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The External Globus Pallidus: Progress and Perspectives

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Abstract

The external globus pallidus (GPe) of the basal ganglia is in a unique and powerful position to influence processing of motor information by virtue of its widespread projections to all basal ganglia nuclei. Despite the clinical importance of the GPe in common motor disorders such as Parkinson's disease, we have only limited information about its cellular composition and organizational principles. In this review, we describe recent advances in our understanding of the diversity in the molecular profile, anatomy, physiology, and corresponding behavior during movement of GPe neurons. Importantly, we attempt to build consensus and highlight commonalities of the cellular classification based on existing but contentious literature. Additionally, we provide an analysis of the literature concerning the intricate reciprocal loops formed between the GPe and major synaptic partners, including both the striatum and the subthalamic nucleus. In conclusion, the GPe has emerged as a crucial node in the basal ganglia macrocircuit. While subtleties in the cellular makeup and synaptic connection of the GPe create new challenges, modern research tools have shown promise in untangling such complexity and will provide better understanding of the roles of the GPe in encoding movements and their associated pathologies.

Keywords

prototypic neurons; arkypallidal neurons; parvalbumin; Npas1; Parkinson's disease

Introduction

The basal ganglia are an ensemble of subcortical nuclei that are critically involved in control of action (Albin *et al.*, 1995; Graybiel, 2008; Redgrave *et al.*, 2010; Turner & Desmurget, 2010; Costa, 2011; Gerfen & Surmeier, 2011; Kravitz *et al.*, 2012). The external globus pallidus (GPe) of the basal ganglia is in a unique and powerful position to influence processing of motor information by virtue of its widespread projections to all basal ganglia nuclei (Difiglia *et al.*, 1982; Beckstead, 1983; Walker *et al.*, 1989; Kita, 1994; Kita & Kitai, 1994; Shammah-Lagnado *et al.*, 1996; Nambu & Llinas, 1997; Bevan *et al.*, 1998; Smith *et al.*, 1998b; Kita *et al.*, 1999; Sato *et al.*, 2000; Kita & Kita, 2001; Kita, 2007). Consistent with this anatomy, phasic changes in the firing of GPe neurons are associated with both passive and active body movements (DeLong, 1971; Georgopoulos *et al.*, 1983; Anderson &

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Horak, 1985; Mitchell *et al.*, 1987; Filion *et al.*, 1988; Nambu *et al.*, 1990; Brotchie *et al.*, 1991; Mink & Thach, 1991b; a; Jaeger *et al.*, 1995; Mushiake & Strick, 1995; Turner & Anderson, 1997; Boraud *et al.*, 2000; Arkadir *et al.*, 2004; Adler *et al.*, 2010; Schmidt *et al.*, 2013; Dodson *et al.*, 2015). Highly synchronous bursting in the GPe correlates with hypokinetic symptoms of Parkinson's disease (PD) (Pan & Walters, 1988; Filion & Tremblay, 1991; Filion *et al.*, 1991; Hutchison *et al.*, 1994; Nini *et al.*, 1995; Rothblat & Schneider, 1995; Hassani *et al.*, 1996; Taha *et al.*, 1996; Bergman *et al.*, 1998; Boraud *et al.*, 1998; Wichmann *et al.*, 1999; El-Deredy *et al.*, 2000; Magill *et al.*, 2000; Magnin *et al.*, 2000; Raz *et al.*, 2000; Brown *et al.*, 2001; Magill *et al.*, 2001; Bar-Gad *et al.*, 2003; Starr *et al.*, 2005; Heimer *et al.*, 2006; Wichmann & Soares, 2006; Kita, 2007; Tang *et al.*, 2007; Zold *et al.*, 2007a; Zold *et al.*, 2007b; Mallet *et al.*, 2008; Starr *et al.*, 2008; Sani *et al.*, 2009; Chan *et al.*, 2011). Similarly, aberrant GPe neuron activity is also observed in Huntington's disease (HD) and dystonia (Starr *et al.*, 2005; Chiken *et al.*, 2008; Starr *et al.*, 2008; Baron *et al.*, 2011; Nambu *et al.*, 2011; Nishibayashi *et al.*, 2011), arguing for the centrality of the GPe in motor function and dysfunction. Despite its critical role in regulating motor activity, the organization of GPe neurons within the basal ganglia circuitry remains poorly understood, preventing us from understanding how GPe activity is regulated in behavioral and disease contexts.

While the traditionally-held belief is that the GPe is a homogeneous population of neurons that act as a mere relay in the indirect pathway of the basal ganglia (Albin *et al.*, 1989; Alexander & Crutcher, 1990; DeLong, 1990; Albin *et al.*, 1995; Parent & Hazrati, 1995b; Joel & Weiner, 1997; Graybiel, 2000), recent studies are challenging this view. A number of important discoveries on neuron diversity were made in the past few years as a result of a resurgence of interest in the GPe. Furthermore, accumulating evidence suggests that striatal inputs to the GPe do not arise strictly from indirect pathway neurons. In this review, we aim to analyze the historical literature and provide a critical update on the recent progress regarding our understanding of the GPe. We will also discuss the fundamental biology of different GPe neuron classes, their synaptic partners, and their potential importance in motor function and disease etiology.

Heterogeneity of neurons in the GPe

Early evidence for distinct neuron types in the GPe

A large body of published work suggests the existence of multiple GPe neuron types. GPe neurons are diverse in their expression of molecular markers (Hontanilla *et al.*, 1994; Kita, 1994; Bevan *et al.*, 1998; Hoover & Marshall, 1999; Kita & Kita, 2001; Cooper & Stanford, 2002; Chan *et al.*, 2004; Domaradzka-Pytel *et al.*, 2007; Mallet *et al.*, 2012; Mastro *et al.*, 2014; Abdi *et al.*, 2015; Hernandez *et al.*, 2015), dendritic morphology (Fox *et al.*, 1974; Danner & Pfister, 1981; Iwahori & Mizuno, 1981; Difiglia *et al.*, 1982; Park *et al.*, 1982; Francois *et al.*, 1984; Yelnik *et al.*, 1984; Millhouse, 1986; Kita & Kitai, 1994; Nambu & Llinas, 1997; Cooper & Stanford, 2000), axonal projections (Difiglia *et al.*, 1982; Beckstead, 1983; Walker *et al.*, 1989; Kita, 1994; Kita & Kitai, 1994; Parent & Hazrati, 1995b; Shammah-Lagnado *et al.*, 1996; Bevan *et al.*, 1997; Bevan *et al.*, 1998; Smith *et al.*, 1998a; Kita *et al.*, 1999; Sato *et al.*, 2000; Kita & Kita, 2001; Mallet *et al.*, 2012), and

electrophysiology (Nambu & Llinas, 1994; Kelland *et al.*, 1995; Nini *et al.*, 1995; Nambu & Llinas, 1997; Cooper & Stanford, 2000; Raz *et al.*, 2000; Paz *et al.*, 2005; Gunay *et al.*, 2008; Mallet *et al.*, 2008; Joshua *et al.*, 2009; Bugaysen *et al.*, 2010; Chan *et al.*, 2011; Chuhma *et al.*, 2011; Benhamou *et al.*, 2012; Mallet *et al.*, 2012; Schmidt *et al.*, 2013; Jin *et al.*, 2014).

Earlier studies were limited by non-categorical expression of a number of phenotypic markers. Analysis of GPe anatomical projections is complicated by the fact that single GPe neurons can project to multiple nuclei (Parent & Hazrati, 1995b; Bevan *et al.*, 1998; Mallet *et al.*, 2012). Both *in vivo* and *ex vivo* studies have demonstrated quantitative differences in the electrophysiological characteristics of GPe neurons. The first classification was provided by DeLong's seminal *in vivo* recording study in behaving monkeys, in which GPe neurons were divided into "high frequency pausers" and "low frequency bursters" on the basis of their spontaneous firing patterns (DeLong, 1971). Several subsequent studies have provided evidence for the existence of subtypes of GPe neurons according to their electrophysiological properties in *ex vivo* slices (Kita & Kitai, 1991; Nambu & Llinas, 1994; Cooper & Stanford, 2000; Bugaysen *et al.*, 2010; Chuhma *et al.*, 2011). As the methodologies and measurements were unique to each experimental setup, the field still awaited reliable classification criteria for GPe neurons.

Recent advances delineate distinct neuron classes in the GPe

More recent multidisciplinary studies using adult rodents have provided compelling data that serve as the basis for newer classification schemes for GPe neurons. Except for a small population of cholinergic ($ChAT^+$) neurons that make up ~5% of all GPe neurons (see below), GPe neurons are GABAergic and autonomously active (Kita & Kitai, 1991; Nambu & Llinas, 1994; 1997; Cooper & Stanford, 2000; Chan *et al.*, 2004; Surmeier *et al.*, 2005; Mercer *et al.*, 2007; Deister *et al.*, 2009; Bugaysen *et al.*, 2010; Nobrega-Pereira *et al.*, 2010; Chan *et al.*, 2011; Miguelez *et al.*, 2012; Mastro *et al.*, 2014; Abdi *et al.*, 2015; Hernandez *et al.*, 2015). These GABAergic GPe neurons largely fall into one of two general categories. Neurons in the first category—'prototypic' GPe neurons—exhibit fast and regular firing rates *in vivo* (Abdi *et al.*, 2015; Dodson *et al.*, 2015), project strongly to the subthalamic nucleus (STN), and constitute ~70% of all GPe neurons (Mallet *et al.*, 2012; Hernandez *et al.*, 2015). Neurons expressing the calcium binding protein parvalbumin (PV) represent the majority of these prototypic neurons (Mallet *et al.*, 2012), making up ~55% of all neurons in the GPe. Two recent studies show that these neurons express the transcription factor Nkx2.1 (Abdi *et al.*, 2015; Dodson *et al.*, 2015). Additionally, at least a subset of these PV^+ neurons also express Lhx6 (Abdi *et al.*, 2015; Hernandez *et al.*, 2015) (but see below). The principal electrophysiological characteristics of PV^+ GPe neurons were recently established in *ex vivo* slices and include robust and regular autonomous firing, narrower action potentials, and lower membrane resistance, as well as large persistent sodium current, HCN current, and Kv4 current (Mastro *et al.*, 2014; Abdi *et al.*, 2015; Hernandez *et al.*, 2015). The Type I and Type A neurons described in early electrophysiological characterizations of GPe neurons (Nambu & Llinas, 1994; Cooper & Stanford, 2000) share these key characteristics with PV^+ neurons and likely correspond to the same class (see Table 1).

Neurons in the second category—'arkypallidal' GPe neurons—exhibit slower and more irregular firing rates *in vivo* (Abdi *et al.*, 2015; Dodson *et al.*, 2015), project heavily to the dorsal striatum (dStr), and constitute ~25% of all GPe neurons. These neurons are devoid of PV (Mallet *et al.*, 2012; Hernandez *et al.*, 2015); instead, they express the opioid precursor preproenkephalin (Mallet *et al.*, 2012; Abdi *et al.*, 2015; Dodson *et al.*, 2015) and the transcription factor Foxp2. Most arkypallidal neurons also express the transcription factor Npas1. However, it is important to emphasize that not all $Npas1^+$ neurons express Foxp2. Additionally, a very small fraction of $Foxp2^+$ GPe neurons do not express Npas1 (Abdi *et al.*, 2015; Dodson *et al.*, 2015; Hernandez *et al.*, 2015). By generating an Npas1-Cre-2A-tdTomato BAC transgenic mouse line and Npas1 antibodies *de novo*, Hernández and colleagues recently demonstrated that $Npas1^+$ neurons are distinct from PV^+ neurons (Hernandez *et al.*, 2015)—a finding that is in agreement with previous studies (Flandin *et al.*, 2010; Nobrega-Pereira *et al.*, 2010). Electrophysiological characterization of $Foxp2^+$ neurons and $Npas1^+$ neurons *ex vivo* find that they have high input resistances and low and variable firing rates (Abdi *et al.*, 2015; Hernandez *et al.*, 2015). These neurons share basic features with the Type II and Type B neurons described in earlier studies and likely correspond to the same class (see Table 1) (Nambu & Llinas, 1994; Cooper & Stanford, 2000). Additionally, these neurons have smaller cell bodies (Kita, 1994; Nambu & Llinas, 1997; Waldvogel *et al.*, 1999; Waldvogel *et al.*, 2004; Kita, 2007). Importantly, in chronic 6-OHDA lesioned mice the autonomous pacemaking activity of $Npas1^+$ neurons is decreased while that of PV^+ neurons is unchanged, corroborating findings from earlier studies that showed disrupted pacemaking of a subset of unidentified GPe neurons (Chan *et al.*, 2011; Miguelez *et al.*, 2012).

