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Cell and circuit complexity of the external globus pallidus

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Abstract

The globus pallidus (GPe) of the basal ganglia has been underappreciated due to poor understanding of its cells and circuits. It was assumed that the GPe consisted of a homogenous neuron population primarily serving as a "relay station" for information flowing through the indirect pathway. However, the advent of advanced tools in rodent models has sparked a resurgence in interest in the GPe. Here, we review recent data that have unveiled the cell and circuit complexity of the GPe. These discoveries have revealed that the GPe does not conform to traditional views of the basal ganglia. Particularly, recent evidence confirms that its afferent and efferent connections span both the direct and indirect pathways. Furthermore, the GPe displays broad interconnectivity beyond the basal ganglia, consistent with its emerging multifaceted roles in both motor and non-motor functions. Altogether, recent data prompt new proposals for computational rules of the basal ganglia.

Keywords

cellular diversity; synaptic connectivity; motor control; Parkinson's disease

Our ability to move is essential to survival. Volitional movements are thought to be controlled by two major forebrain descending pathways—the cortical and basal ganglia circuits. The general organization of the basal ganglia is conserved throughout vertebrate evolution¹. In the simplified basal ganglia circuit, the cortex provides excitatory inputs to both the striatum (dStr) and the subthalamic nucleus (STN). They in turn project to the substantia nigra pars reticulata (SNr) and internal globus pallidus (GPi)—the output of the basal ganglia (see Figure 1). As simplified models of the basal ganglia emphasize feedforward circuitry, intrinsic feedback circuits are often ignored. Importantly, although most circuit models assume a homogenous neuronal population, recent studies argue that neuronal heterogeneity is common across the basal ganglia^{2–10}.

The external globus pallidus (GPe), as part of the basal ganglia, was once thought to be a simple relay nucleus. Pioneering studies using crude manipulations yielded conflicting results regarding the function of the GPe. However, by targeting specific cell types with

improved precision, recent work in rodents has revealed that the GPe is more complex than once thought. We now know that the GPe has a heterogeneous neuronal makeup, containing populations with distinct characteristics and functions. Critically, there is now direct evidence that GPe neuron activity plays causal roles in movement^{11–16}. These results corroborate neural recordings that show phasic changes in the firing of GPe neurons are associated with body movement^{17–19}.

Historical reviews of the GPe are available elsewhere^{20–22}. Here, we focus on the evolving views of neuron classification in the GPe, with particular emphasis on the recent breakthroughs in the circuit properties and functions of GPe neurons. We review evidence supporting the idea that the unique connectivity of GPe neuron subtypes drives their functions and that these functions go awry in disease conditions.

Classification of Neurons

Principal neuron classes

Heterogeneity in the phenotype of GPe neurons was noted in the early 1970's. However, as the descriptions of molecularly-defined GPe neuron subtypes were not established until less than a decade ago^{23,24}, it was not possible to correlate the cellular features with the molecular identity of neurons. Using advanced tools in rodent models, it is now established that the near-exclusive expression of the calcium-binding protein parvalbumin (PV) and the transcription factor *Npas1* identifies the two separate supersets of GABAergic neuron types in the adult GPe^{4,13,23–28}.

PV-expressing (PV⁺) neurons and *Npas1*-expressing (*Npas1*⁺) neurons constitute 50% and 30% of the adult GPe, respectively, and are considered as the two principal neuron classes (see Figure 2). They are distinct across multiple modalities, including axonal patterns, synaptic inputs, electrophysiological properties, alterations in disease states, and behavioral roles^{12–14,25,27–31}. The reported abundance of PV⁺ neurons varies across laboratories in part due to methodological differences (e.g., using cell-specific driver lines, retrograde labeling, fate mapping, and immunohistochemistry)^{23–27,29,30,32–35}. Additionally, some of the observed range in the abundance of PV⁺ neurons is due to the spatial gradients in their distribution. However, by systematically examining a number of transgenic lines, a recent examination definitively confirmed that PV⁺ neurons account for approximately 50% of neurons in the GPe²⁸.

Aside from the two principal neuron classes, neurons lacking expression of either PV or *Npas1* amount to 20% of the GPe. This population includes choline acetyltransferase-expressing (ChAT⁺) neurons, which amount to 5% of the total population^{27,28,30} and project to the cortex³⁰. The remaining GPe neurons (~15%) have not been rigorously characterized. This neuron population expresses the transcription factor *Lhx6* but not *Sox6* (*Lhx6*⁺-*Sox6*⁻)²⁸. Likely due to the relatively low abundance of *Lhx6*⁺-*Sox6*⁻ neurons, no data are available from the previous single-cell transcriptomic dataset^{4,36}, and identifying reliable markers for these neurons has been challenging. Importantly, *Lhx6* expression should not be considered as a classifier as it is seen across multiple GPe neuron populations, including in PV⁺, *Npas1*⁺, and PV⁻-*Npas1*⁻ neurons. Furthermore, the reported expression

of Lhx6 within these subpopulations varies widely across laboratories; some studies show little overlap with other neuron groups, while others show up to a ~95% overlap with other established cell type-specific markers^{4,11,14,16,25,26,28,29,34} (see Neuron subclasses & Figure 2).

While it is likely that there are additional rare neuron types yet to be discovered, we now have a near-complete description of the major neuron types within the GPe. Importantly, while neurons with phenotypic similarities are observed in primate studies, we cannot yet directly equate neuron subtypes in rodents to higher-order species due to methodological limitations in identifying neuron types in primates³⁷. Nevertheless, future analyses such as transcriptome-wide spatial profiling and single-nucleus RNA-sequencing will be useful for characterizing the rare neuron types in the GPe.

Neuron subclasses

Although PV⁺ neuron and Npas1⁺ neuron classes are distinct across multiple modalities, such as electrophysiological and synaptic properties, subtle differences exist within each neuron class. Through harnessing molecular tools to target specific GPe neuron populations, recent studies have identified distinct subclasses of PV⁺ and Npas1⁺ neurons with unique properties. Within the Npas1⁺ class, 60% are Foxp2⁺ (Npas1⁺-Foxp2⁺, also known as ‘arkypallidal’ neurons; see Box 1); these neurons represent the first unique GPe neuron subclass described³⁸. Compelling data show the distinct features of Npas1⁺-Foxp2⁺ neurons, such as their developmental origin and their electrophysiological, anatomical, and molecular profiles²⁶. Importantly, as Foxp2 expression is maintained in adults, the Foxp2-Cre and Foxp2-Flp mouse lines have been successfully used across labs to capture this population of neurons^{14,15,28,39}.

The remaining neurons within the Npas1⁺ class are both Nkx2.1⁺ and Lhx6⁺. Unlike Npas1⁺-Foxp2⁺ neurons that project exclusively to the dStr, Npas1⁺-Nkx2.1⁺ neurons project to the midbrain, cortex, and reticular thalamus^{14,28,30} (see Synaptic Outputs & Figure 3). Accordingly, both Npas1⁺-Foxp2⁺ and Npas1⁺-Nkx2.1⁺ neuron subtypes should be regarded as *bona fide* subclasses, as recent single-cell data^{4,36} further confirmed the unique transcriptomic properties of these two Npas1⁺ neuron subclasses. Notably, these studies led to the discovery that GPe neurons labeled using the Npr3-Cre driver are molecularly and anatomically consistent with Npas1⁺-Nkx2.1⁺ neurons¹⁴.

