Ziausyte U, Gittis AH: **The indirect pathway of the basal ganglia promotes transient punishment but not motor suppression.** *Neuron* 2023, doi:10.1016/j.neuron.2023.04.017.
 - This recent work investigates the mechanism by which optogenetic stimulation of the indirect A2A-SPNs pathway drives motor arrest or transient punishment. While transient punishment requires a cascade of activity changes along the indirect pathway (through the GPe and downstream effects), motor suppression seems to be solely caused by collateral inhibition in the striatum and not by its downstream effects on the GPe. This conclusion challenges the classic view of how motor suppression is achieved in the indirect pathway.
 50. Karube F, Takahashi S, Kobayashi K, Fujiyama F: **Motor cortex can directly drive the globus pallidus neurons in a projection neuron type dependent manner in rat.** *bioRxiv* 2019, doi:10.1101/677377.
 - This paper describes direct projections from M1 and M2 motor cortex to the GPe in rats. These projections are likely formed by pyramidal tract neurons, as they are exclusively ipsilateral. However, it is unclear whether they exclusively innervate the GPe. The synaptic targets of these motor cortex excitatory projections preferentially innervate FoxP2+ Arkypallidal neurons, but not exclusively, as Prototypic Lh6x+ neurons also receive excitatory inputs. In summary, this study highlights the potential roles played by cortico-pallidal connections in modulating the activity of Arkypallidal vs. Prototypic neuronal circuits, although their precise functions remain unknown.
 51. Hunt AJ, Dasgupta R, Rajamanickam S, Jiang Z, Beierlein M, Chan CS, Justice NJ: **Paraventricular hypothalamic and amygdalar CRF neurons synapse in the external globus pallidus.** *Brain Struct Funct* 2018, **0**:0.
 52. Markowitz JE, Gillis WF, Beron CC, Neufeld SQ, Robertson K, Bhagat ND, Peterson RE, Peterson E, Hyun M, Linderman SW, et al.: **The Striatum Organizes 3D Behavior via Moment-to-Moment Action Selection.** *Cell* 2018, doi:10.1016/j.cell.2018.04.019.
 - This impressive study demonstrates that dorsolateral striatum activity systematically represents motor syllables in space and time. The authors also describe that the activity of D1-SPNs and D2-SPNs is complementary during the motor syllable but can appear decorrelated at sub-syllable timescales.
 53. Klaus A, Martins GJ, Paixao VB, Zhou P, Paninski L, Costa RM: **The Spatiotemporal**

- Organization of the Striatum Encodes Action Space.** *Neuron* 2017, **95**:1171-1180.e7.
54. Yttri EA, Dudman JT: **Opponent and bidirectional control of movement velocity in the basal ganglia.** *Nature* 2016, **533**:1–16.
 55. Turner RS, Anderson ME: **Pallidal discharge related to the kinematics of reaching movements in two dimensions.** *J Neurophysiol* 1997, **77**:1051–1074.
 56. Schmidt R, Leventhal DK, Mallet N, Chen F, Berke JD: **Canceling actions involves a race between basal ganglia pathways.** *Nat Neurosci* 2013, **16**:1118–24.
 57. Barbera G, Liang B, Zhang L, Gerfen CR, Culurciello E, Chen R, Li Y, Lin DT: **Spatially Compact Neural Clusters in the Dorsal Striatum Encode Locomotion Relevant Information.** *Neuron* 2016, **92**:202–213.
 58. Farries MA, Faust TW, Mohebi A, Berke JD: **Selective encoding of reward predictions and prediction errors by globus pallidus subpopulations.** *Curr Biol* 2023, **33**:4124-4135.e5.
 59. Vachez YM, Tooley JR, Abiraman K, Matikainen-Ankney B, Casey E, Earnest T, Ramos LM, Silberberg H, Godynnyuk E, Uddin O, et al.: **Ventral arypallidal neurons inhibit accumbal firing to promote reward consumption.** *Nat Neurosci* 2021, **24**.
 60. Morais-Silva G, Campbell RR, Nam H, Basu M, Pagliusi M, Fox ME, Chan CS, Iñiguez SD, Ament S, Cramer N, et al.: **Molecular, Circuit, and Stress Response Characterization of Ventral Pallidum Npas1-Neurons.** *J Neurosci* 2023, **43**:405–418.