The existence of cholinergic neurons in the GPe has been known for several decades. Rather than being part of the basal ganglia, $ChAT^+$ GPe neurons have been considered displaced basal forebrain neurons because of their similar electrophysiological properties and their tendency to be located primarily at the medial and ventral borders of the GPe (Das & Kreutzberg, 1969; Mesulam *et al.*, 1983; Rye *et al.*, 1984; Ingham *et al.*, 1985; Rodrigo *et al.*, 1998; Unal *et al.*, 2012; McKenna *et al.*, 2013; Eid *et al.*, 2014; Saunders *et al.*, 2015). Although it can be argued that the small number of $ChAT^+$ neurons in the GPe are merely a dorsal extension of the much larger group of basal forebrain cholinergic neurons, their inputs from the dStr and the STN (Hernandez *et al.*, 2015; Saunders *et al.*, 2015) suggest they are integrated with, and therefore a part of, the basal ganglia. The membrane properties of these $ChAT^+$ GPe neurons have only been modestly investigated; they likely correspond to the Type III or Type C neurons on the basis of their relative scarcity, very low firing rates, longer-duration action potentials, and large somata (Bengtson & Osborne, 2000; McKenna *et al.*, 2013; Abdi *et al.*, 2015; Hernandez *et al.*, 2015; Saunders *et al.*, 2015).

Classifying GPe neurons: consensus and division

Although recent studies provide a strong foundation for the classification of GPe neurons, several questions remain. Neuronal birthplace was recently proposed to dictate some features of GPe neuron identity (Dodson *et al.*, 2015). In brief, GPe neurons have distinct developmental origins, arising from the medial ganglionic eminence (MGE), lateral ganglionic eminence (LGE), or the preoptic area (PoA). While PV^+ neurons arise from the

MGE, Npas1$^+$ neurons are derived from both the MGE and LGE (Flandin *et al.*, 2010; Nobrega-Pereira *et al.*, 2010; Abdi *et al.*, 2015; Dodson *et al.*, 2015). Though developmental origins likely influence transcriptional programs that control the specifications of neurons, data from Hernández *et al.* (2015) do not fully support this idea. Despite the overlap between the developmental origins of PV$^+$ GPe neurons and Npas1$^+$ GPe neurons, their electrophysiological properties and axonal projections are strikingly different. As previously shown in the hippocampus, neurons can converge on a single anatomical and physiological phenotype despite differences in origin (Chittajallu *et al.*, 2013). It is likely that a combination of transcription factors, chromatin modifiers, and enhancers are critical for the establishment and maintenance of distinct neuronal phenotypes (Deneris & Hobert, 2014).

A subset of GPe neurons express the transcription factor Lhx6, which is a nominal marker for MGE-derived neurons, but the field has yet to come to an agreement on whether Lhx6$^+$ neurons are likely to represent a functionally-unique neuron class within the GPe. While recent studies converge on the existence of a distinct class of Lhx6$^+$ GPe neurons (see below), a substantial population of Lhx6$^+$ GPe neurons express PV or Npas1. Accordingly, Lhx6$^+$ GPe neurons display electrophysiological and anatomical properties that span the range between PV$^+$ GPe neurons and Npas1$^+$ GPe neurons (Mastro *et al.*, 2014; Hernandez *et al.*, 2015). In particular, these studies do not agree upon the extent of the overlap of Lhx6 with PV, covering the range from virtually no overlap to near-complete overlap (Mastro *et al.*, 2014; Abdi *et al.*, 2015; Dodson *et al.*, 2015; Hernandez *et al.*, 2015). Similarly, these studies describe PV$^+$ neurons as constituting anywhere from 30% to 60% of all GPe neurons (Nobrega-Pereira *et al.*, 2010; Mastro *et al.*, 2014; Abdi *et al.*, 2015; Hernandez *et al.*, 2015). It is likely that the discrepancies arise from differences in the detection sensitivity of immunoreactions. In addition, the eGFP expression pattern in the Lhx6-eGFP mice is non-discrete and does not reliably label neurons that natively express the transcription factor Lhx6 (Mastro *et al.*, 2014; Dodson *et al.*, 2015). Differences in the PV-Cre driver lines employed have not been examined and may also contribute.

Figure 1 represents an attempt to bring the different schemes for classification of GPe neuron classes into congruence. Readers should keep in mind that these classifications are only approximations; subtle species differences between rats and mice may exist. However, it is difficult to separate species differences from methodological ones especially given that Magill and colleagues are currently the only group to have published data using rats. Figure 1 highlights the existence of at least four distinct classes of GPe neurons, including a PV$^-$-Npas1$^-$-Lhx6$^+$ neuron class, which represents the distinct Lhx6$^+$ GPe neuron class described in previous studies (Mastro *et al.*, 2014; Dodson *et al.*, 2015; Hernandez *et al.*, 2015). While the precise properties of these neurons have yet to be determined, they may be PoA-derived. This notion is supported by a recent study showing that while MGE-derived neurons express Lhx6, the PoA is another potential source of Lhx6$^+$ neurons (Kanatani *et al.*, 2015). Similarly, as the classification of GPe neurons is based on recent data derived from rodent studies, how such a classification would apply to primates remains to be determined.

Principal GPe projections

STN-projecting GPe neurons

As the GPe-STN projection and its importance in both health and disease is well-established (Canteras *et al.*, 1990; Parent & Hazrati, 1995b; Shink *et al.*, 1996; Joel & Weiner, 1997; Smith *et al.*, 1998a; Bolam *et al.*, 2000; Bevan *et al.*, 2002b; Francois *et al.*, 2004; Nambu, 2004; Bevan *et al.*, 2007; Wilson & Bevan, 2011), only critical updates on the topic are included in the following section. PV^+ GPe neurons constitute the principal GPe projection to the STN (Kita, 1994; Hoover & Marshall, 1999; 2002; Mastro *et al.*, 2014; Abdi *et al.*, 2015; Hernandez *et al.*, 2015), accounting for ~94% of total GPe-STN inputs (Abdi *et al.*, 2015; Hernandez *et al.*, 2015). Subtle differences exist between the projections from PV^+ GPe neurons and those from $Lhx6^+$ GPe neurons to the STN. While PV^+ GPe neurons target primarily the motor area of the STN, $Lhx6^+$ GPe neurons preferentially target the limbic and associative areas of the STN (Mastro *et al.*, 2014). $Npas1^+$ GPe neurons send only a small number of axons to the STN. The vast majority of $Npas1^+$ axonal projections instead run dorsally to the STN, along the lenticular fascicle (Hernandez *et al.*, 2015). The caudal projection pattern of $Npas1^+$ axons has not been examined systematically. However, it should map onto a number of brain regions that were charted previously (Hattori *et al.*, 1975; Bunney & Aghajanian, 1976; Kanazawa *et al.*, 1976; Staines & Fibiger, 1984; Hazrati *et al.*, 1990; Hazrati & Parent, 1991; Kincaid *et al.*, 1991a; Shammah-Lagnado *et al.*, 1996; Saunders *et al.*, 2015). The GPe-STN projection is sparse and distributed; individual GPe neurons contact only 2% of STN neurons and neighboring STN neurons rarely receive input from the same GPe axon (Baufreton *et al.*, 2009). In addition to the classic perisomatic baskets, GPe axons also terminate on the proximal and distal dendrites of STN neurons (Smith *et al.*, 1990a).

The GPe-STN projection plays critical roles in regulating STN neuron activity via a number of mechanisms. In health, the GPe provides phasic inhibition that promotes decorrelated activity between the GPe and the STN (Atherton *et al.*, 2013). Additionally, GPe input limits activation of STN neurons by cortical input through hyperpolarization and shunting inhibition (Chu *et al.*, 2015). Dopamine, via presynaptic D2 receptors, inhibits GABA release at the GPe-STN synapse (Shen & Johnson, 2000; Baufreton & Bevan, 2008). Hypersynchronization of the GPe with the STN in PD is in part attributable to increased presynaptic release and postsynaptic strengthening of the GPe-STN input via an NMDA receptor-dependent mechanism (Fan *et al.*, 2012; Chu *et al.*, 2015). Strengthened GPe inputs then interact with intrinsic, active conductances on STN neurons to generate rhythmic bursting of STN neurons (Baufreton *et al.*, 2005; Baufreton *et al.*, 2009; Fan *et al.*, 2012). A reverberating feedback loop formed between the GPe and STN was proposed to serve as an intrinsic oscillator that drives aberrant network activity throughout the basal ganglia (Bevan *et al.*, 2002b) (see further discussion below).

dStr-projecting GPe neurons

A projection from the GPe to the dStr, the primary input center of the basal ganglia, was postulated over a century ago (Wilson, 1911; 1913), and its existence has since been confirmed in a variety of species. However, very little is known about the identity of the GPe

neurons that provide this input or the postsynaptic neurons they target (Nauta, 1979; Staines *et al.*, 1981; Beckstead, 1983; Jayaraman, 1983; Staines & Fibiger, 1984; Smith & Parent, 1986; Shu & Peterson, 1988; Walker *et al.*, 1989; Kita & Kitai, 1991; Shinonaga *et al.*, 1992; Rajakumar *et al.*, 1994; Shammah-Lagnado *et al.*, 1996; Spooren *et al.*, 1996; Nambu & Llinas, 1997; Bevan *et al.*, 1998; Kita *et al.*, 1999; Sato *et al.*, 2000; Kita & Kita, 2001; Mallet *et al.*, 2012). A major impediment to our understanding of the pallidostriatal pathway arises from the cellular complexity in the dStr and the GPe, as each of these nuclei comprises several types of neurons (Kreitzer, 2009; Tepper *et al.*, 2010; Gittis *et al.*, 2014; Abdi *et al.*, 2015). Therefore, it is evident that we need a systematic analysis to map the connectivity between specific pallidostriatal inputs and identified postsynaptic target neurons.

It was recently demonstrated that Npas1$^+$ GPe neurons project heavily to the dStr but only sparingly to the STN (Hernandez *et al.*, 2015). For this reason, we postulate that spiny projection neurons (SPNs), the principal neurons in the dStr (Kemp & Powell, 1971; DiFiglia *et al.*, 1976; Somogyi & Smith, 1979; Dimova *et al.*, 1980; Preston *et al.*, 1980; Groves, 1983), receive input from Npas1$^+$ GPe neurons. In support of this idea, ultrastructural data suggest that Npas1$^+$-Foxp2$^+$ (arkypallidal) axon terminals form synapses with spine-bearing dendrites in the dStr (Mallet *et al.*, 2012). Although Lhx6$^+$ GPe neurons also target the dStr, Npas1$^+$-Foxp2$^+$ neurons appear to do so to a much higher degree (Mastro *et al.*, 2014; Hernandez *et al.*, 2015); however, unlike Lhx6$^+$ neurons, Npas1$^+$-Foxp2$^+$ neurons do not project to the STN (Abdi *et al.*, 2015). This suggests Npas1$^+$-Foxp2$^+$ neurons and Npas1$^+$-Lhx6$^+$ neurons are distinct (see Figure 1). Considering that Lhx6 expression shows essentially no overlap with Foxp2 and that most Npas1$^+$-Foxp2$^-$ neurons are also Lhx6$^+$ (Abdi *et al.*, 2015; Hernandez *et al.*, 2015), it is tempting to speculate that Npas1$^+$-Foxp2$^+$ neurons and Npas1$^+$-Lhx6$^+$ neurons are both dStr-projecting but preferentially target distinct subsets of striatal neurons—for example, SPNs and GABAergic interneurons, respectively. PV$^+$ GPe neurons also provide a small number of projections to the dStr, where they appear to preferentially target interneurons (Bevan *et al.*, 1998; Kita *et al.*, 1999; Mastro *et al.*, 2014).