In addition to the two distinct Npas1⁺ neuron subclasses, multiple lines of evidence point to at least two subtypes of PV⁺ neurons (Figure 2). One of these populations is identified by their axonal projection to STN and SNr. The marker Kcng4 demarcates a subset of these STN-projecting PV⁺ neurons. However, a marker encompassing all STN-projecting PV⁺ neurons has yet to be determined¹⁴. In addition, parafascicular thalamus (Pf)-projecting PV⁺ neurons constitute a unique subtype of PV⁺ neurons within the GPe—they have distinct synaptic partners, intrinsic properties, and behavioral roles¹⁶. These PV⁺ neuron subclasses are further distinguished by Lhx6 expression, which converging evidence suggests is present in the STN-projecting population but is weak or absent in the Pf-projecting population^{16,29}. While it is clear that STN-projecting (PV⁺-Kcng4⁺) neurons and Pf-projecting (PV⁺-Lhx6⁻) PV⁺ neurons are unique neuron subclasses, how they assimilate into existing fate-map

and transcriptomic data (see also Developmental origins) is unclear. Therefore, it will be paramount for future studies to reconcile how axonal projection profiles align with molecular marker expression within the PV⁺ neuron class. This in turn should facilitate our goal to map specific neuron types to functions. Altogether, the vast differences in marker expression, axonal projections, and physiological properties between GPe neuron subtypes stand in direct contrast to the traditional model of the GPe serving as a homogenous relay nucleus of the indirect pathway.

Developmental origins

The literature converges on the idea that both the embryonic origins and the congruent expression of transcription factors govern cell specifications⁴⁰. A set of transcription factors have been previously identified to dictate the formation of the GPe^{23,24,41–43}. More recent studies have extended our understanding of the molecular landscape of the GPe and have collectively provided a firmer foundation on its neuronal composition^{14,28}.

The GPe primarily arises from the medial and lateral ganglionic eminence (MGE and LGE)^{23,24,26,44} (see Figure 2). Immunolabeling for Nkx2.1 can be used to identify MGE-derived neurons. However, as only 90% of neurons that arise from the Nkx2.1 lineage maintain Nkx2.1 protein expression in adulthood, this approach is not faithful²⁸. While PV⁺ neurons are believed to largely arise from the MGE, their expression of MGE-markers varies—over 80% express Nkx2.1 whereas only ~30–40% maintain Lhx6 in adulthood^{16,27,28}. This is consistent with data suggesting the existence of two pools of PV⁺ neurons that are produced with different temporal patterns and occupy slightly different, but otherwise largely overlapping spatial domains within the GPe⁴⁴.

Npas1⁺ neurons are derived from both the MGE and LGE; MGE-derived Npas1⁺ neurons are Nkx2.1⁺ and Lhx6⁺, while LGE-derived Npas1⁺ neurons are Foxp2⁺^{23–26,28}. Although developmental origins likely influence transcriptional programs that control the specifications of GPe neurons, Npas1⁺-Nkx2.1⁺ neurons and Npas1⁺-Foxp2⁺ neurons have similar electrophysiological properties despite their differing origins²⁸. In contrast, PV⁺ neurons and Npas1⁺-Nkx2.1⁺ neurons have striking differences in their electrophysiological and synaptic properties despite sharing a common developmental derivation (see Synaptic Inputs).

In addition to the MGE and LGE, a small fraction of GPe neurons are derived from the preoptic area (PoA) and descend from the Dbx1-lineage (Dbx1⁺)^{23,28,42,43,45}. The Dbx1⁺ population contains neurons that express, to varying degrees, all established GPe neuron markers²⁸. This is consistent with the literature that PoA progenitors give rise to a small but diverse contingent set of neurons^{42,43}. In particular, most Dbx1⁺ neurons are Sox6-expressing; they primarily express PV (~70%) and to a lesser extent Npas1 (~10%). Accordingly, Dbx1⁺ neurons do not correspond to the Lhx6⁺-Sox6⁻ population, which is PV⁻-Npas1⁻ (see Principal neuron classes). Despite their lineage difference, PV⁺-Dbx1⁺ neurons display a phenotype similar to the general PV⁺ population^{23,24}. The wide diversity of molecular marker expression seen in PoA-derived neurons further indicates that the developmental origin of GPe neurons should not be considered a predictor of their eventual properties. Altogether, recent studies argue that while developmental origin is an important

consideration for neuronal identification, neuronal birthplace itself does not dictate the physiological and synaptic characteristics of GPe neurons.

Synaptic Inputs

The classic model asserts that the GPe is an intrinsic nucleus within the basal ganglia circuit, receiving inputs exclusively from the dStr and the STN. However, accumulating evidence demonstrates that the GPe receives diverse inputs from additional sources (Figure 3). In particular, direct cortical inputs to the GPe reject the hierarchical organization proposed in the classic model. Additionally, the recent generation of whole-brain input maps^{16,28,46–48} reaffirms that the GPe integrates a wide variety of inputs across a number of systems and should therefore no longer be considered an intrinsic nucleus. As the size of inputs in these studies is estimated from cell counts, results cannot be easily interpreted without considering the termination patterns or the physiological properties of the inputs. Regardless, the intersection of a complex set of inputs at the GPe allows the transformation of salient cues to motoric responses. Additionally, inputs from non-basal ganglia regions support the notion that the GPe participates in non-motor functions.

Though different markers and classification schemes are used in the literature, the data from ‘prototypic’ and ‘arkypallidal’ neurons coincide with the PV⁺ and Npas1⁺ neuron classifications, respectively (see Box 1). For simplicity, research findings are discussed in relation to these principal neurons in the following sections. Consistent with the idea that PV⁺ neurons and Npas1⁺ neurons receive distinct sets of inputs, the two neuron classes have different electrophysiological properties^{14,27,28}, suggesting a different mode of input-output transformation between them. The differences in the electrophysiological properties of neuron subclasses are more subtle, and it is still unknown how the complement of inputs varies substantially between neuron subclasses.

GABAergic inputs

The dStr is, by far, the largest input to the GPe—the number of input neurons from the dStr constitutes ~80% of the total projection to the GPe and is at least an order of magnitude larger than that from other brain regions^{47,49}. This observation is consistent with the earlier finding that GABAergic synapses amount to over 80% of all synapses in the GPe²⁰.

Contrary to the simplified basal ganglia model, it has been known since the 1980s that axons from both direct-pathway spiny projection neurons (dSPNs) and indirect-pathway SPNs (iSPNs) converge at the GPe. While iSPN axons terminate exclusively in the GPe, modern techniques confirm that dSPN axons collateralize in both the GPe and the SNr^{47,49–54}; these studies solidify the fact that the GPe receives notable direct pathway input and demonstrate the physiological and targeting properties of dSPN collaterals. Nevertheless, the indirect pathway remains the predominant input to the GPe. While previous studies showed that dSPNs provide roughly half the number of boutons compared to iSPNs in the GPe, more recent estimations of the number of boutons formed by iSPNs is three to eight times higher than that formed by dSPNs^{47,49}. Both viral-tracing and patch-clamp studies demonstrate that iSPNs strongly target canonical STN-projecting PV⁺ (PV⁺-Kcng4⁺) neurons, whereas

dSPNs largely target Npas1⁺ neurons, Pf-projecting PV⁺ (PV⁺-Lhx6⁻) neurons, and ChAT⁺ neurons^{15,16,30,39,47,55,56}.

