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Review

Circuit Mechanisms of Parkinson's Disease

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Parkinson's disease (PD) is a complex, multi-system neurodegenerative disorder. The second most common neurodegenerative disorder after Alzheimer's disease, it affects approximately 1% of adults over age 60. Diagnosis follows the development of one or more of the core motor features of the disease, including tremor, slowing of movement (bradykinesia), and rigidity. However, there are numerous other motor and nonmotor disease manifestations. Many PD symptoms result directly from neurodegeneration; others are driven by aberrant activity patterns in surviving neurons. This latter phenomenon, PD circuit dysfunction, is an area of intense study, as it likely underlies our ability to treat many disease symptoms in the face of (currently) irreversible neurodegeneration. This Review will discuss key clinical features of PD and their basis in neural circuit dysfunction. We will first review important disease symptoms and some of the responsible neuropathology. We will then describe the basal ganglia-thalamocortical circuit, the major locus of PD-related circuit dysfunction, and some of the models that have influenced its study. We will review PD-related changes in network activity, subdividing findings into those that touch on the rate, rhythm, or synchronization of neurons. Finally, we suggest some critical remaining questions for the field and areas for new developments.

Clinical Features of Parkinson's Disease

Motor Features

Though the core, or classic, motor features of Parkinson's disease (PD) include tremor, bradykinesia, and rigidity, there are many other motor symptoms, including alterations in gait and balance, eye movement control, speech and swallowing, and bladder control. In PD patients, bradykinesia manifests as reductions in movement amplitude, movement velocity, and difficulty in initiating movement. It can impact voluntary control of many muscle groups, including eye muscles (resulting in slowed initiation of saccades), muscles of speech (resulting in softer and sometimes slurred speech), and limb muscles (resulting in reduced dexterity). Patients describe difficulties in fine motor tasks like buttoning, writing, and using utensils. Tremor is variable: most, but not all, patients have a tremor, typically present in one or both hands but also possible in the legs or head. Hand tremor is usually present at rest, diminishes during voluntary movement, and consists of rhythmic movement, ~5 Hz in frequency, about the wrist. Many core motor symptoms respond to dopamine replacement therapy with the dopamine precursor levodopa or dopamine agonists.

As the disease progresses, additional motor features such as impaired gait and balance develop, furthering disability. Gait slows, develops a shuffling quality with reduced stride length, and alongside impaired postural reflexes leads to instability and falls; these impairments are only partially responsive to dopamine replacement therapy. Speech and swallowing are typically affected later in the disease course. Speech becomes soft and sometimes difficult to understand, and swallowing deficits can cause choking episodes, drooling, and, eventually, aspiration pneumonia. These symptoms rarely respond to dopaminergic medications. While motor symptoms are useful in clinical diagnosis, there is increasing awareness of the numerous nonmotor features of PD, many of which do not respond to standard pharmacological treatment. Nonmotor features of PD arise both before and after the onset of the classic motor symptoms, increase disability, and reduce quality of life. They can be grouped into behavioral, cognitive, and autonomic categories.

Behavioral Symptoms

Behavioral symptoms, such as mood and sleep disorders, arise throughout the course of PD and may also represent a major complication of current treatments. Anxiety or depression often develops several years before the onset of typical motor symptoms (Faivre et al., 2019), suggesting that these symptoms are driven by the underlying disease process rather than coping with the disease. Anxiety is present in approximately 40% of patients (Pontone et al., 2009), while depression affects approximately 40%–50% of PD patients, depending on how depression is defined (Reijnders et al., 2008). Fortunately, these symptoms are often amenable to the same antidepressant therapies used in patients without PD.

PD is also characterized by multiple changes in sleep, including insomnia and alterations in sleep and wake cycles. Earliest to develop is REM sleep behavior disorder, a phenomenon in which patients physically enact their dreams, thrashing about during sleep, grabbing their bedpartner, or falling out of bed. In healthy individuals, brainstem circuitry produces paralysis during REM sleep (sleep atonia). This process goes awry in many patients with PD or other synucleinopathies (St Louis et al., 2017) and is often present many years before the onset of motor symptoms (Postuma et al., 2009; Galbiati et al., 2019).

Dopamine replacement therapy can alleviate some behavioral symptoms, such as apathy or anhedonia, but may also create new behavioral symptoms in susceptible individuals.

Two well-described behavioral phenomena associated with dopamine replacement therapy are impulse control disorder (ICD) and the dopamine dysregulation syndrome (DDS). In ICD, patients impulsively or compulsively engage in reward-seeking behaviors, such as gambling, electronic-gaming, shopping, eating, and pornography or other sexual activities (Weintraub et al., 2010). DDS is a related condition in which patients develop addictive behaviors toward their dopaminergic medication (dopamine agonists or levodopa), taking larger amounts than prescribed, more frequently, and with dependence/withdrawal-type symptoms (Giovannoni et al., 2000).

Cognitive Symptoms

Cognitive decline is one of the most disabling features of PD, and though some cognitive changes are evident even at the time of diagnosis (Williams-Gray et al., 2007; Aarsland et al., 2009), clinically significant cognitive impairment typically manifests some years later and progresses steadily over time. Though initially PD was considered a movement disorder, without significant cognitive components, longitudinal studies have shown that essentially all PD patients eventually develop dementia (Hely et al., 2008). Historically, PD and the related synucleinopathy Lewy body dementia were distinguished based on the timing and severity of cognitive deficits (late and milder in PD versus early and marked in Lewy body dementia). However, more detailed study of disease symptoms and postmortem brain pathology suggest that these disorders may be part of a single spectrum, sharing cognitive features (Jellinger, 2018).

Symptoms and measurable declines in nearly every cognitive domain have been reported in PD, but deficits can be subdivided into those that are dopamine dependent (alleviated or exacerbated by dopamine replacement therapy) and those that are not (Sethi, 2008). Dopamine-dependent cognitive symptoms tend to emerge earlier and include deficits in attention, processing speed, set-switching, and verbal fluency (Robbins and Cools, 2014). Dopamine-independent cognitive impairments tend to accumulate later and include deficits in episodic memory and visuospatial function. In later-stage disease, visual phenomena such as illusions and hallucinations frequently develop, which can unfortunately be worsened by dopamine replacement therapy (Sethi, 2008). Cognitive deficits in PD are commonly treated with cholinesterase inhibitors (Pagano et al., 2015), which may help compensate for profound loss of cholinergic basal forebrain neurons in PD (Müller and Bohnen, 2013).

Autonomic Symptoms

PD patients also experience symptoms related to dysfunction of the autonomic nervous system, including constipation, sexual dysfunction, urinary symptoms and incontinence, orthostatic hypotension, and changes in thermoregulation. Some symptoms, like constipation, frequently predate the onset of motor symptoms, while others, like orthostatic hypotension and incontinence, tend to become clinically significant at later stages of the disease. These symptoms tend not to respond to dopamine replacement therapy or to be worsened by it (e.g., orthostatic hypotension). These key PD symptoms are rooted in the functional anatomy of the disease. Understanding some of the neuropathological features of PD, including the areas affected by neurodegeneration, informs our knowledge of which symptoms can be explained directly by cell loss versus those that may arise from circuit dysfunction.