We still lack a systematic and quantitative analysis of the targeting properties of the pallidostriatal inputs. However, it is possible to calculate the contact probability of cell-specific GPe axons with individual SPNs, as the number of neurons in both the dStr and the GPe has been previously determined (see Table 2). Similarly, the number of synaptic boutons formed by Npas1$^+$ GPe neurons and PV$^+$ GPe neurons in the dStr has also been estimated. Assuming 100% connectivity between GPe and dStr neurons, each SPN on average receives a small number of boutons from GPe neurons: roughly 40 from Npas1$^+$ GPe neurons and less than ten from PV$^+$ GPe neurons. In contrast, each SPN receives 2,500 symmetrical synapses (Wilson, 2013). From these estimates alone, pallidostriatal inputs arising from GPe neurons would appear unlikely to have an important impact on the output of SPNs. However, we do not yet know if pallidostriatal neurons make contact with striatal neurons in a target cell-specific manner, as is often observed between SPN classes (MacAskill *et al.*, 2012; Wall *et al.*, 2013; Deng *et al.*, 2015; Guo *et al.*, 2015b) (but see Kress *et al.*, 2013), or if they exhibit strategic positioning on the dendrites of SPNs. Either of these features could substantially increase the efficiency of their influence on the network.

Additionally, pre- and postsynaptic mechanisms may exist to provide anatomical and biophysical specialization at these connections. Finally, the temporal relationship between the activation of the pallidostriatal inputs and the excitatory inputs (e.g. from the cortex) will be a crucial factor in determining the impact of the postsynaptic effect.

GPe-dStr inputs and sparse coding in the striatum

What is the biological significance of the pallidostriatal inputs? Could they provide subcellular compartment-specific inhibition? To date, there has been no consensus on the coding scheme employed by SPNs. 'Sparse coding' is one potential computational strategy whereby information is communicated by spatially- and temporally-distributed activity in a relatively small fraction of neurons. This form of neural coding is well-established in sensory systems and allows for efficient and flexible information processing (Vinje & Gallant, 2000; Hromadka *et al.*, 2008; Isaacson, 2010; Wolfe *et al.*, 2010). In line with this idea, the dStr shares several characteristic features with neural networks that support and use sparse coding (Olshausen & Field, 2004). In addition to the large spatial volume of the dStr (Rosen & Williams, 2001), SPNs exhibit burst activity in response to a limited range of stimuli (DeLong, 1973; Wilson & Groves, 1981; Kimura *et al.*, 1990; Stern *et al.*, 1997) as well as an absence of redundancy and a loose temporal correlation between responses of nearby SPNs (Jaeger *et al.*, 1995; Ponzi & Wickens, 2010; Adler *et al.*, 2012; Adler *et al.*, 2013).

In addition, it has been previously demonstrated that a nonspecific inhibitory input can facilitate sparse coding by acting as a gain control (Laurent, 2002; Isaacson & Scanziani, 2011). By dampening excitatory responses across a broad area of the dStr, Npas1^{+} GPe neurons could potentially promote sparse coding in SPNs (Burrone & Murthy, 2003; Semyanov *et al.*, 2004; Silver, 2010). Typically, SPNs rest close to the potassium reversal potential, spiking only when they are driven by glutamatergic input from the cortex (Parent & Hazrati, 1995a; Smith *et al.*, 2004). Specifically, through activation of NMDA receptors, SPNs in the dStr display dendritic plateau potentials in distal dendritic compartments (Plotkin *et al.*, 2011). It is thus intriguing to speculate that pallidostriatal input controls SPN output by limiting the summation of excitatory inputs, preventing the subsequent nonlinear-generation of dendritic plateaus; spiking would be limited to only those SPNs receiving robust or well-timed excitatory input. As the dStr is organized in a somatotopic fashion (Nambu, 2011), spatially-broad inhibition from the GPe could be used to suppress or reset somatotopically-complex motor sequences across the dStr (see below).

Synaptic and neuromodulatory control of the GPe

dStr forms the principal inhibitory input to the GPe

The dStr input to the GPe is topographically organized and highly convergent. In primates, the dStr-GPe projection displays a precise rostrocaudal, mediolateral, and dorsoventral topography. Furthermore, the injection of two different anterograde tracers into two small, adjacent areas of the striatum led to the formation of two clearly distinguishable sets of bands in the GPe (Hazrati & Parent, 1992; Parent & Hazrati, 1995a). In the rat basal ganglia there are roughly three million SPNs but only 46 thousand GPe neurons (Oorschot, 1996).

Assuming all of the SPNs in the dStr are GPe-projecting, individual GPe neurons must on average receive input from at least 60 dStr SPNs. The high level of convergence in the dStr-GPe projection is supported by both anatomical and electrophysiological findings. Retrograde tracer injections into a small area of the primate GPe label neurons in spatially-broad areas of the putamen (Flaherty & Graybiel, 1993; 1994). Moreover, focal stimulation in the GPe induces antidromic activation of multiple striatal neurons over a wide area (Kimura *et al.*, 1996). Anatomically, the dendritic arbor of GPe neurons is oriented perpendicularly to the incoming, radial striatal fibers, creating an ideal arrangement for intercepting axons from broad striatal regions (Chang *et al.*, 1981; Percheron *et al.*, 1984; Yelnik *et al.*, 1984; Kawaguchi *et al.*, 1990; Yelnik *et al.*, 1997). Such an anatomical organization allows dStr axons to contact the dendrites of multiple GPe neurons. The sharing of dStr inputs by multiple GPe neurons provide an anatomical substrate for synchrony and pause-burst firing pattern in a large population of GPe neurons, as demonstrated by both experimental and computational studies (Terman *et al.*, 2002; Elias *et al.*, 2007; Zold *et al.*, 2007a; Zold *et al.*, 2007b; Kita & Kita, 2011b; a; Adler *et al.*, 2012; Schwab *et al.*, 2013; Wilson, 2013; Schechtman *et al.*, 2015). As PD progresses, the activity of GPe neurons transitions from decorrelated, single-spike pacemaking to synchronous, rhythmic bursting (but see Mallet *et al.*, 2008). This pathological network behavior is thought to be critical to the core motor symptoms of PD (Pan & Walters, 1988; Filion & Tremblay, 1991; Filion *et al.*, 1991; Hutchison *et al.*, 1994; Nini *et al.*, 1995; Rothblat & Schneider, 1995; Hassani *et al.*, 1996; Taha *et al.*, 1996; Bergman *et al.*, 1998; Boraud *et al.*, 1998; Wichmann *et al.*, 1999; El-Deredy *et al.*, 2000; Magill *et al.*, 2000; Magnin *et al.*, 2000; Raz *et al.*, 2000; Brown *et al.*, 2001; Magill *et al.*, 2001; Heimer *et al.*, 2002; Bar-Gad *et al.*, 2003; Starr *et al.*, 2005; Heimer *et al.*, 2006; Wichmann & Soares, 2006; Kita, 2007; Tang *et al.*, 2007; Zold *et al.*, 2007a; Zold *et al.*, 2007b; Mallet *et al.*, 2008; Starr *et al.*, 2008; Cruz *et al.*, 2009; Sani *et al.*, 2009; Chan *et al.*, 2011). Although active decorrelating processes have been proposed to prevent synchrony among neighboring GPe neurons in the healthy state (Nini *et al.*, 1995; Bar-Gad *et al.*, 2003; Chan *et al.*, 2011), the exact mechanisms involved and why they collapse in the absence of dopamine remain to be explored.

The dStr inputs originating from SPNs account for 65–80% of the GABAergic synapses within the GPe (Smith *et al.*, 1998a; Kita, 2007). Approximately two-thirds of these dStr-GPe inputs arise from the enkephalin and dopamine D2 receptor-expressing indirect-pathway SPNs (iSPNs), while the remaining one-third originate from collaterals of substance P and dopamine D1 receptor-expressing direct-pathway SPNs (dSPNs) that form en passant synapses (Feger & Crossman, 1984; Gerfen & Young, 1988; Kawaguchi *et al.*, 1990; Parent *et al.*, 1995; Wu *et al.*, 2000; Levesque & Parent, 2005; Nadjar *et al.*, 2006; Matamales *et al.*, 2009; Fujiyama *et al.*, 2011). Recent experimental data directly demonstrate the different roles played by dSPNs (movement facilitation) and iSPNs (movement suppression) in learned-behavior and motor dysfunction, in agreement with those proposed in the classic model (Kravitz *et al.*, 2010; Cui *et al.*, 2013; Freeze *et al.*, 2013; Calabresi *et al.*, 2014; Sippy *et al.*, 2015). While it has yet to be demonstrated how striatal information is processed at the GPe level, Saunders and colleagues find that dSPN and iSPN inputs target both GABAergic and cholinergic GPe neurons (Saunders *et al.*, 2015).

Both types of dStr inputs to the GPe are likely important players in PD, given the remarkable anatomical remodeling following the perturbation of dopaminergic signaling. Direct examination using electron microscopy has revealed pathological enlargement of iSPN terminals in the GPe following chronic dopamine depletion (Ingham *et al.*, 1997). Similarly, alterations in the dSPN axonal arborization within the GPe are observed when dopamine signaling is disrupted (Cazorla *et al.*, 2014; Cazorla *et al.*, 2015). Consistent with this idea that dStr-GPe inputs are remodeled after dopamine depletion, compelling evidence from *in vivo* studies suggests that in PD, increased dStr-GPe input contributes to neuronal synchrony within the GPe. This subsequently leads to pathological network oscillations throughout the basal ganglia (Bevan *et al.*, 2002b; Terman *et al.*, 2002; Kita & Kita, 2011b). It is important to note that, even in the healthy state, coordinated dStr-GPe input exhibits a strong ability to reset—and therefore temporarily promote synchronization of—the pacemaking of GPe neurons in an HCN channel-dependent manner (Chan *et al.*, 2004). While *ex vivo* studies so far do not support the theory of altered dStr-GPe transmission in a chronic 6-OHDA model of PD (Miguelez *et al.*, 2012), they were confounded by co-activation of both dSPN inputs and iSPN inputs with conventional electrical stimulation. Additionally, the identities of the postsynaptic GPe neurons were undefined. A recent modeling study suggests dStr input onto PV^+ (prototypic) GPe neurons is stronger than that onto $Npas1^+$-$Foxp2^+$ (arkypallidal) GPe neurons (Nevado-Holgado *et al.*, 2014), highlighting that much investigation of dStr-GPe signaling still needs to be done, particularly regarding how dSPNs and iSPNs are connected with distinct GPe neuron classes.

Local collaterals are another major inhibitory input to GPe neurons

In addition to the dStr input, local collaterals are a second source of GABAergic input onto GPe neurons. Juxtacellular labeling and intracellular dye-loading of GPe neurons have revealed the presence of local axon collaterals with numerous varicosities, suggesting the presence of lateral GABAergic inhibition within the GPe (Millhouse, 1986; Okoyama *et al.*, 1987; Kita, 1994; Kita & Kitai, 1994; Nambu & Llinas, 1997; Bevan *et al.*, 1998; Sato *et al.*, 2000; Sadek *et al.*, 2007; Mallet *et al.*, 2012). Most, if not all, GPe neurons exhibit local axon collaterals; it is estimated that a single local collateral axon gives rise to as many as 650 boutons within the GPe. However, this number varies with the identity and geographical location of the cell body (Park *et al.*, 1982; Millhouse, 1986; Kita & Kitai, 1994; Nambu & Llinas, 1997; Bevan *et al.*, 1998; Sato *et al.*, 2000; Sadek *et al.*, 2007; Mallet *et al.*, 2012).