GPe neurons provide lateral GABAergic inhibition to neighboring neurons through their local axon collaterals^{14,15,31,39,56–61}. These collaterals give rise to a large number of local synapses, in contrast to the relatively few synapses typically formed by input from individual SPNs⁵⁹. They have not been studied in great detail until recently due to the inherent difficulty in identifying and selectively activating individual classes of GPe neurons and their collateral axons. These technical challenges have been overcome by combining transgenic and optogenetic approaches. Although subtle nuances exist across studies, three key findings have recently emerged. First, PV⁺ neurons provide the largest local input. Second, Npas1⁺-Foxp2⁺ neurons do not produce appreciable levels of local connections. Third, the local collaterals can strongly inhibit neighboring neurons and thus are integral to both local circuit dynamics and downstream network effects^{14,15,31,39,56,57}. While further studies are needed to investigate the functional relevance of the unique organization of the local collaterals, the existence of local inhibitory networks creates an anatomical substrate for feedback and functional opponency across neuron subtypes.

Glutamatergic inputs

Whole-brain input maps verify that the STN is one of the primary glutamatergic inputs innervating the GPe^{16,46,47}. However, the cellular targeting properties of this input were not known until recently. Three independent studies have convincingly demonstrated that STN inputs target PV⁺ neurons more strongly relative to Npas1⁺ neurons^{13,15,39}. While the neuronal makeup of the STN was generally thought to be homogeneous, recent studies show that STN neurons are more heterogeneous than previously expected^{6,9,58,62–64}. Therefore, it will be important to determine if PV⁺-targeting neurons within the STN are distinct from those targeting Npas1⁺ neurons.

Recent studies highlight the existence of cortical inputs to the GPe. Importantly, viral-tracing data argue that the spatially-distributed cortical inputs altogether form the largest source of excitatory inputs to the GPe^{16,28,65–68}, in contrast to the traditional model, which assumes dominant glutamatergic input from the STN. These cortical inputs arise primarily from pyramidal tract neurons^{9,28,67}. However, the precise downstream targets require further characterization, as data from recent studies are somewhat conflicting. While a recent study suggests that secondary motor cortex input selectively targets Npas1⁺-Foxp2⁺ neurons⁶⁵, data from others show that cortical innervations do not target specific neuron subtypes^{9,16,28}.

In addition to the STN and cortex, the Pf and pedunculopontine nucleus send glutamatergic projections to the GPe^{13,16,47,69–71}, two sources that are omitted from the classic model. These inputs do not show a biased connectivity pattern across PV⁺ neuron and Npas1⁺ neuron classes¹³. Taken together, the most recent data indicate that the GPe integrates a wide array of synaptic inputs, including from sources beyond traditional basal ganglia nuclei.

Neuromodulatory inputs

The GPe receives substantial dopaminergic input—recent viral tracing data show that this input arises primarily from the substantia nigra pars compacta, though we have yet to

determine the precise neuronal subpopulation responsible^{3,16,46,47}. However, this is likely an underestimation of the total dopamine input; earlier findings suggest that a much broader area, including the substantia nigra pars compacta, ventral tegmental area, and retrorubral area, give rise to the dopaminergic innervations in the GPe^{62,72–79}.

The GPe is at the intersection of motor-anxiety circuits, as tracing studies reveal inputs from corticotropin releasing factor-expressing neurons in the paraventricular thalamus and the central amygdala^{16,46–48,80}. While the signaling partners of this input remain to be explored, strong evidence argues that PV⁺ neurons and their projections are a major target as they robustly express Crfr1^{46,48,80,81}. Notably, the central amygdala forms one of the largest extrinsic inputs targeting the GPe⁴⁷, and this projection has been recently implicated in fear learning⁸⁰.

Altogether, whole-brain connectome analyses suggest a diverse neuromodulatory control at the GPe level^{3,16,46,47,82} and reinforce the notion that the GPe is a critical node that interfaces signals from a number of systems (see Figure 3). In turn, neuromodulatory control of GPe neurons can influence both motor and non-motor behavior within the same circuit.

Synaptic Outputs and Functions

Although major efferent projections from the GPe have been mapped previously^{20–22}, the circuit elements involved were not previously known. By gaining genetic access to unique neuron types within the mouse GPe, researchers have provided detailed circuit dissections for GPe neuron outputs and their functional implications (see Figure 4). These studies collectively reveal that changes in the activity of GPe neurons *in vivo* are not merely passive responses to movement—in other words, GPe neurons have the capacity to tune or maintain ongoing actions. Furthermore, increasing evidence indicates GPe neuron involvement in non-motor roles, including learning¹⁶, limbic function^{2,46,48,80,81,83}, sleep⁸⁴, and the processing of sensory and reward cues^{37,56}. It is probable that interconnections with classic basal ganglia nuclei (such as dStr and STN) are involved in multiple functions, consistent with the “parallel processing” model (see Figure 5). Additionally, more recently discovered connections (i.e., cortex and thalamus) play important roles in both motor and non-motor functions. Altogether, anatomical and functional data collectively emphasize that the GPe should not be considered merely an intrinsic nucleus within the larger basal ganglia.

PV⁺ neurons

PV⁺ neurons form the principal inhibitory innervation to the STN^{25,27,29,32,33,35}. Consistent with this, optogenetic and chemogenetic stimulation of pan-PV⁺ neurons or selectively STN-projecting GPe neuron subsets promote movement^{11,13,14,16}. In addition, this effect can be recapitulated by direct inhibition of STN neurons¹³. These findings agree with the well-established relationship between STN activity and movement suppression^{85–93}. Along with the projection to the STN, canonical PV⁺ (PV⁺-Kcng4⁺) neurons also collateralize within the SNr and GPi^{14,16,94}. In addition to locomotion, modulation of PV⁺ neuron collaterals in the SNr induces avoidance behavior⁴⁸. These findings are consistent with the idea that both motor and non-motor signals are processed in parallel within the basal ganglia.

Although earlier studies examined the electrophysiological and anatomical properties of the STN-GPe network, the cell-type specificity of this network was unknown until recently. The latest findings collectively emphasize a closed reciprocal loop formed between the STN and PV⁺ neurons (see Synaptic Inputs), adding critical insight into the cellular constituents involved. The recurrent loop formed between the STN and PV⁺ neurons has strong implications for the pathological network activity observed in Parkinson's disease (PD) (see Disease Alterations). However, it is important to note that optogenetic inhibition of PV⁺ neurons does not yield any motor responses¹¹, suggesting the possibility of compensatory network mechanisms, such as the involvement of the local collaterals. Alternatively, the basal ganglia may control motor output by computation through a cascade of logic gates that operate on multiple rules. This idea is consistent with the co-activation of dSPNs and iSPNs during volitional movement^{95–97}.