Patterns of Neurodegeneration in Parkinson's Disease

Though PD is a neurodegenerative disease, some disease symptoms can be directly linked to neuronal loss, while others appear to be caused by aberrant activity or connectivity in surviving neurons. Here we will briefly discuss the neurodegenerative features of PD. Functional components will be discussed subsequently at length.

As with clinical symptoms, PD neuropathology is highly heterogeneous, but patients share some features. The pathological hallmark of PD is the Lewy body, which contains the protein α-synuclein. Lewy bodies are found in different regions of the postmortem brain, often, but not always, accompanied by neurodegenerative cell loss (Surmeier et al., 2017) corresponding to symptom burden. The most well-known site of Lewy body deposition and neurodegeneration is the midbrain, the dopaminergic neurons of the substantia nigra pars compacta (SNc), and, to a lesser degree, the adjacent ventral tegmental area (VTA). The loss of dopamine neurons and their projections to the striatum is believed to produce the core motor symptoms of PD and contribute to some of the cognitive and behavioral features. Chronic loss of dopaminergic signaling is believed to trigger many cellular and circuit changes, detailed in later sections of this Review.

Neurodegeneration is also extensive in brainstem nuclei, including autonomic areas like the dorsal motor nucleus of the vagus, motor nuclei such as the pedunculopontine nucleus, and neuromodulatory nuclei like the locus coeruleus and raphe (Seidel et al., 2015). The timing of changes in noradrenergic and serotonergic projections versus dopaminergic projections may differ significantly (Espay et al., 2014). In fact, in a postmortem immunohistochemical study of PD patients, it appeared that serotonin signaling might be enhanced in the striatum (Bédard et al., 2011), consistent with serotonergic sprouting seen in a study of levodopa-treated parkinsonian patients, monkeys, and rats (Rylander et al., 2010). Loss of serotonergic and noradrenergic neurons might produce secondary effects on synaptic connectivity and function in its projection targets, much like the loss of dopaminergic projections profoundly alters striatal and frontal cortical connectivity and function. Less is known about clinical-pathological correlates in these areas, but positron emission tomography (PET) studies in PD patients show correlations between loss of serotonergic neurons and depression in PD (Pagano et al., 2017) or loss of serotonergic and noradrenergic signaling with sleep disturbances, mood disorders, and cognitive deficits in PD (Espay et al., 2014; Politis and Niccolini, 2015). Neurodegeneration in limbic and neocortical areas is common in PD and correlates strongly with cognitive decline (Horvath et al., 2013), though many older patients have concomitant Alzheimer's disease pathology (Irwin et al., 2017).

Though the pattern of neurodegeneration seen in PD patients explains many aspects of the disease, some of the key clinical features, including the core motor symptoms (tremor, bradykinesia, and rigidity), are suspected to arise from aberrant patterns of activity within surviving neurons.

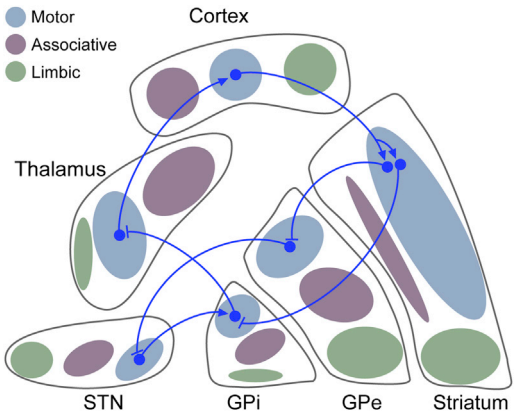

Figure 1. Parallel Circuit Model of the Basal Ganglia
Limbic (green), associative (purple), and sensorimotor (blue) information from excitatory (arrows) cortical afferents is distributed in parallel to regions of the striatum. Anatomical separation of these channels is preserved in downstream basal ganglia nuclei. As an example, inhibitory projections (flat arrows) from sensorimotor striatum innervate sensorimotor regions of the GPi either directly or intermediately through the GPe and STN. Projections from sensorimotor regions of GPi then innervate the motor thalamus, which projects back to sensorimotor regions of the cortex.

Anatomy and Circuit Models of the Basal Ganglia

Understanding the circuit mechanisms that drive motor symptoms of PD requires knowledge of the affected circuit components and their functions. Here, we review the anatomy and several prominent circuit models of the basal ganglia, a group of interconnected subcortical nuclei whose dysfunction following dopamine loss plays a critical role in the motor symptoms of PD. These models greatly simplify the underlying anatomy, and each emphasizes different aspects of basal ganglia function. Later sections addressing changes in basal ganglia activity following dopamine loss will be framed by these models.

Parallel Circuit Model

The parallel circuit model (Figure 1) describes how information progresses through the basal ganglia in anatomically and functionally distinct channels. The primary input nucleus of the basal ganglia, the striatum, integrates glutamatergic input from the cortex and thalamus (centromedian and parafascicular, CM-PF) with dopaminergic input from midbrain regions including the VTA and SNc (Moore and Bloom, 1978). Early anatomical work indicated that gross subdivisions of the striatum receive glutamatergic and dopaminergic innervation from different input regions and that output from these subdivisions to downstream basal ganglia nuclei tended to remain separated, leading to the development of the parallel circuit model (Alexander et al., 1986). This model proposes that different types of information (sensorimotor, associative, limbic) flow in parallel streams through the basal ganglia thalamo-cortical loop. At the simplest level, this model divides the striatum into three broad regions: the ventral striatum, the caudate and pre-commissural putamen, and the post-commissural putamen (Figure 1). The ventral striatum, comprised of the nucleus accumbens and olfactory tubercle, receives glutamatergic input from limbic regions and is predominantly innervated by dopamine neurons in the VTA. The caudate and pre-commissural putamen receive dopaminergic input from the SNc and glutamatergic input from associative regions. The post-commissural putamen also receives dopaminergic input from the SNc but receives greater input from sensorimotor regions of the cortex. Notably, in rodents, the dorsal striatum is contiguous, with the dorsomedial portion receiving greater associative input and the dorsolateral greater sensorimotor input.