In the GPe, these local axon collaterals terminate on somata and proximal dendrites (Kita, 1994; Kita & Kitai, 1994; Nambu & Llinas, 1997; Bevan *et al.*, 1998; Sato *et al.*, 2000; Sadek *et al.*, 2007; Mallet *et al.*, 2012), positioning them to have a powerful influence on the firing of their postsynaptic targets. Early electrophysiological analysis describing the kinetics of putative intrapallidal inhibitory synaptic currents—faster than those arising from dStr inputs—is consistent with this perisomatic location (Sims *et al.*, 2008; Gross *et al.*, 2011). Although local collaterals are integral to GPe circuit dynamics and downstream network effects (Terman *et al.*, 2002), they have not been studied in great detail due to the inherent difficulty in identifying and selectively activating individual classes of GPe neurons and their local collateral axons.

Functional connections between GPe neurons are demonstrated in a recent study with paired-recordings. Connections between GPe neurons are mediated by $GABA_A$ receptors and strongly influence the firing rate of the postsynaptic GPe neuron, even at the level of unitary connections (Bugaysen *et al.*, 2013). However, as connection probability is only ~1–2% (Sadek *et al.*, 2007; Bugaysen *et al.*, 2013), only a handful of recordings were obtained in this study (Bugaysen *et al.*, 2013). In a chronic model of PD, Miguelez and colleagues discovered a strengthening of this intrapallidal connection (Miguelez *et al.*, 2012). While these studies have provided important insights into the basic biology of intrapallidal signaling, the identities of both pre- and postsynaptic neurons were not determined (Sims *et al.*, 2008; Gross *et al.*, 2011). Recent advances in transgenic (Heintz, 2004; Madisen *et al.*, 2010; Madisen *et al.*, 2012; Gerfen *et al.*, 2013; Hernandez *et al.*, 2015; Madisen *et al.*, 2015) and optogenetic approaches (Boyden, 2015; Deisseroth, 2015) will undoubtedly promote future discoveries concerning the intrapallidal signaling between specific GPe neuron classes. Though it remains to be tested empirically, Mallet and colleagues show the existence of various connection types between GPe neuron classes (Mallet *et al.*, 2012). It is likely that the connectivity pattern varies in a cell-specific manner. This idea is supported by a recent computational analysis (Nevado-Holgado *et al.*, 2014) that suggests the inputs from PV^+ (prototypic) GPe neurons to $Npas1^+$-$Foxp2^+$ (arkypallidal) GPe neurons are relatively strong, whereas inputs from $Npas1^+$-$Foxp2^+$ neurons to PV^+ neurons are weaker. This analysis also predicts that the connections between $Npas1^+$-$Foxp2^+$ neurons are modest and that the connections between PV^+ neurons are negligible. As local collateral inhibition plays a pivotal role in governing network synchrony (Jefferys *et al.*, 1996; Paz & Huguenard, 2015), it is tempting to speculate that intrapallidal connections between GPe neurons serve as a decorrelating mechanism in the healthy state. Inappropriate scaling of these connections, as occurs in the absence of dopamine, has been suggested to contribute to hypersynchrony in PD (Cruz *et al.*, 2011). Lastly, gap junctions represent another means by which neurons can be electrically coupled and have been previously found on PV^- GPe neurons at the electron microscopy level (Kita, 1994). Accordingly, the molecular correlates of electrical synapses (connexins 26, 32, 36, and 43) are expressed in the GPe (Dermietzel *et al.*, 1989; Vis *et al.*, 1998; Condorelli *et al.*, 2000; Rash *et al.*, 2000; Schwab *et al.*, 2014; Phookan *et al.*, 2015). However, the existence of electrical coupling between GPe neurons awaits functional confirmation.

Postsynaptic $GABA_A$ receptors

As previously discussed, the majority of synaptic inputs to the GPe are mediated by $GABA_A$ receptors, which are ligand-gated Cl^- channels. Each receptor is a heteromeric structure composed of five out of at least 16 different subunits that are grouped into several classes. Eight subunit classes have been isolated to date (α1–6, β1–3, γ1–3, δ, ε, θ, π, and ρ1–3). It is thought that most functional $GABA_A$ receptors *in vivo* are formed by co-assembly of two α subunits, two β subunits, and an additional subunit from one of the remaining classes (Schofield, 1989; Mohler *et al.*, 1995; Sieghart, 1995; McKernan & Whiting, 1996; Mohler *et al.*, 1996; Barnard *et al.*, 1998; Rudolph & Mohler, 2004; 2006; Olsen & Sieghart, 2008).

Although mRNAs for essentially all cloned $GABA_A$ receptor-subunits are present in the GPe (Laurie *et al.*, 1992; Pirker *et al.*, 2000; Schwarzer *et al.*, 2001), those subunits that are

generally thought to be extrasynaptic and underlie "tonic" inhibition (e.g. α4–α6, β3 and δ subunits) (Danglot *et al.*, 2003; Jacob *et al.*, 2005) are present only at extremely low levels. This may indicate that transfer of information at the GABAergic synapses is accomplished by phasic, point-to-point signaling (Farrant & Nusser, 2005). Concordantly, the α1 subunit is expressed at very high levels in the GPe, richly investing the dStr-GPe synapses (Wisden *et al.*, 1992; Hartig *et al.*, 1995; Somogyi *et al.*, 1996; Riedel *et al.*, 1998; Waldvogel *et al.*, 1998; Waldvogel *et al.*, 1999; Pirker *et al.*, 2000; Schwarzer *et al.*, 2001; Sur *et al.*, 2001; Waldvogel *et al.*, 2004; Charara *et al.*, 2005); zolpidem, an α1 subunit-selective imidazopyridine agonist, slows the decay kinetics of dStr-GPe postsynaptic inhibitory currents in the GPe without changing their frequency or amplitude. Zolpidem has a stronger impact on dStr-GPe inhibitory postsynaptic currents than those arising from local collaterals, suggesting synapse-specific enrichment of the α1 subunit (Chen *et al.*, 2004b). Perhaps the most convincing evidence for an association between dStr-GPe synapses and parkinsonism is an observed downregulation of GPe α1 subunits in PD patients and animal models (Chadha *et al.*, 2000a; Yu *et al.*, 2001), as well as the therapeutic efficacy of zolpidem (Chen *et al.*, 2008b; Huang *et al.*, 2012).

At the same time, investigation of both the striatopallidal and local collateral inputs with TP003, an α3 subunit-selective agonist (Dias *et al.*, 2005), suggests that the α3 subunit is uniquely present at local collateral synapses in the GPe and not at striatopallidal synapses (Gross *et al.*, 2011). While these findings put the α3 subunit forward as a potential target for local collateral-specific therapy in motor disease, the data were collected using relatively young (postnatal 18–22 days) rats. Not only have α1 and α2 subunit expression levels in the GPe been shown to change considerably during the first month of development in rats (Fritschy *et al.*, 1994), but *in situ* and immunohistochemical analyses have also confirmed that expression of the α3 subunit is present in the GPe in young rats but fades to low to undetectable levels once adulthood is reached (Laurie *et al.*, 1992; Fritschy & Mohler, 1995). Interestingly, immunohistochemical evidence from adult human brains indicates that α3 subunit expression is present but restricted to PV^+ neurons (Waldvogel *et al.*, 1999). Given that $GABA_A$ receptor pharmacology may allow specific therapeutic targeting of PV^+ prototypic neurons via the α3 subunit, further investigation in a cell- and input-specific fashion is warranted.

$GABA_B$ signaling in the GPe

$GABA_B$ receptors are heteromeric G protein-coupled receptors composed of one $GABA_BR1$ subunit and one $GABA_BR2$ subunit (Kaupmann *et al.*, 1998; White *et al.*, 1998; Kuner *et al.*, 1999; Ng *et al.*, 1999). At the presynaptic sites, $GABA_B$ receptors suppress release by inhibiting voltage-gated calcium channels (Dolphin & Scott, 1986) and directly impeding synaptic vesicle exocytosis (Blackmer *et al.*, 2001; Yoon *et al.*, 2007; Rost *et al.*, 2011), while at the postsynaptic membrane, they constrain excitability by activating an inward-rectifying potassium conductance (Newberry & Nicoll, 1984b; a; Gahwiler & Brown, 1985; Luscher *et al.*, 1997) in addition to inhibiting voltage-gated calcium channel activity and NMDA receptor calcium signaling (Mintz & Bean, 1993; Perez-Garci *et al.*, 2006; Chalifoux & Carter, 2010; 2011; Lur & Higley, 2015).

Immunogold labeling and immunocytochemistry have shown that the $GABA_BR1$ subunit is present in monkeys at the presynaptic membrane of both symmetric and asymmetric synapses in the GPe (Charara *et al.*, 2000; Charara *et al.*, 2005). Using the same approach, it has also been demonstrated that $GABA_B$ receptors are found at the postsynaptic membrane of both symmetric synapses and asymmetric synapses in the GPe, but that the majority are extrasynaptic (Chen *et al.*, 2004a; Charara *et al.*, 2005). Direct agonist of $GABA_B$ receptors in the GPe *in vivo* produces ipsilateral turning behavior in rats (Chen *et al.*, 2002; Ikeda *et al.*, 2010). Activation of postsynaptic $GABA_B$ receptors in the GPe neurons slows their pacemaking in *ex vivo* rodent brain slices (Chan *et al.*, 2004; Kaneda & Kita, 2005). Additionally, in rat brain slices baclofen acts presynaptically in the GPe to reduce the release of glutamate (Chen *et al.*, 2002; Kaneda & Kita, 2005; Jin *et al.*, 2012) and GABA (Kaneda & Kita, 2005). It should be noted that electrophysiological assessment of $GABA_B$ signaling on *bona fide* striatopallidal and subthalamic inputs to the GPe has yet to be documented; previous assessments have either measured unidentified miniature events (Chen *et al.*, 2002; Kaneda & Kita, 2005; Jin *et al.*, 2012) or used contamination-prone terminal field electrical stimulation to evoke IPSCs and EPSCs (Kaneda & Kita, 2005), leaving open the possibility that the measured IPSCs and EPSCs were of pallidal and thalamic origins, respectively (see further discussion below).

To date, concrete information concerning the expression of $GABA_B$ subunits in GPe neuron subpopulations is lacking. Immunohistochemistry in human brains has indicated that the vast majority (98%) of PV^+ GPe neurons express some combination of $GABA_BR1$ and $GABA_BR2$ while the same is true for two thirds of PV^- GPe neurons (Waldvogel *et al.*, 2004), contrasting with results from Chen and colleagues, who reported postsynaptic inhibitory $GABA_B$ currents in response to baclofen in only a minority of GPe neurons (Chen *et al.*, 2002). In addition to detection sensitivity, this discrepancy between immunological labeling and electrophysiological function may be explained by receptor trafficking. The proportion of total $GABA_BR1$ located intracellularly as opposed to membrane-bound has been calculated to be 70% in rats (Chen *et al.*, 2004a) and 80% in monkeys (Charara *et al.*, 2005), perhaps limited by the availability of $GABA_BR2$, pairing with which is required for the localization of the $GABA_B$ heteromeric receptor complex to the membrane surface (Couve *et al.*, 2000).

Similarly, changes in trafficking may produce the sensitized response to $GABA_B$ signaling that is seen in MPTP-treated monkeys (Galvan *et al.*, 2011), as no increases in $GABA_B$ receptor expression have been noted in human PD patients (de Groote *et al.*, 1999) or MPTP-treated monkeys (Galvan *et al.*, 2011). It is tempting to speculate that that the minority of GPe neurons that display a significant outward postsynaptic current in response to baclofen in the healthy state (Chen *et al.*, 2002) corresponds to the $Npas1^+$ GPe neuron population (Hernandez *et al.*, 2015), with a sensitized $GABA_B$ response contributing to the decrease in pacemaking of GPe neurons seen in 6-OHDA lesioned mice (Chan *et al.*, 2011; Hernandez *et al.*, 2015). Given that $GABA_B$ receptor pharmacology could offer a method of therapeutic modulation of GPe excitability, the field will benefit from a thorough investigation of $GABA_B$ receptor expression and signaling in identified GPe neurons in both healthy and PD model animals (Chen *et al.*, 2002).