Additionally, a small subset of PV⁺ neurons target the Pf (see Neuron subclasses). These non-canonical PV⁺ (PV⁺-Lhx6⁻) neurons are not involved in motor control, but are associated with reversal learning¹⁶. Given that STN-projecting (PV⁺-Kcng4⁺) and Pf-projecting (PV⁺-Lhx6⁻) PV⁺ neurons receive distinct sets of synaptic inputs, their respective roles in motor and non-motor functions reinforce the concept that GPe neuron subtypes enact their functions through their unique circuit architecture.

Npas1⁺-Foxp2⁺ neurons

Based on relative spike timing, earlier literature inferred that Npas1⁺-Foxp2⁺ neurons mediate motor inhibition by broadcasting an inhibitory signal across the dStr⁹⁸—their exclusive projection target. However, this causality had not been demonstrated. Importantly, recent optogenetic and chemogenetic approaches demonstrate that stimulation of either pan-Npas1⁺ neurons or the Npas1⁺-Foxp2⁺ subset leads to motor inhibition during both spontaneous ambulation and a trained-task^{12–15}, further establishing that GPe neurons directly modulate motor behavior. Additionally, optogenetic inhibition of Npas1⁺ neurons leads to motor promotion¹³, arguing that the observed phenotype with excitatory actuators is not a spurious gain-of-function. As discussed earlier, Npas1⁺-Foxp2⁺ neurons do not form an extensive local collateral network within the GPe; it is therefore likely that they exert their circuit effects within their terminal field (i.e., within the dStr). While Npas1⁺-Foxp2⁺ axons impinge on dendrites of SPNs^{12,38}, the biological significance of this anatomical arrangement has not been examined.

Npas1⁺-Nkx2.1⁺ neurons

In contrast with Npas1⁺-Foxp2⁺ neurons, the projection and function of Npas1⁺-Nkx2.1⁺ neurons are less well-characterized. These neurons project to the midbrain, cortex, and reticular thalamus^{14,28,30}. However, it is unclear if a single Npas1⁺-Nkx2.1⁺ neuron projects to multiple brain regions or if separate neurons are responsible for each of these projections.

The projection to the midbrain agrees with previous electrophysiological, neurochemical, and viral tracing data^{99–103}. While there is evidence suggesting PV⁺ neurons target the midbrain⁹⁹, additional studies strongly argue that this projection is more consistent with the axonal projection patterns of Cre-expressing neurons from the Lhx6 driver^{29,104}; the

discrepancies may be related to the nuances of rabies virus tracing¹⁰⁵. While this projection is likely constituted by Npas1⁺-Nkx2.1⁺ neurons, it remains to be determined if other neurons target midbrain dopamine neurons. More importantly, the behavioral relevance of this projection awaits further clarification. In particular, the feedback loop formed between GPe and midbrain dopamine neurons (see also Neuromodulatory inputs) may create complex circuit effects.

The GPe projections to the cortex arise from Npas1⁺-Nkx2.1⁺ neurons and ChAT⁺ neurons^{28,30}. A mixture of neurons in the cortex has been shown to receive this GPe input^{30,106,107}. While the functions of these projections await further characterization, recent data suggest that they are involved in regulating sleep^{84,108,109}. Additionally, indirect evidence suggests that Npas1⁺-Nkx2.1⁺ neurons may contribute to other non-motor functions. Specifically, Nkx2.1⁺ neurons that are PV⁻ and Foxp2⁻ innervate lateral habenula-targeting neurons in the internal globus pallidus; however, it is possible that these neurons are Lhx6⁺-Sox6⁻ rather than Npas1⁺. Nonetheless, these data further implicate the contribution of GPe neurons to the limbic functions of the basal ganglia^{2,83}.

Disease Alterations

The selection of desired actions and concomitant suppression of competing actions is key to volitional movement. Disruption of the ability to facilitate desired movements and inhibit unwanted movements results in disorders such as PD, Huntington's disease (HD), and dystonia. As GPe neurons are critically involved in motor control, we survey the emerging observations of the GPe in these disease conditions.

Parkinson's disease

The loss of nigral dopamine neurons in PD leads to widespread basal ganglia circuit alterations. GPe neuron activity is altered following the loss of dopamine, shifting from autonomous decorrelated pacemaking to highly synchronous burst firing. This aberrant GPe neuron activity correlates with the emergence of motor symptoms in both animal models and human patients¹¹⁰⁻¹¹³, emphasizing the importance of the GPe in PD. Additionally, one of the hallmarks of PD is the widespread development of synchronized basal ganglia activity known as β -oscillations (13–30 Hz), which are implicated in motor suppression¹¹⁴⁻¹¹⁸. Recent evidence indicates that the GPe plays a critical role in the development of pathological β -oscillations. Specifically, optogenetic inhibition of GPe neurons robustly suppresses β -oscillations in chronic 6-OHDA lesioned rodents, a well-established model of PD. Additionally, optogenetic patterning of GPe neuronal firing at β frequency leads to key circuit changes reminiscent of naturally occurring β -oscillations¹¹⁹.

Recent studies using animal models of PD show that dopamine neuron loss has cell type-specific effects in the GPe. Following chronic 6-OHDA lesion, Npas1⁺ neurons display a reduction in spontaneous activity (where fast transmission was intact) *ex vivo*²⁷. More recent studies suggest that the hypoactivity of Npas1⁺ neurons is at least in part due to changes in GABAergic signaling rather than alterations in their intrinsic properties¹³. In contrast, following acute or chronic 6-OHDA administration, PV⁺ neurons display only subtle or no detectable changes in their firing compared to control mice *ex vivo*^{16,27,120}.

Synaptic inputs to GPe neurons are altered in models of PD. Following chronic 6-OHDA lesion, STN input targeting PV⁺ neurons is weakened in *ex vivo* slices. This alteration is likely due to a net loss in synaptic contacts and the associated postsynaptic receptors. In contrast, STN-Npas1⁺ input is unaltered. These results agree with earlier findings that AMPA and NMDA receptors are downregulated in rodent models of PD¹³. Furthermore, both systemic administration and GPe-specific application of NMDA antagonists are effective in ameliorating motor symptoms in animal models of PD^{121–123}, arguing that the initial alteration may be useful for compensating the hyperactivity of STN input *in vivo*; however, the loss of NMDA receptor activity is likely maladaptive. The altered glutamate imbalance is further exacerbated by the disrupted glutamate homeostasis that is normally maintained by local astrocytes¹²⁴.

In addition to STN input, striatal input to the GPe is also altered in the chronic 6-OHDA model. An *ex vivo* examination of dStr-GPe input revealed a net increase in the strength of the total striatal input to the GPe following chronic 6-OHDA lesion¹²⁴. Although this finding is consistent with the prediction from the classic model, the observed alteration was mediated by a local disruption of glutamate homeostasis within the GPe. However, a more recent examination reveals that the indirect-pathway inputs to PV⁺ neurons are unchanged. This contrasts with the direct-pathway input to Npas1⁺ neurons, which is strengthened following chronic 6-OHDA lesion⁴⁷. As the ascending Npas1⁺ projections to the striatum are strengthened under the same condition¹², it is likely that this recurrent loop contributes to the hypokinetic symptoms of PD. It is unclear at this point why there is a discrepancy between studies; it is worth noting that the method of stimulation (electrical vs. optogenetic) can be a key disparity.