In all striatal subdivisions, GABAergic output neurons, termed medium spiny neurons (MSNs, also known as spiny projection neurons or SPNs), project either directly or via several synapses (indirectly) to basal ganglia output nuclei, the globus pallidus pars interna (GPi, referred to as the entopeduncular nucleus in rodents) and substantia nigra pars reticulata (SNr). Indirect projections are relayed through GABAergic connections in the globus pallidus pars externa (GPe) and glutamatergic neurons in the subthalamic nucleus (STN), which in turn project to GPi and SNr. GPi and SNr projections inhibit the brainstem motor centers or to the ventral anterior (VA) and ventral lateral (VL) thalamus (Parent and Parent, 2004). Limbic, associative, and sensorimotor channels arise at the level of striatal input but are preserved—in part—through downstream basal ganglia structures. Channel-specific information at the level of the cortex may crosstalk with other channels as it re-enters the basal ganglia loop (Calzavara et al., 2007; Frank, 2011). Thus, while many brain regions and functions are affected by PD, the preferential loss of SNc dopamine neurons that innervate motor regions of the striatum (Bernheimer et al., 1973) may partially account for the early prominence of motor deficits. How nonmotor basal ganglia channels are affected in PD, and whether these changes are causal in the cognitive and behavioral symptoms, remains a crucial area for further investigation.

The Classical Model

The classical model of basal ganglia function has critically shaped understanding of how dopamine contributes to motor output and how loss of midbrain dopamine neurons leads to circuit-level changes underlying the motor symptoms of PD. Developed in the late 1980s and early 1990s (Albin et al., 1989; Alexander and Crutcher, 1990; DeLong, 1990), the classical model divides striatal MSNs into two populations, direct and indirect pathway MSNs, based on their projection targets (Figure 2). Direct pathway MSNs (dMSNs) project directly to basal ganglia output (GPi/SNr) and express $G_{\alpha olf}$-coupled D1-like dopamine receptors (Gerfen et al., 1990; Hervé et al., 1995; Deng et al., 2006). Thus, activation of the direct pathway is thought to decrease basal ganglia output, disinhibiting the thalamus and promoting movement. In contrast, indirect pathway MSNs (iMSNs) project to basal ganglia output indirectly via the GPe and STN and express G_i-coupled D2-like dopamine receptors (Gerfen et al., 1990; Hervé et al., 1995; Deng et al., 2006). Activation of this pathway is thought to increase basal ganglia output, inhibiting the thalamus and suppressing movement. Importantly, dopamine is hypothesized to have opposing effects on these two populations, increasing dMSN activity and decreasing iMSN activity. The net effect of dopaminergic signaling, according to this model, is to promote movement by suppressing basal ganglia output from the GPi. In PD, dopamine loss is predicted to cause imbalanced activity between the two pathways at the striatal level. Excessive indirect pathway activity is hypothesized to suppress GPe firing, increase STN activity, and drive an increase in GPi-mediated

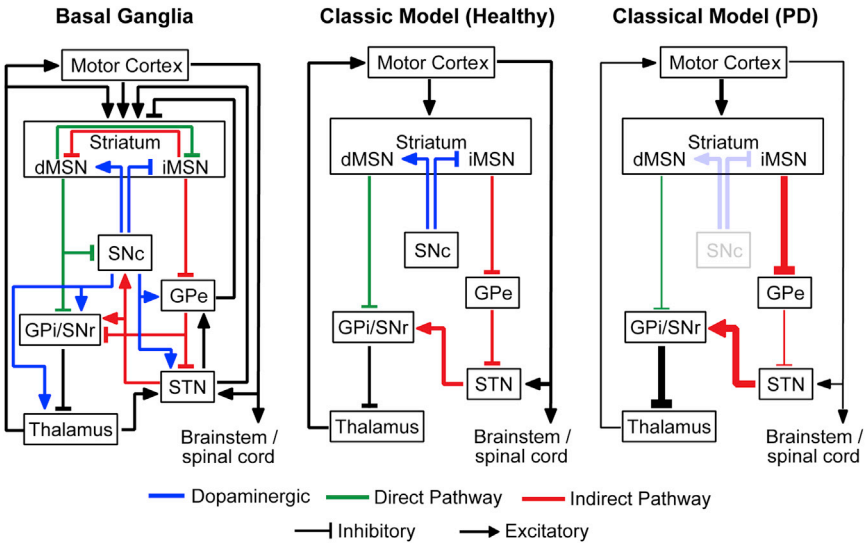

Figure 2. Classical Model of the Basal Ganglia

The classical model (center) simplifies basal ganglia connectivity (left) by highlighting the role of dopamine on direct and indirect pathway activity and motor output. In the healthy condition (center), dopamine (blue) from the SNc to the striatum activates direct pathway (green) and inhibits indirect pathway (red) MSNs. This effect decreases GPi output, releasing inhibition on the thalamus and cortex and promoting movement. In the parkinsonian condition (right), loss of SNc dopamine causes hypoactivity of the direct pathway and hyperactivity of the indirect pathway that leads to excessive GPi output. As a result, over inhibition of the thalamus and cortex leads to a suppression of movement. Adapted from DeLong (1990).

thalamic inhibition. Concurrently, diminished direct pathway firing is thought to disinhibit GPi neurons, furthering suppression of the thalamus and cortex. The classical model generated testable predictions regarding changes in firing rate throughout the basal ganglia in Parkinson's disease and served as a foundation for subsequent models of basal ganglia function.

Center-Surround Model

Accumulating evidence indicates an essential role for the basal ganglia not only in action initiation, but action selection. We use the term "center-surround model" to refer to ideas first proposed by Mink (Mink and Thach, 1993; Mink, 1996) but subsequently developed by multiple investigators. The center-surround model provides a conceptual framework for how basal output might control selection of actions and shape motor deficits (Nambu, 2005). The underlying concept of this model is that to execute an action, other similar or competing actions must be simultaneously suppressed. In this model, activation of direct cortical-STN projections—the hyperdirect pathway (Monakow et al., 1978)—produces broad increases in GPi firing, which in turn inhibit thalamus and cortex to suppress competing actions (Figure 3). Simultaneously, activation of striatal dMSNs focally inhibits GPi, releasing downstream inhibition and permitting action selection (see Figure 3). STN excitation is also shaped by release of GPe-mediated inhibition by the striatal iMSNs. Evidence for such interactions between the hyperdirect pathway and striatal output in guiding action selection was found in rodents trained in a cued stopping task (Schmidt et al., 2013). The center-surround and classical models make similar predictions regarding basal ganglia activity in parkinsonism: excessive STN and GPi activity, as well as decreased activity in some dMSNs and the GPe. However, while the classical model emphasized opposing responses of direct and indirect pathway MSNs to dopamine, the center-surround model highlights the complementary function of these two pathways in movement initiation and action selection, a concept in line with evidence that dMSNs and iMSNs co-activate during action initiation (Cui et al., 2013).

The center-surround concept may also be recapitulated at different levels of the basal ganglia circuit not only by the divergence and convergence present in between nodes, but also by lateral connections and resultant patterns of activity within nodes. These connections may also be a potent substrate for PD-related circuit dysfunction.

Rate-Based Models of Parkinson's Disease Pathophysiology

While neuronal activity can be characterized in numerous ways, an underlying assumption in many models of basal ganglia function is that information is encoded in the firing *rate* of individual neurons. Here, we explore evidence linking changes in basal ganglia firing rates with PD motor deficits, including both observational and interventional evidence obtained from PD patients, as well as parkinsonian nonhuman primate and rodent models. Notably, while these studies are highlighted for their findings relating to parkinsonism-associated alterations in firing rate, many also consider changes in firing *patterns* and *synchrony*, which are addressed in a later section.