STN forms the principal excitatory input to the GPe

Both anatomical and physiological studies historically show that the principal glutamatergic input to the GPe is from the STN (Kita & Kitai, 1987; Smith *et al.*, 1990b; Smith *et al.*, 1998a). Recent estimations (Koshimizu *et al.*, 2013), however, have found fewer STN-GPe synapses than expected, calling into question the prominence of the STN-GPe input (Wilson, 2013). The boutons of STN terminals form medium-sized, asymmetrical synapses on the largely aspiny dendrites of GPe neurons. Anatomical approaches have shown that both AMPA and NMDA receptors are present at these synapses (Bernard & Bolam, 1998). This observation is consistent with pharmacological studies in which local application of AMPA and NMDA receptor blockers reduce spontaneous activity of GPe neurons in awake monkeys (Kita *et al.*, 2004). Furthermore, stimulation of the STN evokes fast excitatory postsynaptic potentials mediated by AMPA receptors and slower, strong excitatory postsynaptic potentials mediated by NMDA receptors in GPe neurons (Kita & Kitai, 1991). Computational modeling suggests a preferential connection from the STN to $Npas1^{+}$-$Foxp2^{+}$ (arkypallidal) GPe neurons (Nevado-Holgado *et al.*, 2014). No experimental investigation yet delineates the difference in the connection strength and biophysical properties of STN inputs to distinct GPe neuron classes.

Of potentially major importance in understanding the influence of the STN on GPe neurons is the weak voltage-dependence of the NMDA component of the excitatory postsynaptic potentials induced by STN stimulation. Though NMDA receptor opening normally requires relatively depolarized membrane potentials to dislodge pore-blocking Mg^{2+} ions (Kutsuwada *et al.*, 1992; Monyer *et al.*, 1992; Ishii *et al.*, 1993; Kuner & Schoepfer, 1996; Dingledine *et al.*, 1999; Traynelis *et al.*, 2010), this may not be a requirement in adult GPe neurons, as they express relatively high levels of the GluN2C and GluN2D subunits (Standaert *et al.*, 1994; Wenzel *et al.*, 1995; Wenzel *et al.*, 1996; Kosinski *et al.*, 1998), diminishing the efficacy of the Mg^{2+} block (Kuner & Schoepfer, 1996; Momiyama *et al.*, 1996). NMDA channels containing GluN2C and GluN2D subunits also have a higher affinity for glutamate and slower deactivation kinetics than GluN2A- or GluN2B-containing NMDA receptors (Cull-Candy *et al.*, 2001; Traynelis *et al.*, 2010). Thus, prominent expression of GluN2C- and GluN2D-containing NMDA receptors could serve to enhance the impact of STN inputs on GPe neurons. We do not know if the expression of GluN2C and GluN2D at the STN inputs can be generalized across all GPe neurons.

The assertion that the STN-GPe synapse grows in functional significance in PD is consistent with two other lines of evidence. First, both AMPA receptors and NMDA receptors in the GPe are downregulated in animal models of PD, suggesting a compensatory response to increased glutamatergic input (Porter *et al.*, 1994; Betarbet *et al.*, 2000). Consistent with this, systemic administration of NMDA receptor antagonists is effective in ameliorating motor symptoms in animal models of PD (Starr *et al.*, 1997; Kelsey *et al.*, 2004). NMDA receptor antagonists also lessen parkinsonian tremor and levodopa-induced motor fluctuations (Butzer *et al.*, 1975; Koller, 1986; Danysz & Parsons, 1998; Verhagen Metman *et al.*, 1998; Chase *et al.*, 2000; Marjama-Lyons & Koller, 2000). However, there have not been any detailed functional studies of the STN-GPe synapse in animal models of PD. In spite of their efficacy in alleviating motor symptoms, broad spectrum glutamate receptor antagonists are

unlikely to be adopted therapeutically because of undesirable side-effects in other brain circuits. Recently, GluN2B-specific ligands have been developed, providing clinicians with an important tool for dissecting neural circuitry that has incidentally proven to be particularly important in treating pain (Chizh *et al.*, 2001). The very restricted distribution of GluN2C- and GluN2D-containing subunits could make the side-effect profile of GluN2C- and GluN2D-selective antagonists and negative allosteric modulators very acceptable.

In addition to ionotropic receptors, metabotropic glutamate receptors (mGluRs) also exist in the GPe. On the basis of amino acid sequence homology, intracellular second messengers, and ligand selectivities, mGluRs are categorized into eight subtypes that are divided into: group I (mGluR1 and 5), group II (mGluR2 and 3), and group III (mGluR4, 6–8) (Nakanishi, 1994; Pin & Duvoisin, 1995; Conn & Pin, 1997).

In the GPe, group I mGluRs are abundantly expressed (Testa *et al.*, 1994; Testa *et al.*, 1998; Smith *et al.*, 2000). Immunohistochemistry and electron microscopy studies show that group I mGluRs localize postsynaptically along dendritic processes (Testa *et al.*, 1998; Hanson & Smith, 1999; Kaneda *et al.*, 2005). The activation of group I mGluRs depolarize GPe neurons to increase their excitability (Stefani *et al.*, 1998; Poisik *et al.*, 2003; Kaneda *et al.*, 2007). Group II mGluRs have a more modest expression (Ohishi *et al.*, 1993; Poisik *et al.*, 2005). Electron microscopy studies show group II mGluRs localize presynaptically on glutamatergic axon terminals (Poisik *et al.*, 2005). However, as mGluR3 is robustly expressed in the striatum (Ohishi *et al.*, 1993; Tanabe *et al.*, 1993; Testa *et al.*, 1994), it is also possible that they are targeted to the axon terminals in the GPe. Activation of group II mGluRs decreases neurotransmitter release from axon terminals (Poisik *et al.*, 2005). Group III mGluRs are abundantly expressed in the GPe (Kinoshita *et al.*, 1998; Bradley *et al.*, 1999; Kosinski *et al.*, 1999; Corti *et al.*, 2002) and are primarily presynaptically localized (Kinoshita *et al.*, 1998; Bradley *et al.*, 1999; Corti *et al.*, 2002; Bogenpohl *et al.*, 2013). Functionally, group III mGluRs act as homo- and heteroreceptors by decreasing glutamate release from putative STN terminals and GABA release from inhibitory terminals (Marino *et al.*, 2003; Matsui & Kita, 2003; Valenti *et al.*, 2003; Gubellini *et al.*, 2014). Much remains unknown about the purpose of mGluRs in the GPe. For example, the source of glutamate for these mGluRs has not been determined. As discussed below, the GPe receive a wide range of glutamatergic inputs in addition to the STN (see below). Coupled with the rich variety of mGluRs in the GPe, this suggests that these receptors may act as specific local regulators of network and neuronal activity. Astrocytes are abundant within the GPe and may play an important role in regulating the activation of mGluRs associated with neuronal elements within the GPe. This is likely in part through the detection of synaptic and ambient glutamate via the surface expression of mGluR3 and quite possibly mGluR5 on these cells (Testa *et al.*, 1994; Sun *et al.*, 2013; Panatier & Robitaille, 2015) (see further discussion below).

Intrapallidal and intracerebroventricular delivery of group III mGluR agonists have been explored as PD treatment with promising results (Valenti *et al.*, 2003; MacInnes *et al.*, 2004; Lopez *et al.*, 2007; Agari *et al.*, 2008). Given the therapeutic potential of mGluR pharmacology in PD, the field will benefit from addressing the current dearth of data on the

origin of presynaptic terminals expressing mGluRs and the expression of mGluRs in specific GPe neuron subpopulations.

GPe-STN loop in health and disease

Topographically, the excitatory STN-GPe and inhibitory GPe-STN projections form a reciprocally-connected loop. Compelling evidence from experimental and modeling studies suggests that the GPe-STN loop supports oscillatory activity (Shink *et al.*, 1996; Smith *et al.*, 1998a; Plenz & Kital, 1999; Bevan *et al.*, 2002b). Like GPe neurons, STN neurons are spontaneously active (Beurrier *et al.*, 2001; Bevan *et al.*, 2002a; Do & Bean, 2003), and the contribution of STN inputs to GPe firing has been examined in several preparations. In organotypic cultures, oscillatory activity in the GPe was abolished after cutting the input from the STN (Plenz & Kital, 1999). In awake rodents, silencing of the GPe after injection of the $GABA_A$ receptor agonist muscimol in the STN was seen only in 6-OHDA lesioned animals; control animals instead had only a slight reduction in GPe neuron activity (Chan *et al.*, 2011). In primates, while muscimol blockade of STN initially decreased and even silenced GPe neuron activity for five to ten minutes, the activity eventually settled into a pattern of high frequency active phases separated by pauses (Nambu *et al.*, 2000; Kita *et al.*, 2004), perhaps due to the effects of the inhibitory intranuclear collaterals that had been released from STN influence and regulation. Importantly, these studies highlight the role of excitatory STN input in regulating firing of GPe neurons.

In the normal state, activity in GPe neurons and STN neurons is uncorrelated and asynchronous, with complex spatiotemporal firing related to movement (Bevan *et al.*, 2002b). In parkinsonian animals, however, activity in GPe and STN neurons becomes synchronous and correlated, with an increase in tremor-related (3–8 Hz) and beta-frequency (13–30 Hz) oscillations (Cruz *et al.*, 2011; Tachibana *et al.*, 2011). It is proposed that the $Npas1^+$-$Foxp2^+$ (arkypallidal) GPe neurons receive much stronger input from the STN than do the PV^+ (prototypic) GPe neurons (Nevado-Holgado *et al.*, 2014). When combined with the strengthening of intrapallidal connections between GPe neurons that is seen in *ex vivo* slices from PD model rats (Miguelez *et al.*, 2012), this would likely contribute to the pathological synchrony of the GPe-STN loop that develops in PD. It is clear that the organization of the GPe-STN network is more complex than just the simple reverberating feedback loop that was proposed originally (Bevan *et al.*, 2002b).

As GPe and STN projections also converge on neurons in the internal globus pallidus and substantia nigra pars reticulata (the basal ganglia output nuclei), pathological oscillatory activity in the GPe-STN loop could have a major influence on basal ganglia dysfunction in PD (Terman *et al.*, 2002; Hashimoto *et al.*, 2003). In fact, the GPe-STN loop has been implicated in the onset, progression, and maintenance of dysfunctional oscillatory activity in PD (Bergman *et al.*, 1994; Nini *et al.*, 1995). In support of this theory, high-frequency (130–180 Hz) electrical stimulation (HFS) of the STN improves motor symptoms and is the neurosurgical treatment of choice for mid- to late-stage PD (Starr *et al.*, 1998; DeLong & Wichmann, 2001; Wichmann & Delong, 2006; Johnson *et al.*, 2008; Bronstein *et al.*, 2011; Wichmann & Delong, 2011; DeLong & Wichmann, 2012; DeLong & Wichmann, 2015). However, it is not clear that the therapeutic effects of HFS result from an increase in STN

activity (McIntyre & Hahn, 2010), as lesioning of the STN alleviates motor symptoms in the MPTP primate model of PD (Bergman *et al.*, 1990) while a similar effect is achieved by application of HFS directly to the GPe in both MPTP monkeys (Johnson *et al.*, 2012; Vitek *et al.*, 2012) and PD patients (Vitek *et al.*, 2004). Furthermore, repetitive activation of STN neurons leads to a reduction in their excitability as a consequence of decreased voltage-gated sodium channel availability (Beurrier *et al.*, 2001; Do & Bean, 2003). However, microdialysis measurements in the GPe have shown increased extracellular glutamate levels after STN-HFS, supporting the notion that HFS functions through activation of STN neurons instead (Windels *et al.*, 2000). Consistent with this, STN-HFS induced *c-fos* expression in GPe neurons (Shehab *et al.*, 2014). STN-HFS in awake monkeys also increased the average firing rate in the GPe (Hashimoto *et al.*, 2003). Additionally, using an MPTP monkey model of PD, Bar-Gad and colleagues demonstrate that HFS of the STN induces phase-locking of GPe neuron to the stimuli (Bar-Gad *et al.*, 2004).