The loss of dopamine neurons alters efferent projections and *in vivo* function of GPe neurons. For example, the GPe-STN projection is strengthened following chronic 6-OHDA lesion¹²⁵. This process is heterosynaptically induced, such that excessive cortical input to STN neurons leads to an increase in the strength of the GPe-STN projection¹²⁶, indicating that GPe output can be regulated by wider basal ganglia circuit alterations in pathological states. Additionally, the PV⁺-SNr projection is weakened in 6-OHDA mice via a reduction in presynaptic transmitter release¹⁶, suggesting this alteration may contribute to hypokinetic symptoms in PD. Importantly, optogenetic activation of pan-PV⁺ neurons or STN-projecting PV⁺ (PV⁺-Kcng4⁺) neurons rescues motor deficits in both acute^{11,16} and chronic¹³ 6-OHDA animals. These results strongly argue for the adaptive nature of the GPe outputs. Furthermore, following partial dopamine loss, chemogenetic inhibition of Pf-projecting PV⁺ (PV⁺-Lhx6⁻) neurons rescues impairment in a reversal learning task¹⁶, suggesting that these neurons may have therapeutic potential for the cognitive symptoms of PD.

Remarkably, targeting PV⁺ neurons has profound effects on rescuing locomotor activity in preclinical models of PD. Although optogenetic stimulation of PV⁺ neurons produces reliable locomotor rescue in 6-OHDA models of PD across multiple laboratories, the duration of the motor improvement following GPe neuron stimulation varies across studies (see Figure 5). For example, in a chronic 6-OHDA model, the motor improvement following PV⁺ neuron stimulation only lasts for the duration of the optical stimulation¹³. However,

studies using acute 6-OHDA models report motor improvements that persist beyond the duration of the stimulation^{11,16,127}, suggesting that the recovery period following 6-OHDA lesion may be of critical importance in determining whether motor-promoting effects of PV⁺ neuron stimulation are acute or persistent. Furthermore, these studies differ in the duration and intensity of their stimulation of PV⁺ neurons, thus making it difficult to compare results across laboratories. Therefore, it is important for future studies to carefully consider the translational applicability of different 6-OHDA lesion models and stimulation paradigms when interpreting functional results.

Huntington's disease

HD is an inherited neurodegenerative movement disorder that leads to basal ganglia dysfunction. Currently, the precise roles of GPe neurons in HD are still unclear. However, hyperactivity of the GPe is presumed to underlie some of the behavioral symptoms of HD^{128,129}, and deep brain stimulation of the GPe provides symptomatic relief in human patients¹³⁰.

Contrary to the widespread loss of SPNs in the striatum, there is typically no GPe neuron loss in human patients until late in the disease progression^{131,132}. Consistent with this observation, GPe neuron loss is only observed at 18 months in the Q175 mouse model of HD. Although the abundance of PV⁺ neurons is maintained for up to 18 months, the abundance of Npas1⁺-Foxp2⁺ neurons is significantly reduced at 18 months, but not at 6 or 12 months¹³³. It will be important to determine if the susceptibility of Npas1⁺-Foxp2⁺ neurons is associated with pathological hallmarks of HD, such as neuronal intranuclear inclusions and mutant huntingtin load.

Increases in $\alpha 1$, $\beta 2/3$, and $\gamma 2$ GABA_A receptor subunits on GPe neurons are observed in human patients¹³⁴. Additionally, increased postsynaptic responses in GPe neurons to striatal inputs are seen across the Q175, YAC128, and R6/2 models of HD^{135,136}. The data from mouse models argue that increased striatal responses are independent of cell loss in the dStr. Instead, this alteration is likely a homeostatic reaction to decreased iSPN input, as the coupling between cortical input and iSPNs is weakened¹³⁷⁻¹³⁹. Although the intrinsic properties of PV⁻ neurons are unaltered, their activity *in vivo* is suppressed by the increased collateral input from PV⁺ neurons¹⁴⁰.

Dystonia

Dystonia is characterized by uncontrollable muscle contractions, resulting in involuntary and abnormal movements and postures^{141,142}. Data from animal models and human patients suggest that abnormal GPe neuron activity contributes to dystonia symptoms¹⁴³⁻¹⁴⁷. Importantly, in the DYT1 mouse model of dystonia, there is reduced firing of PV⁺ neurons due to impaired function of HCN channels. Pharmacological enhancement of HCN channel activity restores physiological PV⁺ neuron pacemaking and improves motor performance¹⁴⁸. These data suggest GPe neurons play important roles in dystonia symptomatology and highlight PV⁺ neurons as potential therapeutic targets in some forms of dystonia. However, the roles of other neuron subtypes in dystonia models remain to be examined.

Concluding Remarks

Methodological revolutions have greatly advanced our understanding of the GPe. Its complex neuron types, diverse synaptic inputs, and widespread axonal projection patterns argue that the architecture of GPe does not conform to the traditional direct-indirect model of the basal ganglia. In particular, new data that show interconnections between the GPe and “upstream nuclei” (such as the cortex and dStr) go against the hierarchical organization of the classic model. Furthermore, the causal roles that GPe neurons play in movement strongly argue that new theories of how the basal ganglia compute motor commands are needed. For example, can neural signals from the GPe veto decisions that are already committed at the cortical, striatal, or STN level? Rules governing these outcomes are likely brain state-dependent; therefore, it will be important to establish the actions of various neuromodulators within the GPe with behavioral context.

We are still in the beginning stages of understanding the full behavioral capacity of the GPe, especially the non-motor aspects. Brain-wide inputs to the GPe have now been mapped; given the extent of connectivity between non-classic motor regions, it is conceivable that the GPe is involved in further undiscovered non-motor functions. Future characterization of physiological properties and activation patterns of these inputs in relation to natural behaviors will help further pinpoint the precise roles of the GPe. This should be a reasonable goal as we make major headways in computer vision techniques, artificial intelligence, and biosensor development. Finally, while a consensus on GPe neuron subtypes and their functions is emerging, we need to develop more powerful models that consider how they integrate with specific action selection networks both within and beyond the basal ganglia.

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Box 1. Evolving classification of GPe neurons

GPe neurons are often classified into two main groups: ‘arkypallidal’ and ‘prototypic’ neurons. The defining features of these neurons have emerged over time since the early 2000s^{38,150}. Recent evidence confirmed that arkypallidal neurons directly correspond to the Npas1⁺-Foxp2⁺ neuron subclass. These neurons have a unique molecular signature, developmental origin, and axonal projection pattern. On the other hand, prototypic neurons (aka non-arkypallidal neurons) encompass a heterogeneous population of neurons that differ widely in their anatomical projections, electrophysiological properties, and functional output, thus limiting the effectiveness of the classification and contributing to less rigorous comparisons within the field. It is important to note that while all PV⁺ neurons are prototypic, not all prototypic neurons are PV⁺. Furthermore, not all GPe neurons with ascending projections to the dStr are arkypallidal neurons. We propose the term prototypic be avoided, as it is repeatedly misused, and suggest that GPe neurons be classified using more descriptive designations, such as by molecular signature or principal projection target(s) to avoid confusion.