Observations in Humans and Nonhuman Primates

Significant evidence for rate-based models of basal ganglia function was obtained from studies using nonhuman primate models of disease (Figure 4). The discovery that injection of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induced chronic parkinsonism in humans (Langston et al., 1983) and dopaminergic degeneration in nonhuman primates (Burns et al., 1983) provided a key tool to explore how loss of dopamine changes neural activity. Initial studies using a metabolic estimate of afferent terminal activity suggested increased activation of iMSNs, the STN, and the GPi (Crossman et al., 1985; Mitchell et al., 1986) and decreased activation of the GPe and thalamus (Schwartzman and Alexander, 1985). Later, extracellular single-unit recordings in parkinsonian primates and humans revealed increased average firing of GPi neurons, suggesting that parkinsonian motor deficits may be due to excessive basal ganglia output (Filion and Tremblay, 1991; Hutchison et al., 1994; Boraud et al., 1996, 1998; Heimer et al., 2002), though similar changes were not observed within the SNr (Wichmann et al., 1999). Consistent with elevated GPi

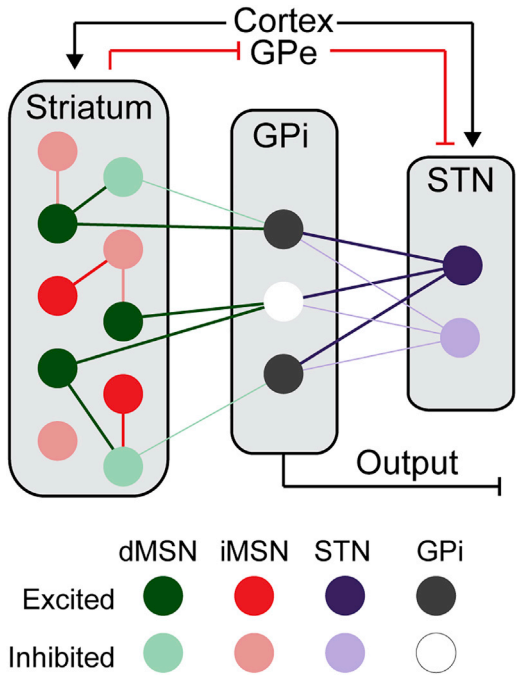

Figure 3. Center-Surround Model of the Basal Ganglia
Cortical input activates STN neurons (purple) that broadly excite GPi neurons (black), suppressing actions. Concurrently, cortical input to the striatum activates iMSNs that shape STN activity through the GPe, as well as dMSNs (green) that converge and inhibit a subset of GPi neurons to permit selective execution of movement. At the striatal level, inhibitory connections between MSNs may contribute to conceptually similar center-surround patterns.

firing, increased firing rates were also observed in the STN (Bergman et al., 1994; Benazzouz et al., 2002). Furthermore, both firing of GPe neurons and tonic GABA in the STN were found to be reduced in parkinsonian primates (Boraud et al., 1998; Filion and Tremblay, 1991; Heimer et al., 2002; Soares et al., 2004). Together, such findings supported the classical model of basal ganglia function.

Notably, changes in iMSN and dMSN firing were largely inferred from recordings in downstream nuclei. The classical model predicts increased iMSN and decreased dMSN activation. However, evidence from humans and nonhuman primates is conflicting, showing either marked increases in MSN firing (Liang et al., 2008; Singh et al., 2016) or no change (Deffains et al., 2016). Recent studies in rodents may clarify the picture (see below).

The classical model predicts that increased basal ganglia output induces excessive inhibition of thalamus and cortex, leading to a paucity of movement. Consistent with these predictions, firing rates in primary motor cortex were reduced in parkinsonian primates (Pasquereau and Turner, 2011; Pasquereau et al., 2016). At the level of the VA and VL thalamus, however, baseline firing was reportedly unchanged in parkinsonian primates (Pessiglione et al., 2005), though decreased rates have been reported in parkinsonian cats (Schneider and Rothblat, 1996) and PD patients (Molnar et al., 2005). Thus, rate changes in the basal ganglia, thalamus, and cortex of nonhuman primates and PD patients directionally support predictions of the classical models. However, as discussed later, manipulations of the basal ganglia in parkinsonian and healthy animals suggest that other changes in activity likely contribute to PD motor deficits.

Manipulations in Humans and Nonhuman Primates

To support causal relationships between basal ganglia firing and parkinsonian motor symptoms, like bradykinesia, investigators have taken two broad approaches: (1) measuring physiological parameters before and after a therapeutic manipulation, such as administration of a dopaminergic agent or deep brain stimulation (DBS) and (2) pharmacological inactivation or electrolytic/chemical lesions of circuit nodes. Prior to development of the MPTP primate model, basal ganglia lesions were known to alleviate motor deficits in PD. GPi lesions reduce rigidity in PD patients (Narabayashi et al., 1956; Cooper and Bravo, 1958), a result later replicated in parkinsonian primates (Baron et al., 2002). Dopaminergic agents also decrease GPi firing (though notably no significant change in STN or GPe firing has been observed) (Boraud et al., 1998; Filion et al., 1991; Levy et al., 2001) in parkinsonian nonhuman primates and PD patients. The advent of levodopa treatment diminished the use of surgical lesions, but interest climbed again in the early 1990s when STN lesions were also found to alleviate motor symptoms in MPTP-treated primates (Bergman et al., 1990; Wichmann et al., 1994), followed by the development of STN and GPi DBS (Aziz et al., 1991; Benazzouz et al., 1993; Limousin et al., 1995). While electrical stimulation may induce complex effects on activity in target structures, high-frequency DBS was initially hypothesized to decrease output of target structures, functionally acting as a reversible lesion (see Chiken and Nambu, 2016 for review). With this assumption, these findings support classical model predictions that STN hyperactivity contributes to PD motor symptoms (Bergman et al., 1990; Wichmann et al., 1994). However, the efficacy of lesions and DBS also supports alternative models postulating these interventions disrupt propagation of abnormal activity. Indeed, some studies indicate that DBS inhibits cell bodies near the stimulation site (Meissner et al., 2005; Moran et al., 2011), but others find evidence of increased target structure output, including increased GPi firing during STN DBS (Reese et al., 2011; McConnell et al., 2012). Furthermore, many studies, in both nonhuman primates and PD patients, call into question whether abnormal firing rates, as predicted by the classical model, are a causal mechanism of PD motor symptoms. For example, motor output is either unaffected or reduced by GPe and GPi lesions in healthy animals (see Nambu et al., 2015 for review), suggesting that rate changes in these regions are insufficient to drive PD motor deficits. Thus, while observed firing rate changes appear consistent with classical rate models, manipulations of the basal ganglia in parkinsonian and healthy animals suggest that other measures of activity such as pattern and synchrony play a role in driving PD motor symptoms.