While STN-HFS impacts the activity of the neurons in the STN, the subsequent effects on their synaptic partners may be a possible explanation for the results obtained in these studies, HFS in MPTP monkeys supports the notion that antidromic stimulation of GPe neurons can contribute to the relief of bradykinesia (Johnson *et al.*, 2012). Similarly, recent evidence suggests that STN-HFS exerts a therapeutic effect by antidromically activating layer 5 neurons in the motor cortex (Gradinaru *et al.*, 2009; Li *et al.*, 2012). This idea is supported by the literature showing STN-HFS is effective in suppressing abnormal activity in the motor cortex of PD patients (Sabatini *et al.*, 2000; Payoux *et al.*, 2004; Haslinger *et al.*, 2005) and transcranial stimulation of the motor cortex is also efficacious in ameliorating motor symptoms of PD (Cioni, 2007; De Rose *et al.*, 2012; Broeder *et al.*, 2015) and levodopa-induced dyskinesias (Ferrucci *et al.*, 2015). In summary, it is very likely that STN-HFS alters the temporal structure and dynamics of a complex set of pathways within the entire cortico-basal ganglia-thalamocortical loop.

Multiplicity of excitatory inputs to the GPe

In addition to the STN, other sources of excitatory input to the GPe come from the thalamus, the cortex, and the pedunculopontine nucleus (PPN). Overall, very little is known about these projections, including whether or not they target distinct classes of GPe neurons.

Thalamic input to the GPe arises from the caudal intralaminar nuclei, consisting of centromedian (CM) and parafascicular (Pf) nuclei. Though these structures are anatomically less well-defined, the CM-Pf complex is conserved in rodents. As such, tracing experiments have shown that the CM-Pf projects topographically to the GPe in a manner that parallels the thalamo-dStr projections (Kincaid *et al.*, 1991b; Sadikot *et al.*, 1992; Deschenes *et al.*, 1996; Smith *et al.*, 2004; Yasukawa *et al.*, 2004). These thalamic inputs to the GPe arise from collaterals that travel parallel to the GPe-dStr border, with some en passant boutons along the course, and terminate in dense aggregates of various sizes on the proximal dendrites of GPe neurons (Yasukawa *et al.*, 2004). Electrophysiological data show that electrical stimulation of the thalamus evokes large excitatory postsynaptic potentials in some GPe neurons, suggesting that the thalamic input can have a powerful influence on a subset of GPe neurons (Yasukawa *et al.*, 2004). It is tempting to speculate that at least a subset of Npas1^{+}

neurons are the major recipient of thalamic (or cortical—see below) inputs; a recent modeling study further reinforces this notion (Nevado-Holgado *et al.*, 2014). CM-Pf also receives inputs from PV^+ GPe neurons (Shammah-Lagnado *et al.*, 1996; Mastro *et al.*, 2014). The importance of this complex feedback is not understood. Importantly, neuronal loss in the CM-Pf is observed in PD, and though it does not appear to correlate with the severity of motor symptoms, it may impact non-cognitive aspects of PD via altered GPe function (Brown *et al.*, 2010; Kato *et al.*, 2011; Bradfield *et al.*, 2013; Smith *et al.*, 2014).

While cortical input has traditionally been thought to reach the GPe through the cortico-dStr-GPe and the cortico-STN-GPe pathways (Ryan & Clark, 1991; Kita, 1992; Yoshida *et al.*, 1993; Nambu *et al.*, 2000; Nambu, 2004; Kita & Kita, 2011a), there is increasing evidence of a direct cortical input to the GPe. Imaging data from humans suggest a direct projection from motor, orbitofrontal, and dorsolateral prefrontal cortex to the GPe (Milardi *et al.*, 2015). Tracer injections into the precentral medial and lateral cortices in rodents anterogradely label the ipsilateral but not contralateral GPe (Naito & Kita, 1994). In monkeys, cortical terminals labeled by VGluT1 target the dendritic spines and small dendrites throughout the GPe (Smith & Wichmann, 2015). At the same time, the cortex receives direct inputs from both GABAergic and cholinergic GPe neurons (Chen *et al.*, 2015; Saunders *et al.*, 2015); the neuronal identity of the former is at present unknown. As the cortex and its downstream synaptic influence undergo remodeling in models of PD (Kita & Kita, 2011a; Guo *et al.*, 2015a), further investigation of the functional properties of the direct cortical projection to the GPe is warranted.

The PPN is reciprocally connected with the GPe, sending mixed glutamatergic and cholinergic projections (Saper & Loewy, 1982; Gonya-Magee & Anderson, 1983; Moriizumi & Hattori, 1992; Charara & Parent, 1994; Lavoie & Parent, 1994; Mena-Segovia *et al.*, 2004; Dautan *et al.*, 2014; Eid *et al.*, 2014). Tracing experiments show that PPN input is sparse, but arborizes profusely in the ventral third of the GPe, with some poorly branched fibers found dorsally (Lavoie & Parent, 1994). These inputs synapse onto the soma and proximal dendrites of the GPe neurons and elicit action potentials after electrical stimulation of the PPN (Gonya-Magee & Anderson, 1983; Lavoie & Parent, 1994).

Dopaminergic and other neuromodulatory inputs to the GPe

Dopamine, its metabolites, and its associated metabolic enzymes are present in the GPe at relatively high levels (Carlsson, 1959; Bernheimer, 1964; Hornykiewicz, 1966; Hornykiewicz *et al.*, 1968; Vogel *et al.*, 1969; Broch & Marsden, 1972; Rosengren *et al.*, 1985). Accordingly, dopaminergic fibers traverse the rodent, primate, and human GPe (Mettler, 1970; Fallon & Moore, 1978; Lindvall & Bjorklund, 1979; Arluison *et al.*, 1984; Parent & Smith, 1987; Lavoie *et al.*, 1989; Ciliax *et al.*, 1995; Gaykema & Zaborszky, 1996; Rodrigo *et al.*, 1998; Ciliax *et al.*, 1999; Cossette *et al.*, 1999; Gauthier *et al.*, 1999; Hedreen, 1999; Jan *et al.*, 2000; Kirik *et al.*, 2000; Prensa *et al.*, 2000; Prensa & Parent, 2001; Fuchs & Hauber, 2004; Eid & Parent, 2015). There is evidence that dopaminergic neurons in both the substantia nigra and the ventral tegmental area project to the GPe (Lindvall & Bjorklund, 1979; Smith *et al.*, 1989; Kincaid *et al.*, 1991b; Charara & Parent, 1994; Gauthier *et al.*, 1999; Debeir *et al.*, 2005); as diverse subtypes of dopaminergic neurons are intermingled in

the midbrain (Poulin *et al.*, 2014; Anderegg *et al.*, 2015), having genetic access to distinct classes of midbrain dopamine neurons will help determine if the GPe-projecting dopaminergic neurons belong to a mixture of cell classes or a single cell class.

Ultrastructural analysis confirms the presence of direct dopaminergic synaptic contacts on pallidal neurons (Rodrigo *et al.*, 1998; Smith & Kieval, 2000; Eid & Parent, 2015). Moderate levels of D1- and D2-class receptor binding are evident in rodent, primate, and human GPe (Martres *et al.*, 1985; Boyson *et al.*, 1986; Dawson *et al.*, 1986; Dubois *et al.*, 1986; Savasta *et al.*, 1986; Charuchinda *et al.*, 1987; Richfield *et al.*, 1987; Beckstead, 1988; Beckstead *et al.*, 1988; Dawson *et al.*, 1988; Richfield *et al.*, 1989; Mansour *et al.*, 1990; Bouthenet *et al.*, 1991; Fremeau *et al.*, 1991; Joyce *et al.*, 1991; Mansour *et al.*, 1991; Mengod *et al.*, 1991; Rao *et al.*, 1991; Janowsky *et al.*, 1992; Mansour *et al.*, 1992; Mengod *et al.*, 1992; Wamsley *et al.*, 1992; Kessler *et al.*, 1993; Levant *et al.*, 1993; Herroelen *et al.*, 1994; Murray *et al.*, 1994; Hall *et al.*, 1996; Carey *et al.*, 1998; Gurevich & Joyce, 1999). *In situ* hybridization, tissue-level PCR, and immunohistochemical studies have argued that at least some of these receptors are postsynaptically expressed by cells residing within the GPe (Meador-Woodruff *et al.*, 1989; Najlerahim *et al.*, 1989; Mansour *et al.*, 1990; Bouthenet *et al.*, 1991; Joyce *et al.*, 1991; Mansour *et al.*, 1991; Weiner *et al.*, 1991; Mansour *et al.*, 1992; Fox *et al.*, 1993; Larson & Ariano, 1995; Mrzljak *et al.*, 1996; Ariano *et al.*, 1997; Gurevich & Joyce, 1999; Marshall *et al.*, 2001; Shin *et al.*, 2003; Billings & Marshall, 2004; Hoover & Marshall, 2004). Nevertheless, an overwhelming majority of the dopamine D2 receptors are associated with dStr axons and their terminals (Hadipour-Niktarash *et al.*, 2012). Local activation of dopamine receptors in the GPe produces stereotypy and increased locomotor activity, while local dopamine receptor blockade in the GPe produces profound akinesia and catalepsy (Costall *et al.*, 1972a; b; Hauber & Lutz, 1999). Although the cellular effects of D1-class receptors on GPe neurons are poorly understood, the activation of D2-class receptors generally suppresses the responsiveness of GPe neurons to dStr GABAergic inputs via both pre- and postsynaptic mechanisms (Cooper & Stanford, 2001; Shin *et al.*, 2003; Hernandez *et al.*, 2006; Watanabe *et al.*, 2009; Chuhma *et al.*, 2011; Miguelez *et al.*, 2012). Overall, the effects of dopaminergics on GPe neurons *in vivo* are more heterogeneous. In general, a decrease in the firing of GPe neurons is reported following systemic administration of haloperidol, a D2-class receptor antagonist. On the contrary, apomorphine, a non-selective dopamine receptor agonist, increases firing of GPe neurons (Bergstrom *et al.*, 1982; Carlson *et al.*, 1987; Walters *et al.*, 1987; Napier *et al.*, 1991; Kelland *et al.*, 1995; Mamad *et al.*, 2015). Finally, nigral dopaminergic neurons are subjected to feedback regulation by a heavy projection from the GPe itself (Celada *et al.*, 1999; Paladini *et al.*, 1999; Cobb & Abercrombie, 2003; Lee *et al.*, 2004; Brazhnik *et al.*, 2008; Watabe-Uchida *et al.*, 2012). The circuit effects arising from this feedback regulation may be responsible for the variation in the responses of GPe neurons to dopaminergic agents.

Compelling evidence has suggested that disruption of dopamine signaling within the GPe is causally linked to motor symptoms. Severe loss (up to 90%) of dopamine (and its metabolites) as well as dopaminergic fibers within the GPe have been observed in human patients and animal models of PD (Jan *et al.*, 2000; Kirik *et al.*, 2000; Rajput *et al.*, 2008). Accordingly, intrapallidal administration of dopamine is capable of restoring normal sensorimotor behavior and ameliorating the motor symptoms of dopamine-depleted animals

(Galvan *et al.*, 2001). As nigral dopamine neurons also release sonic hedgehog, brain-derived neurotrophic factor, and other trophic factors (Seroogy *et al.*, 1994; Gonzalez-Reyes *et al.*, 2012), it remains to be determined if toxin-animal models and human patients of PD suffer from additional complex alterations of neurochemistry following the loss of dopaminergic neurons. It will be important in the future to specifically manipulate different nodes along these signaling cascades to pinpoint where in a pathway and what molecules are crucial to proper cellular and circuit function.