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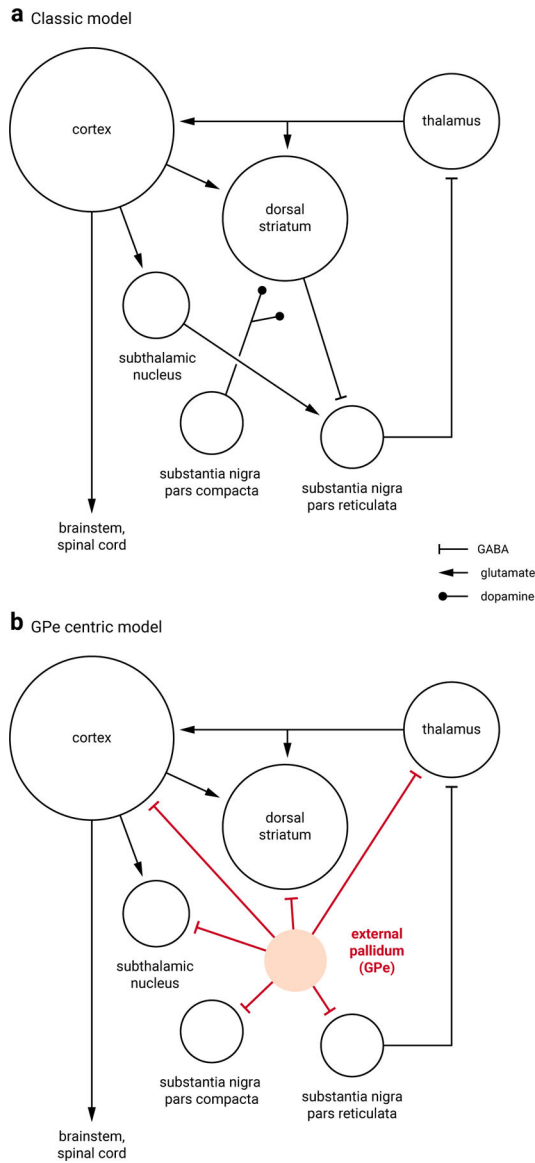
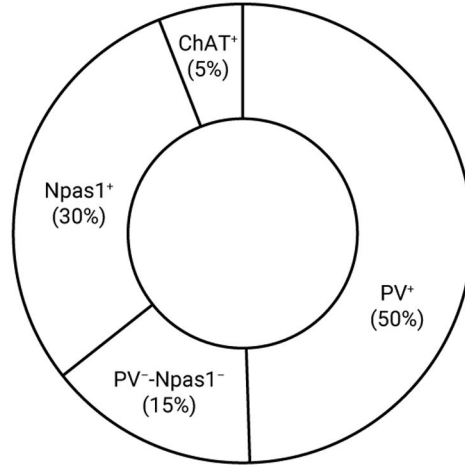


Figure 1. Classic model and GPe-centric model of the basal ganglia.

a. A simplified classic circuit diagram showing the key nodes within the basal ganglia; the circuit role of the GPe is often ignored. The dorsal striatum and subthalamic nucleus are the two input stations that receive excitatory cortical inputs; the substantia nigra pars reticulata is the output station that provides inhibitory projection to the thalamus. Dopamine exerts a broad influence over the entire basal ganglia circuit, especially the dorsal striatum. Size of the target areas (circles) is an artistic rendering based on the volume of the brain areas. **b.** The GPe sends inhibitory projections to all key structures within the circuit. Some of the connections are removed for illustration purposes to highlight the central role of the GPe within the basal ganglia.

a GPe composition



b Developmental origins

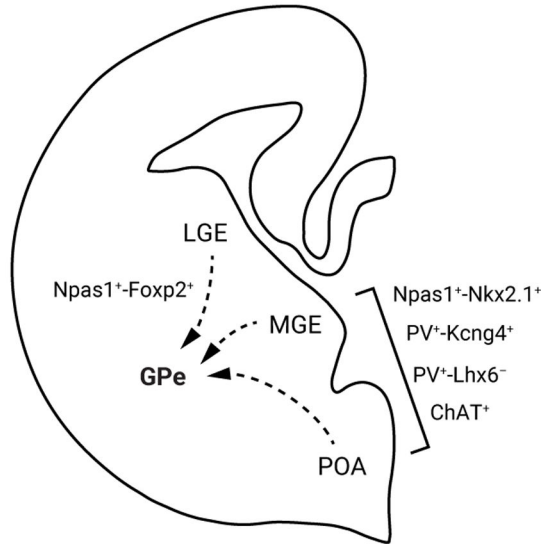


Figure 2. Developmental and marker heterogeneity of GPe neurons.

a. Pie chart summarizing the neuronal composition of the rodent GPe. The area of the sectors represents the approximate size of each neuron class. PV⁺ neurons (which constitute 50% of the GPe) can be subdivided based on their projections to the subthalamic nucleus and substantia nigra pars reticulata vs. parafascicular nucleus. Npas1⁺ neurons are 30% of the GPe; they can be subdivided into two subclasses that differ in their marker profiles and axonal projections. ChAT⁺ neurons are ~5% of the total GPe neuron population, show no overlap with other known classes of GPe neurons, and project broadly to cortical areas. PV⁻-Npas1⁻ neurons amount to ~15% of the total GPe and are the least characterized neuron subtype.

b. Diagram of a cross section of the rodent fetal forebrain illustrating the contributions of lateral ganglionic eminence (LGE), medial ganglionic eminence (MGE), and preoptic area

(PoA) to GPe neurons subtypes. The MGE and PoA give rise to the majority of GPe neuron subtypes, except $Npas1^+$ - $Foxp2^+$ neurons, which are derived from the LGE.