Observations in Rodents

Electrophysiological recordings in healthy and parkinsonian rodents largely support those made in parkinsonian primates, showing firing rate changes in multiple basal ganglia nuclei after dopamine depletion. Advancements in genetics, large-scale electrophysiology, and optical methods have enabled (1) cell-type-specific and (2) large-ensemble recordings, which reveal

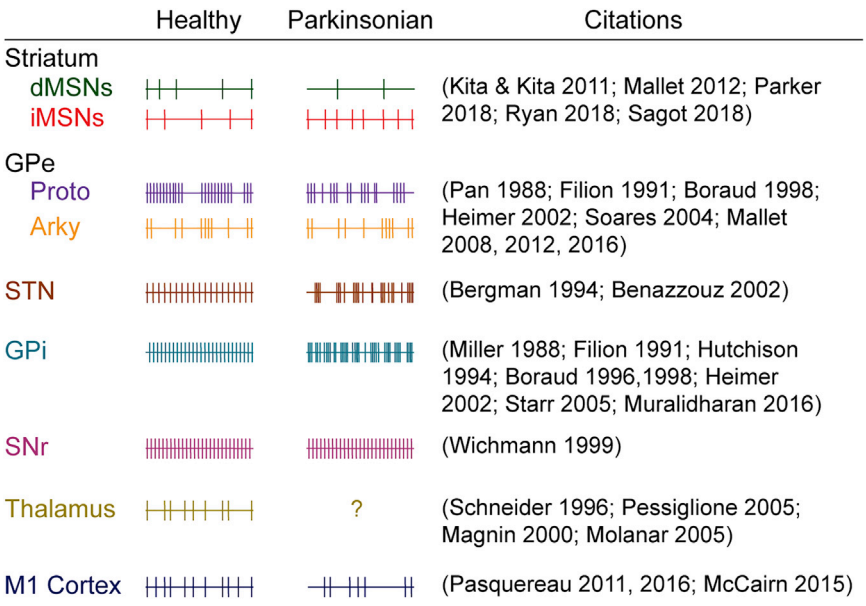

Figure 4. Changes in Firing between Healthy and Parkinsonian Conditions
Schematic depiction of pattern and rate changes observed across healthy and parkinsonian conditions in the basal ganglia, thalamus, and cortex. Arky, arkypallidal; proto, prototypical; M1, primary motor cortex.

heterogeneous responses within individual regions. As in nonhuman primates, most investigators have used toxin-based models that target midbrain dopamine neurons, such as 6-hydroxydopamine (6-OHDA). Consistent with primate studies, evidence in parkinsonian rodents is variable for increased STN firing, as predicted by the classical model. While some studies utilizing single-unit recordings have observed increased firing rates (Kreiss et al., 1997), others have observed no change (Delaville et al., 2015). In the STN, changes in activity *pattern* appear more consistent (see next section). Cell-type-specific manipulations of STN neurons to alleviate parkinsonian motor symptoms also point toward a central role of patterned activity.

GPe unit recordings in awake parkinsonian rats demonstrated decreases in baseline firing (Pan and Walters, 1988) comparable to that observed in primates (Filion and Tremblay, 1991; Boraud et al., 1996). In anesthetized parkinsonian rats, GPe firing was also decreased (Mallet et al., 2008). This and a subsequent study further distinguished two populations of GPe neurons, whose firing rate and synchrony to cortical oscillations differed in the parkinsonian state: prototypical neurons that project to the STN and arkypallidal neurons that send inhibitory projections back to the striatum (Mallet et al., 2008, 2012). Consistent with the classical model predictions on the role of the GPe, activation of both prototypical and arkypallidal neurons has been associated with movement cessation (Mallet et al., 2016) in healthy animals, though recent work in parkinsonian rodents indicates GPe subpopulations may play distinct roles (see below).

Whereas studies in parkinsonian nonhuman primates are conflicting regarding changes in striatal activity, rodent studies demonstrate bidirectional changes in iMSN and dMSN activity consistent with classical models. In anesthetized parkinsionian rats, antidromically identified dMSNs showed decreased firing as compared to healthy animals, while presumed iMSNs showed elevated firing (Mallet et al., 2006; Kita and Kita, 2011). Recent single-unit recordings of optically and antidromically identified iMSNs and dMSNs in freely moving parkinsonian mice similarly show bidirectional changes in firing rate (Ryan et al., 2018; Sagot et al., 2018). Notably, the firing of both iMSNs and dMSNs lost its normal correlation to locomotion, and iMSN firing was specifically enhanced during periods of immobility. Another recent study in parkinsonian mice using two-photon calcium imaging to measure the activity of thousands of MSNs made similar observations (Parker et al., 2018). As numerous changes in plasticity at the striatal level have been reported following dopamine loss (Surmeier et al., 2010; Villalba and Smith, 2018), future work will likely aim to link pathway-specific changes with alterations in activity that may underlie PD motor symptoms. Together, results like these highlight the utility of parkinsonian rodents, which can extend findings from humans and primates by linking activity changes to discrete populations with potentially distinct contributions to parkinsonian motor symptoms.

Manipulations in Rodents

Rodent models of PD have provided a genetic platform for linking circuit level and cell-type-specific changes in firing to motor output. Basal ganglia nuclei that have recently been targeted for study using optogenetics or chemogenetics include the STN, GPe, and striatum. While we consider how manipulations of these regions relate to firing rate changes, it is important to keep in mind that other measures of neuronal activity are inevitably perturbed as well.

Manipulations in rodent models of PD have provided key insights into the contribution of STN firing to motor deficits and the therapeutic mechanisms underlying DBS. As in parkinsonian primates, lesions and inactivation of the STN ameliorate motor deficits in rodent models of PD (Klockgether and Turski, 1990; Piallat et al., 1996; Henderson et al., 1999). The discovery that high-frequency STN DBS results in comparable behavioral effects led to the hypothesis that DBS works through functional inactivation. Testing this hypothesis directly, Gradinaru and others optogenetically inhibited excitatory STN neurons in parkinsonian rats (Gradinaru et al., 2009), which surprisingly had no impact on behavior (though notably, a more recent study observed improvements in akinesia with optical STN inhibition; Yoon et al., 2014). However, optical activation of cortico-STN terminals, which are likely activated during electrical stimulation (Li et al., 2012), robustly reversed parkinsonian deficits (Gradinaru et al., 2009). These findings have led to the hypothesis

that STN DBS may alleviate motor deficits by altering cortical activity through antidromic activation rather than by altering basal ganglia output.

The classical model predicts reduced GPe firing following dopamine loss and that enhancement of GPe firing should alleviate motor symptoms. While single-unit recordings and chemogenetic activation of the GPe support the first prediction (Assaf and Schiller, 2018), a recent study using optogenetic stimulation of subpopulations within the GPe paints a more complicated picture (Mastro et al., 2017). Global optical activation of GPe neurons in severely parkinsonian mice failed to rescue motor deficits, but optical activation of parvalbumin-expressing GPe neurons, as compared to those expressing Lim homeobox 6, produced persistent motor improvements. Together, these data suggest that different GPe outputs play distinct roles in regulating parkinsonian behavior.