In addition to dopaminergic inputs, the GPe receives abundant serotonergic innervation from the dorsal raphe (DeVito *et al.*, 1980; Pasik *et al.*, 1984; Vertes, 1991; Charara & Parent, 1994; Di Matteo *et al.*, 2008; Bang *et al.*, 2012; Eid *et al.*, 2013; Ogawa *et al.*, 2014; Pollak Dorocic *et al.*, 2014) and expresses a plethora of serotoninergic receptors (Appel *et al.*, 1990; Hoyer *et al.*, 1990; Sijbesma *et al.*, 1990; Sijbesma *et al.*, 1991; Waeber *et al.*, 1994; Waeber & Moskowitz, 1995; Wright *et al.*, 1995; Compan *et al.*, 1996; Vilaro *et al.*, 1996; Bonaventure *et al.*, 1998; Castro *et al.*, 1998; Morales *et al.*, 1998; Sari *et al.*, 1999; Bonaventure *et al.*, 2000; Clemett *et al.*, 2000; Riad *et al.*, 2000; Neumaier *et al.*, 2001; Li *et al.*, 2004; Martin-Cora & Pazos, 2004; Sari, 2004; Mostany *et al.*, 2005). Accordingly, stimulation of the dorsal raphe nucleus evokes an increase of serotonin levels in the GPe (McQuade & Sharp, 1997). Serotoninergic receptor activation controls GPe neuron activity via complex mechanisms (Chadha *et al.*, 2000b; Kita *et al.*, 2007; Chen *et al.*, 2008a; Hashimoto & Kita, 2008; Zhang *et al.*, 2010; Miguelez *et al.*, 2014). Hyperinnervation by serotonergic axons and increased serotonergic receptor responses occur following dopamine depletion (Di Matteo *et al.*, 2008; Zhang *et al.*, 2010) (but see Zeng *et al.*, 2010). However, serotoninergic neurons eventually degenerate in advanced stages of PD (Halliday *et al.*, 1990; Jellinger, 1990; Chinaglia *et al.*, 1993; Kish, 2003). Finally, additional neuromodulatory inputs such as those from cholinergic neurons also target the GPe while there is no evidence for the existence of a noradrenergic innervation (Rodrigo *et al.*, 1998).

Astrocytic regulation of the GPe

Glia are the most abundant cell type in the GPe. Astrocytes alone are estimated to outnumber neurons by an order of magnitude (Lange *et al.*, 1976; Karlsen & Pakkenberg, 2011; Salvesen *et al.*, 2015). This abundance implies that astrocytes play a crucial role in regulating GPe function. Astrocytes are important integral elements of neural circuits, where they integrate local and long-range modulatory signals through the expression of a myriad of surface receptors and transporters (Theodosis *et al.*, 2008; Perea *et al.*, 2009; Nedergaard & Verkhratsky, 2012; Araque *et al.*, 2014). It has been shown that GPe astrocytes express glutamate (Glt1 and Glast) and GABA (GAT1 and GAT3) transporters (Furuta *et al.*, 1997; Galvan *et al.*, 2010; Jin *et al.*, 2011; Scimemi, 2014). Astrocytes in turn regulate the spatiotemporal dynamics of activation, deactivation, and desensitization of neuronal receptors. In addition, astrocytes have the potential to release neuroactive substrates onto neurons (Halassa *et al.*, 2007; Perea *et al.*, 2009). While we have begun to understand the role of astrocytes in a few selective brain areas (Halassa *et al.*, 2007; Araque *et al.*, 2014), the biological importance and disease relevance of astrocytes in the basal ganglia is largely unexplored (Maragakis & Rothstein, 2006; Sofroniew & Vinters, 2010; Villalba & Smith, 2011; Chan & Surmeier, 2014; Tong *et al.*, 2014; Martin *et al.*, 2015). In light of this, it will

be important to study how astrocytic regulation of synaptic inputs and chemical homeostasis in the GPe is altered in neurological diseases, such as PD.

Behavioral and clinical relevance of the GPe

The role of the GPe in movement

Results from lesion and pharmacological activation studies provide conflicting evidence as to the role of the GPe in movement. Unilateral ibotenic acid or kainic acid lesion of the GPe leads to ipsilateral turning behavior (Ossowska *et al.*, 1983; Konitsiotis *et al.*, 1998), bilateral quinolinic acid lesion of the GPe leads to a decrease in spontaneous movement (Hauber *et al.*, 1998), and selective activation of the GPe by $GABA_A$ antagonist microinjection increases spontaneous movement (Grabli *et al.*, 2004) and dyskinesias (Crossman *et al.*, 1984; Matsumura *et al.*, 1995) in monkeys; all of these phenotypes are predicted by the classic basal ganglia model. Conversely, ibotenic acid GPe lesions in monkeys produce no motor deficits (Soares *et al.*, 2004), and increased spontaneous movement has also been observed in rats with bilateral GPe lesion (Norton, 1976; Joel *et al.*, 1998), findings that are inconsistent with the classic model. Furthermore, rats with bilateral GPe lesions display increased inaccuracy in a reaching task but not gross movement, suggesting a specific deficit in performance of organized limb movements (Schneider & Olazabal, 1984). There are several possibilities for the discrepancies between findings from different research groups, such as differences in the extent of lesion or the spread of drugs.

Studies of movement-related electrophysiological activity in the GPe have provided additional insight into its role in movement. Like neurons of other basal ganglia nuclei, GPe neuron firing patterns are related to movement amplitude, velocity, and direction (Georgopoulos *et al.*, 1983; Mitchell *et al.*, 1987; Turner & Anderson, 1997; Gage *et al.*, 2010). This activity is context-dependent and can be modulated by the presence of external cues that signal whether a particular movement should be performed (Turner & Anderson, 1997; 2005; Gage *et al.*, 2010). This cue-related activity in the GPe is consistent with the involvement of the basal ganglia in the integrative processing of movement with sensory information.

It is proposed that the basal ganglia control sequences of behavior via “chunking” (Graybiel, 1998; Smith & Graybiel, 2014). In other words, the basal ganglia piece together related individual movements into single movement sequences to accomplish complex movement patterns (Levesque *et al.*, 2007; Tremblay *et al.*, 2009; Tremblay *et al.*, 2010). Previous studies have found that GPe neurons can have distinct patterns of firing activity within different temporal phases of a movement or movement sequence, preferentially firing before, after, or throughout a movement (Anderson & Horak, 1985; Shi *et al.*, 2004; Turner & Anderson, 2005; Jin *et al.*, 2014); these movement-related firing behaviors have been found to correlate with the molecular identity of the GPe neurons (Dodson *et al.*, 2015) and are thought to collectively represent a chunked motor sequence (Jin *et al.*, 2014).

The integrative role of the GPe—a circuit perspective

The GPe may play a role in reactive action cancellation, or suppression of planned actions (Schmidt *et al.*, 2013; Gittis *et al.*, 2014; Leventhal *et al.*, 2014). Action cancellation is often studied in animals performing a stop-signal task, in which a "Go" cue is given to cue a rapid, specific movement, and a "Stop" cue is given just after the "Go" cue in a subset of trials to indicate the subject should cancel the movement (Schmidt *et al.*, 2013; Leventhal *et al.*, 2014). Studies suggest that the behavioral response to these signals—whether subjects are able to successfully stop after hearing the "Stop" cue—involves a competition between distinct basal ganglia circuits (Schmidt *et al.*, 2013). Specifically, dSPNs in the dStr mediate relatively slow "Go" signals, whereas STN neurons, likely by receiving direct input from the cortex, mediate faster "Stop" signals. However, as "Stop" signals from the STN lead to only transient inhibition of substantia nigra pars reticulata neurons, it is thought that an additional pathway must mediate inhibition of "Go" signals for full behavioral stopping to occur (Schmidt *et al.*, 2013). A recent study suggests that the projection from the GPe to the dStr could provide this inhibition of "Go" signals (Mallet *et al.*, 2016). However, this raises the question of whether the GPe projection to the dStr is also involved in the facilitation of action by appropriately inhibiting "No-go" signals immediately prior to movement initiation. Conversely, it is possible that excessive inhibition of the dStr by the GPe could underlie the hypokinetic symptoms (i.e., bradykinesia and akinesia) that are characteristic of PD.

The GPe is clinically important

As we have only begun to reliably identify GPe neurons, very little is known about how different classes of GPe neurons are involved in the symptomatology of movement disorders. An overview of the relevant literature has been provided throughout this review. The following section highlights a number of movement disorders in which the GPe is critically involved.

Dopamine loss leads to altered physiology in the GPe in PD. The altered firing behavior of GPe neurons is one of the most striking and consistent electrophysiological signatures of PD. Compelling evidence suggests that disruption of dopamine signaling within the GPe is causally linked to hypokinetic symptoms of PD. The loss of dopamine shifts the firing pattern of GPe neurons from decorrelated spiking to synchronized, oscillatory bursts (Pan & Walters, 1988; Filion & Tremblay, 1991; Filion *et al.*, 1991; Hutchison *et al.*, 1994; Nini *et al.*, 1995; Rothblat & Schneider, 1995; Hassani *et al.*, 1996; Taha *et al.*, 1996; Bergman *et al.*, 1998; Boraud *et al.*, 1998; Wichmann *et al.*, 1999; El-Deredy *et al.*, 2000; Magill *et al.*, 2000; Magnin *et al.*, 2000; Raz *et al.*, 2000; Brown *et al.*, 2001; Magill *et al.*, 2001; Bar-Gad *et al.*, 2003; Starr *et al.*, 2005; Heimer *et al.*, 2006; Wichmann & Soares, 2006; Kita, 2007; Tang *et al.*, 2007; Zold *et al.*, 2007a; Zold *et al.*, 2007b; Mallet *et al.*, 2008; Starr *et al.*, 2008; Sani *et al.*, 2009; Chan *et al.*, 2011). Accordingly, administration of dopamine to the GPe is capable of reversing abnormal synchrony among GPe neurons (Heimer *et al.*, 2002) and restoring normal sensorimotor behavior and ameliorating the motor symptoms of dopamine-depleted animals (Galvan *et al.*, 2001). In addition, high frequency stimulation of the GPe leads to symptomatic improvement in parkinsonian monkeys (Johnson *et al.*, 2012; Vitek *et al.*, 2012) and PD patients (Vitek *et al.*, 2004).

In addition to PD, HD is another major basal ganglia disorder. It is an autosomal dominant neurodegenerative disease that leads to progressive impairments in motor function, cognition, and behavior. A characteristic feature of HD is the presence of chorea (Zuccato *et al.*, 2010; Plotkin & Surmeier, 2015). There is no apparent cell death in the GPe in HD until late in the disease progression (Reiner *et al.*, 2011; Waldvogel *et al.*, 2015). Instead, loss of GABAergic SPNs results in a dramatic upregulation of $GABA_A$ receptor-subunits in the GPe (Faull *et al.*, 1993; Waldvogel & Faull, 2015). Currently, there is very little information available concerning the firing behavior of GPe neurons in HD. Consistent with its presumptive hyperactivity (Temel *et al.*, 2006; Starr *et al.*, 2008), GPe lesioning or electrical stimulation leads to symptomatic relief in both animal models and human patients (Ligot *et al.*, 2011; Beste *et al.*, 2015; Nagel *et al.*, 2015). Further investigation of the changes that occur in the GPe in HD will be facilitated by the array of genetic mouse models that have been developed (Plotkin & Surmeier, 2015).

Finally, though its etiology has yet to be discovered, there is compelling evidence from both human patients and animal models of dystonia that aberrant activity is present in the GPe (Starr *et al.*, 2005; Chiken *et al.*, 2008; Baron *et al.*, 2011; Nambu *et al.*, 2011; Nishibayashi *et al.*, 2011). Dystonia is characterized by involuntary repetitive twisting and sustained muscle contractions that result in abnormal movements and postures (Breakefield *et al.*, 2008; Schwarz & Bressman, 2009; Tanabe *et al.*, 2009; Albanese *et al.*, 2013; Jinnah & Factor, 2015). Recent evidence further suggests that altered cortico-dStr-GPe signaling may underlie the altered firing of GPe neurons in dystonia (Nishibayashi *et al.*, 2011).

Concluding remarks

In summary, despite the clinical importance of the GPe, we have only limited information about its cellular composition and organizational principles. This undermines our understanding of the GPe in motor function and dysfunction.