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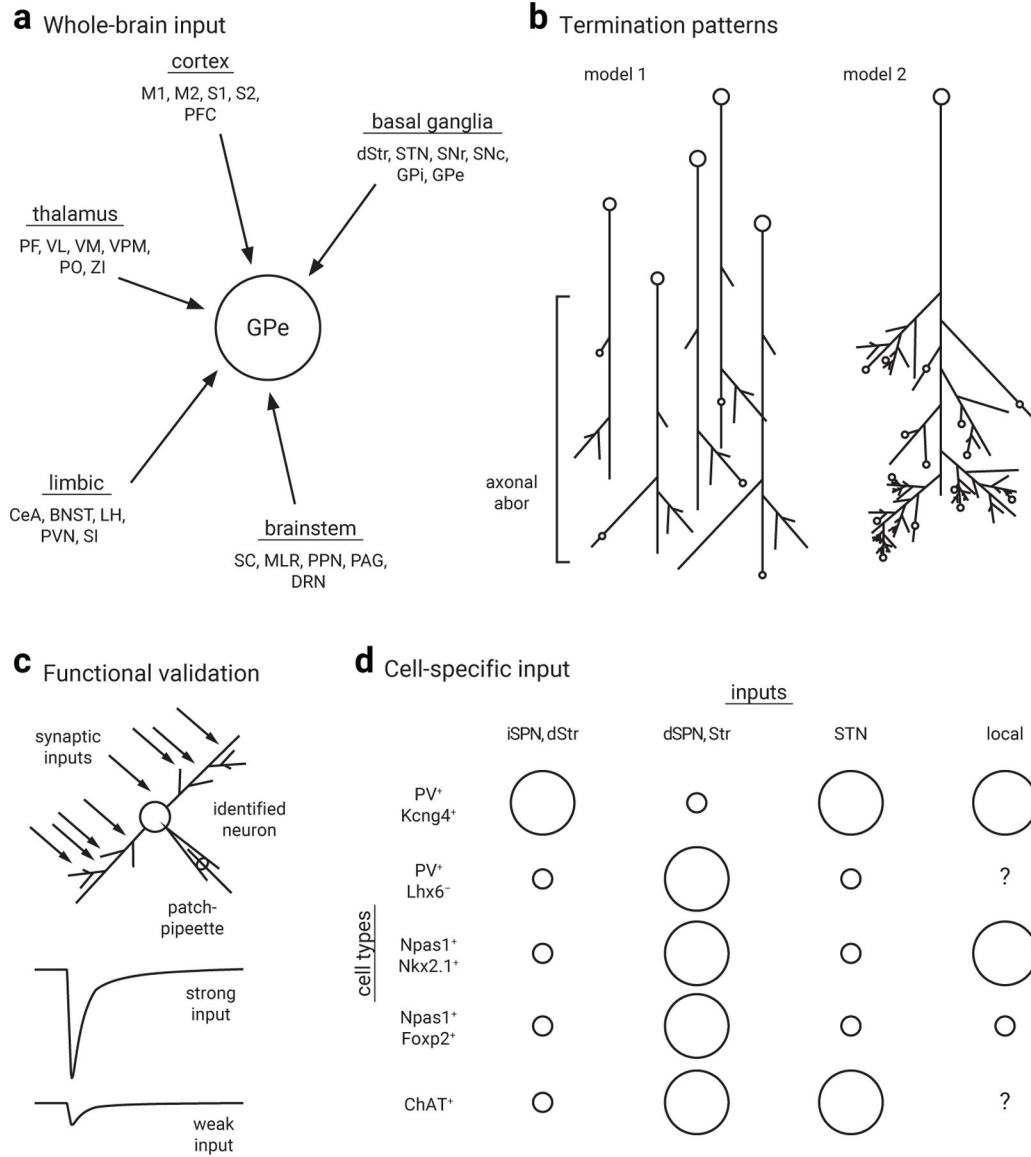


Figure 3. Input to the GPe.

a. Diagram highlighting the diversity of inputs to the GPe across the entire brain. Data are summarized from viral tracing studies^{16,46–48}. Differences are observed across studies due to technical nuances, such as tropism of viral preparations. Connectome results should be interpreted with both the termination patterns (**b**) and functional properties of inputs in mind. Additional characteristics, such as the physiological properties, chemical nature, and cell-targeting patterns remain to be studied systematically. Abbreviations: BNST, bed nucleus of the stria terminalis; CeA, central nucleus of the amygdala; DRN, dorsal raphe nucleus; dStr, dorsal striatum; GPe, external globus pallidus; GPi, internal globus pallidus; LH, lateral hypothalamus; M1, primary motor cortex; M2, MLR, mesencephalic locomotor region; PAG, periaqueductal gray; PF, parafascicular nucleus; PFC, prefrontal cortex; PPN, pedunculopontine nucleus; S1, primary sensory cortex; S2, secondary motor cortex; SC, superior colliculus; SI, substantia innominata; SNc, substantia nigra pars compacta; SNr,

substantia nigra pars reticulata; STN, subthalamic nucleus; VL, ventrolateral nucleus; VM, ventromedial nucleus; VPM, ventral posteromedial nucleus; ZI, zona incerta.

b. Input to the GPe shows varied termination patterns. Model 1 describes input formed by a large number of neurons giving rise to only a small number of synapses (e.g., striatal projection neurons). Model 2 describes input formed by a small number of neurons that give rise to a large number of synapses (e.g., PV⁺ neuron local collaterals).

c. While widespread inputs have been mapped via tracing studies, relatively few inputs have been functionally validated. However, a select subset of inputs to the GPe has been characterized using patch-clamp recordings either *ex vivo* or *in vivo*. For simplicity, these inputs are categorized into strong vs. weak inputs in both **c** and **d**.

d. Simplified visualization of the relative strength of basal ganglia inputs to GPe neuron subtypes. Note that GPe neurons receive substantial direct pathway input, inconsistent with the classic model. Size of the circles is used as a binary categorization to differentiate between strong vs. weak inputs across GPe neuron subtypes; it is an approximation and not intended for comparisons among inputs within a given GPe neuron subtype. Question marks denote inputs that have not been studied; cell-type specificity of inputs from other regions remains to be examined.

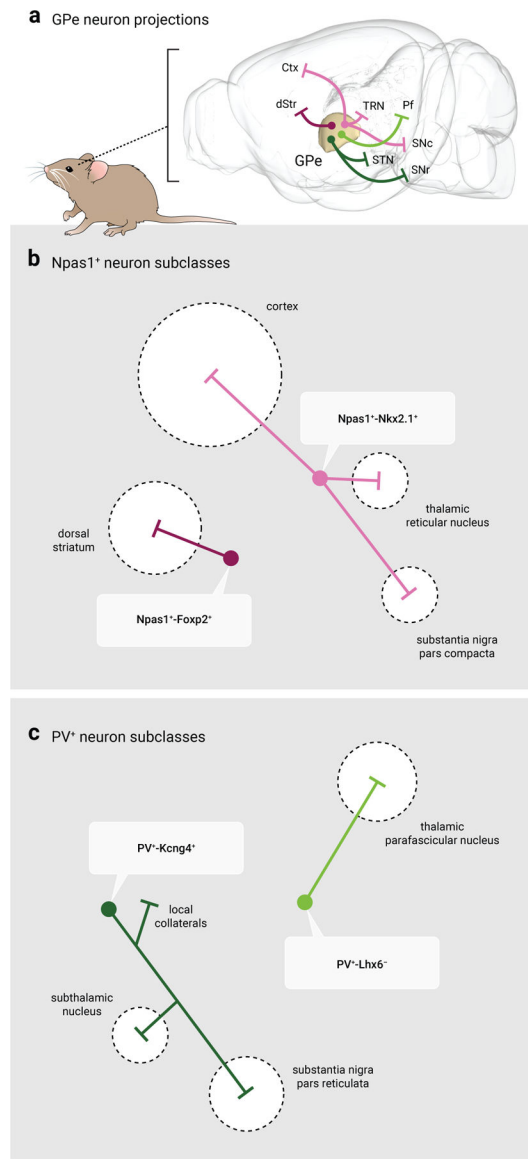


Figure 4. Distinct efferent projections of GPe neuron subtypes.