The impact of dMSNs and iMSNs on motor output and other brain regions has been investigated using optogenetics and chemogenetics. In line with the classical model, optogenetic and chemogenetic activation of dMSNs increased locomotion in healthy mice and rescued parkinsonian motor deficits, while iMSN activation reduced locomotion and promoted freezing (Kravitz et al., 2010; Alcacer et al., 2017). Consistent with these findings, cortical and thalamic activity was found to be increased by dMSN stimulation and reduced by iMSN stimulation (Oldenburg and Sabatini, 2015; Lee et al., 2016) in healthy rodents, though bidirectional activity changes have also been observed in other downstream regions (Freeze et al., 2013; Lee et al., 2016). Together, manipulations in rodents highlight the distinction between activity changes that cause PD motor deficits and those sufficient to alleviate them. As multiple manipulations appear sufficient to reverse PD motor deficits, however, future work will likely need to determine which activity changes are required to cause motor deficits.

Patterned Neural Activity in Parkinson's Disease

While firing rates clearly change across the basal ganglia-thalamocortical loop in both PD patients and animal models, extensive evidence suggests that parkinsonism is characterized by significant alterations in the pattern of single-cell firing and synchronization between circuit nodes. In fact, many investigators have challenged the idea that static changes in rate causally underlie PD motor symptoms and instead postulate that changes in pattern are central. Despite accumulating evidence for such activity changes, investigators are now trying to determine whether patterned activity actually *causes* different symptoms of PD. Many experiments are consistent with the idea that pattern is a key causal mechanism, but there are some data suggesting that these markers of patterned activity do not consistently correlate with motor impairments in both rodent and nonhuman primate models (Leblois et al., 2007; Muralidharan et al., 2016).

Bursting and Synchronization

Bursting of individual neurons and synchronization between neurons are two phenomena commonly associated with PD and animal models of PD (Bevan et al., 2002; Figure 4). Bursting may reflect changes in intrinsic properties or synaptic input of neurons and, together with PD-related changes in local and long-range connectivity, may be a key contributor to changes in the local field potential (LFP) in basal ganglia circuit structures. Though changes in these measures have been reported across many nuclei in the basal ganglia circuit, their functional contribution to PD symptoms remains unclear. At the level of basal ganglia output, several groups have found altered bursting activity in GPi neurons in human PD patients (Hutchison et al., 1994; Starr et al., 2005), as well as parkinsonian nonhuman primates (Miller and DeLong, 1988; Boraud et al., 1998; Muralidharan et al., 2016). Bursting has also been observed in the GPe and STN of both PD patients and parkinsonian nonhuman primates (Bergman et al., 1994; Soares et al., 2004). The motor cortex has also been identified as a site of abnormal patterned activity in parkinsonian monkeys (McCairn and Turner, 2015). Though thalamic bursting is sometimes found under normal conditions, there appear to be increased numbers of bursting neurons in the motor thalamus of PD patients (Magnin et al., 2000). The same group observed bursting neurons in the centromedial/parafascicular (CM-PF) thalamus, whose activity corresponded to patients' tremor. Though far less studied, one group found that about half of striatal projection neurons (predominantly putative dMSNs) had irregular and bursty firing in parkinsonian nonhuman primates (Singh et al., 2015).

As with firing rate, it has been challenging to causally link bursting specifically with parkinsonian motor deficits. Measuring bursting before and after pharmacological treatment or DBS is one approach. However, such treatments may also alter rate, synchronization, and oscillations (see below), complicating interpretation. Dopamine replacement therapy reduces bursting in striatum, GPe, and GPi of parkinsonian nonhuman primates in parallel with improvement in motor function (Filion et al., 1991; Singh et al., 2015); similar observations have been made in the GPi of human patients administered levodopa (Boraud et al., 1998). Additionally, in a rat model of PD, STN electrical stimulation relieved bradykinesia when calibrated to reduce burst firing, but not when a similar protocol was used that increased burst firing (Tai et al., 2012). The same group explicitly tested whether STN neuronal burst firing versus oscillations produce bradykinesia and found that bursting was the critical component (Pan et al., 2016). In other experiments in parkinsonian nonhuman primates, however, it appears synchronization, rather than firing rate or bursting, is reduced by therapeutic DBS at the level of basal ganglia output and motor cortex (McCairn and Turner, 2009, 2015).

Synchronization between cells is another key alteration in single-unit activity. Such synchrony has several potential neural substrates, including alterations in local connectivity and shared synaptic input. In PD patients and animal models, synchronization has been measured between multiple simultaneous single-unit recordings or between single-unit activity and LFP (Shimamoto et al., 2013) and has been both widely observed and closely correlated with symptom severity (reviewed in Hammond et al., 2007). Synchronized firing was seen in the STN of PD patients undergoing DBS (Levy et al., 2000) and across individual motor cortex neurons in parkinsonian primates (Goldberg et al., 2002). A key caveat of such studies, however, is that sensorimotor input may trigger synchronized activity. For example, tremor, which is present in many PD patients, may result from or cause abnormal

rhythms and synchrony. While few animal models exhibit tremor (an exception is MPTP-treated African green monkeys), recordings in PD patients revealed synchrony between GPe, GPi, and SNr neurons only in patients with tremor and that oscillated at tremor frequency (Levy et al., 2002).

Beta Oscillations

Convergent evidence from both human patients and animal models suggests that parkinsonism is accompanied by changes in the LFP across multiple basal ganglia circuit nodes, which has been reviewed extensively elsewhere (Hammond et al., 2007; Brittain et al., 2014). Most evidence supporting a role for such changes in LFP in PD symptoms are correlative, but over the past few years there has been increasing interest in determining whether these changes are epiphenomenonal or causal. In PD patients, microelectrode LFP recordings of the STN and GPi can be performed intraoperatively, both in the parkinsonian state and after administration of dopamine replacement therapy. In addition, the DBS device itself can be used to obtain LFP recordings, which has permitted similar LFP measurements postoperatively. Finally, more recent DBS devices have chronic recording functionality (Quinn et al., 2015; Swann et al., 2018), such that LFP signals can be measured in patients outside the operating room. Some of these devices, designed for closed-loop stimulation using electrophysiological signals in the cortex to trigger STN stimulation, permit LFP measurements in two locations, such as the motor cortex (via electrocorticography) and STN (via the DBS device).