This article reviews the literature on neuron diversity in the GPe. The discovery of novel cellular markers revealed that the heterogeneity in GPe neurons' anatomical and electrophysiological properties observed in early studies could be correlated to their molecular signatures. We have only begun to understand the cellular makeup of the rodent GPe. An important next step is to refine the classification schemes that have been developed and to identify the specific inputs and outputs of distinct GPe neuron classes. We can begin to accomplish this goal using currently available genetic tools, including the Npas1 mouse line developed by our group. The identification of novel cell-specific markers will undoubtedly continue to shape future research. Neuronal diversity is an emerging theme in the basal ganglia (Kreitzer, 2009; Tepper *et al.*, 2010; Antal *et al.*, 2014; Barrot, 2014; Poulin *et al.*, 2014; Anderegg *et al.*, 2015; Xiao *et al.*, 2015), and it will be important to fully understand how distinct classes of GPe neurons are integrated into large-scale computations.

In conclusion, this review provides an overview of the complex reciprocal loops formed between GPe neurons and their synaptic partners in addition to neuronal diversity in the GPe. As a whole, the literature now argues that the GPe should no longer be considered a simple relay in which information flows unidirectionally from the dStr to GPe.

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Abbreviations

ChAT	choline acetyltransferase, cholinergic
CM	centromedian nucleus of thalamus
dSPNs	direct-pathway spiny projection neurons
dStr	dorsal striatum
GABA	γ-aminobutyric acid
GPe	external globus pallidus
HD	Huntington's disease
HFS	high-frequency stimulation
iSPNs	indirect-pathway spiny projection neurons
LGE	lateral ganglionic eminence
MGE	medial ganglionic eminence
mGluRs	metabotropic glutamate receptors
PD	Parkinson's disease
Pf	parafascicular nucleus of thalamus
PoA	preoptic area
PPN	pedunculopontine nucleus
PV	parvalbumin
SPNs	spiny projection neurons
STN	subthalamic nucleus

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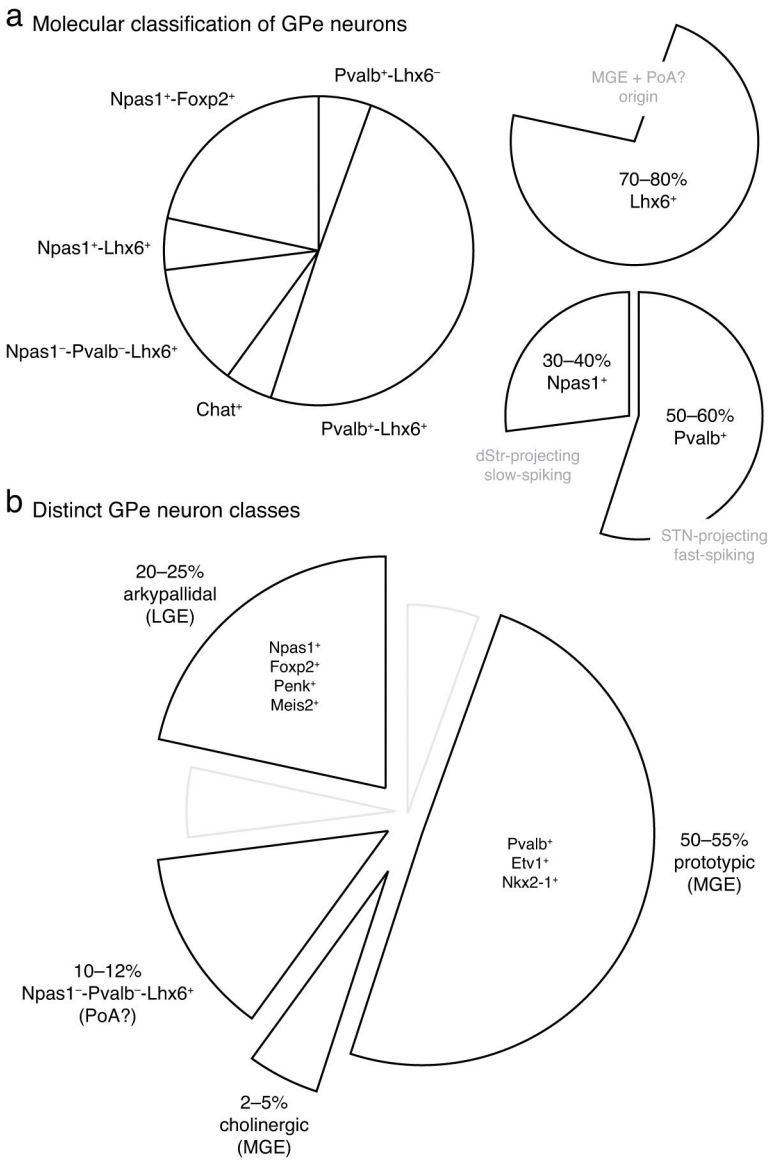

Figure 1. Diagrams summarizing the classification of GPe neurons

(**a**) Six different GPe neuron classes are identified based on the expression of various molecular markers. For consistency, only gene names are used throughout (though for readability they are not italicized). Plus and minus signs denote positive and negative-expression, respectively. Alternative names are listed below to cross reference with the main text. Percentages given are only approximations because of the ranges in the results reported in the literature. The relative numbers of different classes of GPe neurons listed is a deduction based on comparative analysis across several experimental findings in Abdi et al. (2015), Dodson, et al. (2015), and Hernández et al. (2015). Though it is clear that a unique class of $Lhx6^+$ neurons exist, there is evidence for the expression of Lhx6 in multiple classes of GPe neurons. The field has yet to come to a consensus on the abundance and origin of $Lhx6^+$ GPe neurons. In contrast, it is now well-established that $Npas1^+$ GPe neurons and $Pvalb^+$ GPe neurons form two distinct classes that project heavily to the dorsal striatum and

subthalamic nucleus, respectively. Their relationships with arkypallidal GPe neurons and prototypic GPe neurons are illustrated in (**b**). See Table 1 for further description on their electrophysiological characteristics. (**b**) Four unique GPe neuron classes are identified so far based on the molecular signature, electrophysiological characteristics, projection patterns, and developmental origins. An additional list of molecular markers are listed for arkypallidal neurons and prototypic neurons. Prototypic neurons are more broadly defined in the literature than in the figure, which highlights the most well-defined subclass.
Alternative names: Chat, ChAT, choline acetyltransferase; dStr, dorsal striatum; Etv1, ER81; GPe, external globus pallidus; LGE, lateral ganglionic eminence; MGE, medial ganglionic eminence; Penk, PPE, preproenkephalin; PoA, preoptic area; Pvalb, PV, parvalbumin; STN, subthalamic nucleus.

Table 1

Characteristics of GPe neurons

	General properties						Anatomical and circuit properties					Intrinsic properties							
	Approximate historical neuron type	Chemical content	Abundance	Defining markers	Other markers	Origin	Cell body size	Primary projection target	Formation of local collaterals	Extrinsic synaptic inputs	Intrinsic synaptic inputs	Input resistance	Spike rate	Rate variability	Spike width	Ionic conductances: NaP	HCN	Kv4	Delayed rectifier
PV$^+$ (prototypic)	Type I, Type A	GABA	~55%	Pvalb	Nkx2-1, Er81, Shh	MGE	Large	STN	Yes	dStr	Yes	Medium	High	Low	Narrow	High	High	High	High
References	1,2,3,4,5,6,7	8	4,5,6,7,8	4,5,9	5,8,10	2,8,10	1,6,7	3,4,5,9	1,3,11	1,4,7,11,12	11	4,6,7,9	2,4,5,9	4,5,9	4,6,9	4,5	4,6	4,7	4
Npas1$^+$- Foxp2$^+$ (arkypallidal)	Type II, Type B	GABA	~25%	Foxp2, Penk, Ascl1, Meis2	Npas1, Pax6	LGE	Small	dStr	Yes	dStr	Likely	High	Low	High	Wide	Low	Low	Very low	Low
References	1,2,3,4,5,6,7	8	4,5,6,7,8	4,5	4,5,8	2,8	1,6,7	1,3,4,5	1,3,11	1,4,7,12	15	4,6,7	2,4,5	4,5	4,6	4	4,6	4	4
ChAT$^+$ (cholinergic)	Type III, Type C	Ach, GABA	~5%	Chat	Nkx2-1	MGE	Very large	Ctx	Yes	dStr, STN	n.d.	Low	Very low	High	Very wide	n.d.	Very low	High	n.d.
References	3,4,5,6,7	8,13	4,6,7	4,8,13	5,8	2,8	6,13	13	13	4,13		4,6,7	4,13	4	4,7		6	6	

Alternative names: Ascl1, Mash1; Chat, choline acetyltransferase; Ctx, cortex; dStr, dorsal striatum; Etv1, ER81; LGE, lateral ganglionic eminence; MGE, medial ganglionic eminence; NaP, persistent sodium current; n.d., not determined; Penk, PPE, preproenkephalin; Pvalb, PV, parvalbumin; STN, subthalamic nucleus.

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Table 2

Calculation of GPe-dStr connectivity

Cell count						**Refs**
1a	Total no. of dStr neurons		2,791,000			Oorschot (1996)
1b	Total no. of GPe neurons		45,960			Oorschot (1996)
1c	PV^+ GPe neurons	(1b × 55%)	25,278			Abdi *et al.* (2015), Dodson *et al.* (2015), Hernández *et al.* (2015)
1d	$Npas1^+$-$Foxp2^+$ GPe neurons	(1b × 25%)	11,490			Abdi *et al.* (2015), Dodson *et al.* (2015), Hernández *et al.* (2015)
No. boutons produced by each GPe neuron			Approximation			
2a	PV^+ *		1,000			Bevan *et al.* (1998), Mallet *et al.* (2012)
2b	$Npas1^+$-$Foxp2^+$ **		10,000			Mallet *et al.* (2012)
Total no. of boutons formed by each GPe neuron class			Approximation			
3a	PV^+	(1c × 2a)	25,278,000			Bevan *et al.* (1998), Mallet *et al.* (2012)
3b	$Npas1^+$-$Foxp2^+$	(1d × 2b)	114,900,000			Mallet *et al.* (2012)
3c	$Npas1^+$-$Foxp2^+$/PV^+	(3c/3a)	5			
			Contact probability			
Total no. of contacts per dStr neuron from GPe inputs			100%	10%	1%	
4a	PV^+	(3a/1a)/contact prob.	9	91	906	
4b	$Npas1^+$-$Foxp2^+$	(3b/1a)/contact prob.	41	412	4,117	
4c	Total no. symmetrical synapses per SPN		2,500			Wilson (2007)
4d	PV^+ (% total)	(4a/4c)	0.36%	3.62%	36.23%	
4e	$Npas1^+$-$Foxp2^+$ (% total)	(4b/4c)	1.65%	16.47%	164.67%	
Total no. of contacts per SPN branchlet						
5a	No. of primary dendrites per dSPN		8			Gertler *et al.* (2008)
5b	PV^+ to dSPN	(4a/5a)	1	11	113	
5c	$Npas1^+$-$Foxp2^+$ to dSPN	(4b/5a)	5	51	515	
5d	No. of primary dendrites per iSPN		6			Gertler *et al.* (2008)

Cell count						Refs
5e	PV^+ to iSPN	(4a/5d)	2	15	151	
5f	$Npas1^+$-$Foxp2^+$ to iSPN	(4b/5d)	7	69	686	

*The axonal arborization patterns in Bevan *et al.* (1998) are highly consistent with those of the more recently described TI neurons, which are primarily PV^+ (Mallet *et al.*, 2012). Minimum and maximum number of PV^+ boutons described by the literature cited is 329 and 1,353, respectively.

**Given that Foxp2 and preproenkephalin show completely overlapping expression in the GPe (Abdi *et al.*, 2015; Dodson *et al.*, 2015) and that essentially all $Foxp2^+$ neurons are also $Npas1^+$ (Abdi *et al.*, 2015; Dodson *et al.*, 2015; Hernández *et al.*, 2015), it can be inferred that $Npas1^+$-$Foxp2^+$ neurons represent the arkypallidal neurons that exhibit extensive axonal arborizations in the dStr (Mallet *et al.*, 2012). Minimum and maximum number of $Npas1^+$-$Foxp2^+$ boutons described by the literature cited is 9,085 and 13,789, respectively.