a. Map displaying the major projection targets of PV⁺ neurons and Npas1⁺ neurons. Note that GPe neuron projections are widespread and extend beyond the traditional basal ganglia nuclei, in contrast to the classic indirect pathway model. Magenta: Npas1⁺-Foxp2⁺ neurons; Pink: Npas1⁺-Nkx2.1⁺ neurons; Dark green: PV⁺-Kcng4⁺ neurons; Light green: PV⁺-Lhx6⁻ neurons. Abbreviations: Ctx, cortex; dStr, dorsal striatum; Pf, thalamic parafascicular nucleus; SNr, substantia nigra pars reticulata; SNc, substantia nigra pars compacta; STN, subthalamic nucleus; TRN, thalamic reticular nucleus.

b. Schematic of the projection targets of Npas1⁺ neuron subtypes. Npas1⁺-Foxp2⁺ neurons represent 60% of the total Npas1⁺ neuron class and project exclusively to the dorsal striatum, targeting spiny projection neurons. Npas1⁺-Nkx2.1⁺ neurons represent 40% of the total Npas1⁺ neuron class and project to the cortex, thalamic reticular nucleus, and substantia nigra pars compacta.

c. Schematic of the projection targets of identified PV⁺ neuron subtypes. PV⁺-Kcng4⁺ neurons overlap with canonical PV⁺ neurons; they project to the subthalamic nucleus, substantia nigra pars reticulata and provide collateral inhibition to local GPe neurons. PV⁺-Lhx6⁻ neurons project to the thalamic parafascicular nucleus. Size of the target areas (dotted circles) in **b**, **c** are artistic renderings based on the volume of the target areas and do not reflect the axonal density, synaptic strength, or contacts formed by GPe neuron subclasses.

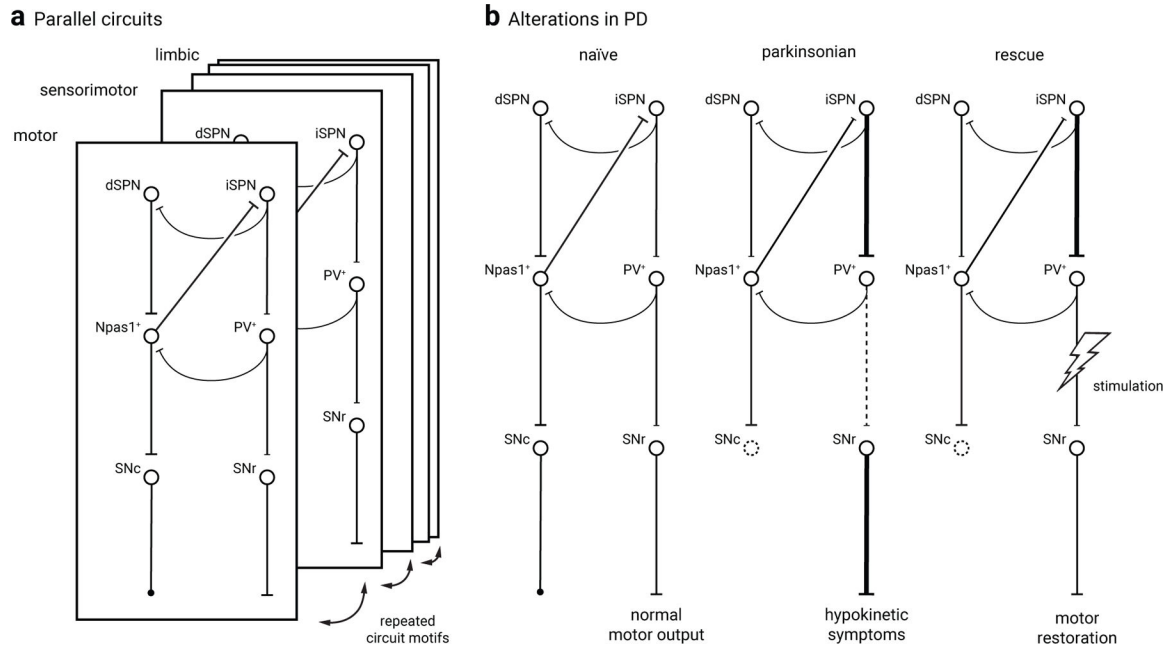


Figure 5. Cellular and circuit substrates for functional regulation by GPe neurons.

a. A simplified diagram of the GPe and its associated circuit. PV⁺ neurons and Npas1⁺ neurons are illustrated as the principal cell classes within the GPe and are differentially organized with the input and output of the basal ganglia. Consistent with their distinct electrophysiological properties, PV⁺ neurons and Npas1⁺ neurons have unique behavioral roles: PV⁺ neurons are motor-promoting, while Npas1⁺ neurons are motor-inhibiting. The PV⁺ neuron and Npas1⁺ neuron classes jointly tune motor behavior through a push-pull mechanism; local inhibitory connections between these neuron classes may control this process. Importantly, the same circuit motif is conserved across motor, sensorimotor, and limbic domains of the basal ganglia to support parallel processing of information.

b. A proposed model of circuit alterations in 6-OHDA lesioned mice and therapeutic rescue via PV⁺ neuron stimulation. PV⁺ neuron output to the SNr is functionally weakened (dotted line) in the absence of dopamine. Stimulation of the PV⁺ neuron output has been shown to restore motoric function in mouse models of Parkinson’s disease, putatively through restoring a normal level SNr output (e.g.¹⁴⁹).

Neuron class (% of GPe neurons)	Neuron subclass (% of principal class)	Marker expression; (additional feature)	Validated driver and reporter line(s)	Neurotransmitter(s)
PV ⁺ (50%)	^a PV ⁺ -Kcng4 ^{4,14}	^b Etv1, Lhx6, Nkx2.1, Npy2r, Scna4b ^{4,11,14,16,23-28,32-34}	PV-Cre, PV-Flp, PV-tdTomato, ^c Kcng4-Cre ^{14,16,27-29,33,35}	GABA
	PV ⁺ -Lhx6 ^{-16,29}	Nkx2.1, Scna4b ^{4,16}	PV-Cre, PV-Flp ¹⁶	GABA
Npas1 ⁺ (30%)	Npas1 ⁺ -Foxp2 ²⁶ (60%)	Meis2, ^b Penk, Sox6 ^{4,25,26,28,38}	Npas1-Cre, ^c Foxp2-Cre, ^c Foxp2-Flp ^{14,15,27,28,39}	GABA
	Npas1 ⁺ -Nkx2.1 ^{26,28} (40%)	Lhx6, Npr3, Npy2r, Sox6 ^{4,14,23-28}	Npas1-Cre, ^c Npr3-Cre, Lhx6-GFP ^{14,28}	GABA
ChAT ⁺ (5%)	N/A	Nkx2.1 ^{23,25}	ChAT-Cre ^{27,30}	acetylcholine, GABA ³⁰
PV ⁻ -Npas1 ⁻ (15%)	N/A	Lhx6; (Sox6 ⁻) ²⁸	unknown	unknown

Footnotes:

^a Kcng4 demarcates a subset of canonical STN-projecting PV⁺ neurons. However, a marker encompassing all STN-projecting PV⁺ neurons has yet to be determined.

^b alternative names: Etv1, ER81; Penk.

^c subclass-specific driver.