Measurements of LFP consistently show higher power in the beta frequency range (8–35 Hz, but typically around 20 Hz) in the STN of PD patients compared to control patients (Brown et al., 2001). Indeed, STN LFP beta power correlates well with parkinsonian symptoms such as bradykinesia and rigidity (Kühn et al., 2009) and is reduced in response to dopamine replacement therapy (Giannicola et al., 2013) and basal ganglia DBS (Quinn et al., 2015). Not only are such LFP signals seen at individual circuit nodes, but these rhythms may also synchronize across brain regions. Nevertheless, beta oscillations also occur in many regions during normal movement in healthy individuals (Engel and Fries, 2010), so there is nothing intrinsically pathological about beta-range LFP power. However, recent work indicates that the duration of beta bouts is more specific to parkinsonism (Deffains et al., 2018). Similar LFP beta oscillatory activity has been seen in parkinsonian nonhuman primates, though evidence in rodent models has been somewhat less consistent. In awake-behaving parkinsonian rats, enhanced beta-range power is at a somewhat higher frequency (approx. 35 Hz) than is seen in humans but has been found in the STN (Delaville et al., 2015), SNr (Avila et al., 2010; Brazhnik et al., 2014), thalamus (Brazhnik et al., 2016), and motor cortex (Brazhnik et al., 2012). In anesthetized parkinsonian rats, cortical activation led to increased beta-range LFP power in the GPe, and individual GPe units frequently entrained to this rhythm (Mallet et al., 2008). Fewer instances of beta oscillations have been observed in parkinsonian mice, with most reports from anesthetized animals, which may differ from freely moving (Lobb and Jaeger, 2015). While models suggest that beta oscillations could originate in the striatum (McCarthy et al., 2011), in parkinsonian mice, increased striatal beta oscillations have only been reported once, in mildly parkinsonian mice, in association with movement rather than during immobility (Chen et al, 2018). The discrepancies between primate, rat, and mouse recordings may be due to differences in the recording configurations (anesthetized, head-fixed, freely moving), symptomatology, or perhaps the complexity or density of connections between circuit nodes across species. However, as all of these PD models display bradykinesia, the lack of demonstrated beta in awake-behaving parkinsonian mice is puzzling and may call into question its causality in bradykinesia.

It is challenging to directly test whether altered LFP power in different frequency ranges causally contributes to parkinsonism. Part of the difficulty is that LFP changes are most robust in human patients and parkinsonian monkeys, where fewer specific interventional techniques are available. In addition, efforts to modulate LFP beta power often entail changing the overall spiking activity and/or synchronization of a group of neurons. However, investigators have attempted to test whether changes in beta oscillations cause parkinsonism. First, investigators have compared features of neural activity before and after therapeutic interventions. As mentioned above, nonhuman primate DBS studies have yielded a variety of results, but in some studies, rate changes appear relatively minor, whereas synchronization and beta oscillations are potently reduced (McCairn and Turner, 2009). In rats, treatment also reduced beta-range LFP power in parallel with therapeutic effects (Brazhnik et al., 2014). Second, some have tried to induce beta oscillations in healthy human subjects to test whether such a manipulation can provoke bradykinesia, using transcranial current stimulation (Krause et al., 2014; Pogosyan et al., 2009). Additionally, there is evidence that STN DBS at low frequencies (which might be hypothesized to enhance beta oscillatory activity in the STN or connected structures) may worsen bradykinesia (Timmermann et al., 2004) and that more specific stimulation of hyperdirect pathway neurons at low frequencies in rodents can worsen bradykinesia (Gradinaru et al., 2009). Another way to examine the causal role of different firing patterns and/or LFP oscillations is to look at alternative models of PD. One group compared SNr activity in an α-synuclein overexpression model, which recapitulates many of the motor and nonmotor features of PD but does not show the same dopaminergic cell loss seen in toxin-based models. They found much more subtle changes in firing rate in the overexpression model, and if anything, beta oscillations were reduced, rather than enhanced, in this model of PD (Lobb et al., 2013). Together, this work begins to address the question of whether increased beta oscillations are part of causal network changes in PD.

Loss of Functional Segregation in Parkinsonian Basal Ganglia Circuits

Sensorimotor, associative, and limbic channels are one form of basal ganglia functional segregation (Figure 1). Within each channel, information appears to be segregated further, for example, by specific somatosensory or motor maps. Though less well studied than the simpler rate- or pattern-based changes in parkinsonian subjects, the aberrant mapping of sensory responses or actions is likely to be another major form of PD circuit dysfunction. The advent of chronic recordings in patients, high-density recordings in awake behaving parkinsonian nonhuman primates, and

calcium imaging in freely moving parkinsonian rodents (Barbera et al., 2016; Klaus et al., 2017; Markowitz et al., 2018) makes possible the more detailed investigation of these maps across multiple neurons in a given circuit node.

While there is evidence for somatotopy and motor mapping at several levels of the basal ganglia circuit, the exact cellular and synaptic structure supporting these maps (and action selection) is as yet unclear. However, several studies have examined the sensory receptive fields of basal ganglia neurons during single-unit recordings and have observed changes in parkinsonian animals. In the striatum of rats and cats, clusters of units responsive to somatosensory stimulation shrank in size and showed diminished spatial specificity (Rothblat and Schneider, 1995; Cho et al., 2002). Similarly, while most GPi neurons in healthy primates responded to one type of passive joint movement, in parkinsonian animals the majority of neurons responded to multiple joint movements (Boraud et al., 2000). Results at the level of the motor thalamus have proven more variable. Increases in responsiveness of single units to somatosensory stimulation have been reported (Pessiglione et al., 2005), though no change (Kiss et al., 2003) and even decreases (Schneider and Rothblat, 1996) have been reported as well. Changes in receptive fields suggest the possibility that dopamine-related changes in synaptic connectivity may lead to deficits in action selection. The underlying cellular and synaptic substrate of these changes may include alterations in connectivity between or within individual basal ganglia nuclei. Recently, alteration of striatal iMSN excitability has been demonstrated to bidirectionally regulate the density of collateral projections from dMSNs to the GPe, suggesting that structural plasticity may follow changes in striatal activity (Cazorla et al., 2014). Additionally, lateral connection between MSNs within the striatum are potently regulated by dopamine (Dobbs et al., 2016), and in parkinsonian mice, the likelihood of lateral connections between iMSN-iMSN or dMSN-dMSN pairs was shown to decrease significantly, while connections from iMSNs to dMSNs were largely spared (Taverna et al., 2008). Such changes may help explain differences in striatal information processing observed *in vivo*. Still, how alterations in sensorimotor mapping and connectivity within the basal ganglia contribute to activity patterns underlying PD motor symptoms remains to be explored.

Basal Ganglia Mechanisms of Cognitive Parkinson's Disease Symptoms

As mentioned above, some PD cognitive symptoms correlate with primary neurodegeneration in the cortex and higher cognitive regions. However, given that some cognitive features of PD (1) are modulated by dopamine replacement therapy and (2) can be observed in toxin-based animal models (where cortical neurodegeneration is not present), these features may be mediated by aberrant neural activity. Aberrant neural activity may be present in the cognitive/associative or behavioral/limbic streams that course through the basal ganglia loops and in turn contribute to impaired action selection-like phenomena in cognitive (poor set-switching and reward-based learning) and behavioral (depression, apathy) domains. Though this theory has not been investigated extensively, there are indications that some of the same impairments seen in the dorsolateral, motor portions of basal ganglia nuclei and motor cortex are also seen in the more medial and ventral portions of the same basal ganglia nuclei (Kish et al., 1988; Carriere et al., 2014) and cognitive portions of frontal cortex (Wang et al., 2017; Chung et al., 2018). However, in parkinsonian rats, the high beta-range oscillatory activity seen in the primary motor cortex is far less prominent in prefrontal cortical areas important for cognitive function (Delaville et al., 2015). Some studies have directly measured circuit activity during more cognitive tasks in patients. In one such study, investigators correlated changes in STN LFP oscillations with performance on a speeded cognitive task (Siegert et al., 2014). Another recent study measured STN LFP during chronic recordings in PD patients during a response inhibition task and showed correlations between STN oscillatory activity and task performance (Hell et al., 2018). These types of studies are relatively rare but may yield important information about how circuit changes contribute to cognitive deficits. To date, it remains unclear whether the same neural signatures contribute to cognitive and behavioral dysfunction or whether distinct physiological phenomena mediate these symptoms. In a similar fashion, the loss of cholinergic basal forebrain neurons is likely to have profound neuromodulatory effects on their normal synaptic targets, which include many higher cognitive areas. The fact that PD patients are especially sensitive to the cognitive side effects of anticholinergic agents, and also often respond briskly to cholinesterase inhibitors, supports the idea that some PD cognitive features are also related to aberrant neural activity, mediated by loss of cholinergic signaling.

There are very few studies attempting to link parkinsonian cognitive deficits with circuit dysfunction in rodents or nonhuman primate models. A major obstacle is that toxin-based models produce fairly profound motor dysfunction, and the outcome in most cognitive assays is motor. However, other models show potential for such studies. In nonhuman primates, several groups have characterized a PD-like frontal pattern of cognitive deficits in lower-dose MPTP-treated primates that have minimal or no motor deficits (Schneider and Kovelowski, 1990). Interestingly, in this type of model (as in many patients), doses of levodopa that greatly ameliorate motor symptoms do not improve (and can even worsen) cognitive performance (Schneider et al., 2013). The Mito-Park mouse model, which replicates several motor, nonmotor, and pathological features of human PD, may likewise be useful. At early time points (before marked motor impairment develops), Mito-Park mice show deficits on the Barnes maze and novel object recognition (tests of visuospatial learning and memory) (Li et al., 2013). There is also evidence for a relationship between non-dopaminergic circuit changes and cognitive dysfunction in PD animal models. In mouse α-synuclein overexpression models: in an extensive behavioral study, investigators found many cognitive deficits that mirror those of PD patients: reversal learning, habit learning, and visuospatial memory (Magen et al., 2012), some of which can be linked to cortical cholinergic deficits. These models of PD-related cognitive deficits may be a good platform in which to more directly link circuit changes to cognitive deficits.

Future Directions

The recent advances in neural monitoring technology, both in humans and animal models, represent a major opportunity for

gathering additional and more representative data about the patterns of neural activity that accompany PD symptoms. In patients, there are opportunities to probe neural activity in multiple brain regions. For example, an investigational DBS system developed for closed-loop stimulation has also been used to monitor motor cortex and STN activity, both intraoperatively and chronically, in patients with PD (Swann et al., 2018). This approach can help establish the relationship between neural activity and specific disease symptoms (Swann et al., 2016). In animal models, tools now allow simultaneous electrical recordings of hundreds of neurons in a given brain region, but also across multiple brain areas, during behavior. The development of genetically encoded calcium indicators and voltage sensors facilitates even larger single-cell datasets, though the temporal characteristics of these indicators cannot currently match traditional electrophysiology for determining tight synchronization between single cells. In rodents, and now nonhuman primates (Galvan et al., 2017), the use of optogenetic and chemogenetic tools permits more direct tests of whether specific patterns of activity (changes in rate, pattern, or synchronization) mediate the clinical features of PD.

Despite the accumulation of extensive supportive evidence for different circuit mechanisms in driving PD symptoms, a number of major questions remain. We have listed some of the questions that we think are particularly critical to address.

1. How do low-level changes in synaptic connectivity and firing rate or pattern contribute to higher-level phenomena such as synchronization between neurons or brain regions and local field potential oscillations at particular frequencies? Connecting cellular and synaptic observations to the disease-related changes in the LFP at different nodes in the basal ganglia thalamocortical loop is an important basic science question but will also help bridge extensive work at these two levels of analysis in the PD field.
2. Do changes in firing rate, pattern, or synchronization *cause* disease symptoms? It will likely require both more sophisticated observational studies (a more detailed look at the timing of neural activity and behavioral changes) and causal manipulation studies to fully address this question. Observational studies will be greatly facilitated by new technology permitting high channel-count electrophysiology, as well as deep imaging methods that permit physiological measurement from tens to hundreds of neurons at the same time. Though tools like optogenetics will no doubt be useful in this quest, we should be careful to use them to mimic healthy or disease-related activity (informed by the decades of work in this area) rather than imposing yet new rates or patterns of activity on neural circuits. Otherwise, results may be difficult to interpret.
3. How do our major therapies for PD work? Ongoing studies involving current therapies, such as oral medications (levodopa, dopamine agonists) or DBS, in both patients and animal models may also give us insights into which circuit changes cause, versus correlate with, disease symptoms. Investigators may identify multiple therapeutic mechanisms, which could guide development of new treatments.
4. Do motor and nonmotor aspects of PD have shared or distinct circuit mechanisms? Mechanistic studies of the nonmotor aspects of PD have been limited to date, largely because of the challenges in identifying and quantifying these symptoms. However, the advent of chronic ambulatory recordings in PD patients now allows recordings of neural activity in conjunction with cognitive task performance or alignment with patient-identified symptoms that arise at home. In addition, improvements in high-throughput testing of higher cognitive function in rodents will allow more invasive testing of the hypotheses generated by observational studies in both patients and nonhuman primates.
5. Are changes in circuit function at the level of connectivity and neural activity not just a feature of pathophysiology, but also a contributor to ongoing pathogenesis? Historically, most PD research has been separated into two branches: pathogenesis (focused on cellular and molecular mechanisms of neurodegeneration) and pathophysiology (focused on circuit mechanisms mediating symptoms). However, it may be that these two processes are intertwined. Activity may be a key contributor to neurodegeneration (Surmeier, 2018), and synaptic connectivity may be a mechanism of disease spread (Braak et al., 2003).

Key to progress is communication and collaboration between investigators studying human patients, nonhuman primate, rodent, and even cellular models of PD. Those of us who work with animal models need to identify which questions can be answered with our current tools (including the animal models themselves), which should be set aside until the tools improve, or which would be best answered by our colleagues working with patients. In addition, as each group of scientists makes progress in unraveling the circuit mechanisms of PD, it will be important to check findings against those in other models and ultimately in the disease itself.

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