Changing Views of the Pathophysiology of Parkinsonism

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ABSTRACT: Studies of the pathophysiology of parkinsonism (specifically akinesia and bradykinesia) have a long history and primarily model the consequences of dopamine loss in the basal ganglia on the function of the basal ganglia/thalamocortical circuit(s). Changes of firing rates of individual nodes within these circuits were originally considered central to parkinsonism. However, this view has now given way to the belief that changes in firing patterns within the basal ganglia and related nuclei are more important, including the emergence of burst discharges, greater synchrony of firing between neighboring neurons, oscillatory activity patterns, and the excessive coupling of oscillatory activities at different frequencies. Primarily focusing on studies obtained in nonhuman primates and human patients with Parkinson's disease, this review summarizes the current state of this field and highlights several emerging areas of research, including studies of the impact of the heterogeneity of external pallidal neurons on parkinsonism, the importance of extrastriatal dopamine loss, parkinsonism-associated synaptic and morphologic plasticity, and the potential role(s) of the cerebellum and brainstem in the motor dysfunction of Parkinson's disease. © 2019 International Parkinson and Movement Disorder Society

The term "parkinsonism" encompasses the classical motor signs of Parkinson's disease (PD), that is, the combination of bradykinesia, akinesia, tremor, and rigidity (as well as gait/balance problems). These signs and symptoms are assumed to be triggered by the loss of dopaminergic neurons in the substantia nigra pars compacta (SNc). Discussions of the pathophysiology of parkinsonism are therefore mostly discussions of the immediate and chronic brain circuit effects of the degeneration of dopaminergic neurons in the SNc.

In the following paragraphs, a basic understanding of the anatomical structure of the basal ganglia and related brain areas (see Fig. 1) is assumed. We will first discuss past and current findings pertaining to a brain circuit-level understanding of the pathophysiology of parkinsonism, coming from experiments in parkinsonian animals and patients with PD. This will be followed by a discussion of recent conceptual changes that are beginning to shape our knowledge in this field. Most of the information presented here will focus on results obtained from studies in nonhuman primates and patients with PD.

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Parkinsonism as Dysfunction of the Basal Ganglia Thalamocortical Network

Most studies of brain dysfunction in parkinsonism assume that the primary brain activity changes that account for the parkinsonian state occur within the basal ganglia/thalamocortical circuitry (Fig. 1). The fact that motor impairments dominate early stages of PD is understandable considering that dopamine loss in (early) PD preferentially affects the dopamine supply to the *motor* circuit of the basal ganglia,[1] which is spatially segregated from nonmotor circuits within the basal ganglia/thalamocortical network of connections.[2] This section summarizes the current knowledge within this framework.

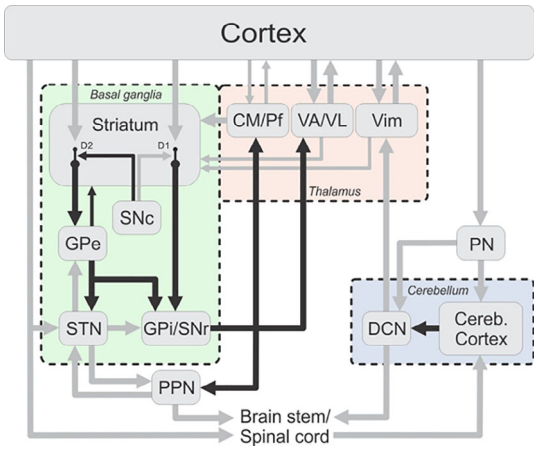

FIG. 1. Corticosubcortical motor circuits involved in the pathophysiology of parkinsonism. Dark arrows indicate inhibitory connections; gray arrows indicate excitatory connections. CM/Pf, centromedian and parafascicular nuclei of the thalamus; Cereb. Cortex, cerebellar cortex; CMA, cingulate motor area; DCN, deep cerebellar nuclei; DP, direct pathway; D1, D1-like dopamine receptor subtype; D2, D2-like dopamine receptor subtype; HP, hyperdirect pathway; IP, indirect pathway; MC, motor cortex; PMC, premotor cortex; PN, pontine nuclei; SMA, supplementary motor area; VA/VL, ventral anterior and ventral lateral nuclei of the thalamus. Figure published in a previous work,[285] here shown with permission. [Color figure can be viewed at wileyonlinelibrary.com]

Changes of Firing Rates

Thirty years ago, the results of anatomical, metabolic, and electrophysiologic studies were summarized in an influential model of global activity changes in the basal ganglia nuclei that described the emergence of parkinsonism and chorea as opposite ends of a spectrum of activity changes in these nuclei.[3,4] In this model, the lack of striatal dopamine in the parkinsonian state increases striatal inhibition of neurons in the external pallidal segment (GPe), which would then lead to disinhibition of the glutamatergic STN, and subsequent increased driving of basal ganglia output neurons in the internal pallidal segment (GPi) and the substantia nigra pars reticulata (SNr). In parallel, striatal dopamine loss was also thought to reduce direct striatal inhibition of GPi and SNr. In combination, these changes result in *increased* tonic firing in the GABAergic output neurons in the GPi and SNr, leading to downstream inhibition of thalamocortical projection neurons and reduced activation of dependent areas in the frontal cerebral cortex, triggering the behavioral manifestations of parkinsonism. Events of inverse polarity were predicted to underlie chorea and other hyperkinetic disorders in which *reduced* output of the basal ganglia would lead to release of thalamocortical neurons from tonic inhibition and the emergence of involuntary movements.

Support for this "rate" model of movement disorders came from studies of the effects of inactivation (lesions) of the STN and GPi in parkinsonian animals. By reducing basal ganglia output, this was thought to "normalize" the (rate-model) disturbance underlying parkinsonism. As predicted, these interventions improved parkinsonism in parkinsonian animals and in patients with PD.[5-29] Recent studies in rodents have further emphasized the importance of rate changes in basal ganglia output for the regulation of movements, by showing that optogenetic or chemogenetic activation of the striatal neurons that give rise to projections to the GPe reduces movement in normal animals.[30,31]

However, the model would also predict that interventions that lower GPi/SNr output below its normal range would produce involuntary movements, but this is not the case. In fact, lesions of the GPi are used to *treat* hyperkinetic states such as chorea.[32,33] Furthermore, according to the rate model, inactivation of the thalamic regions that receive basal ganglia input would be expected to worsen parkinsonism, but this is also not observed in humans or monkeys.[34,35] In addition, recent optogenetic rodent studies have cast doubt on the rate-model notion that parkinsonism arises from an imbalance between the (antikinetic) actions of striatal neurons that project to the GPe and the (prokinetic) actions of neurons that project to the GPi. These studies emphasize that movement initiation and execution is accompanied by combined activation of *both* populations of striatal neurons,[36-38] inconsistent with the rate model. These and other discrepancies suggest that rate changes in the basal ganglia/thalamocortical circuits may not be important for the pathophysiology of movement disorders than originally thought.

Altered Firing Patterns and Oscillations

Even the earliest reports documenting neuronal activity changes in MPTP-treated parkinsonian monkeys showed that there are prominent changes in firing patterns of basal ganglia neurons.[39] In the 1990s, these pattern changes quickly evolved from being regarded as a curiosity to being considered to be a central component of the pathophysiology of parkinsonism. Since then, many researchers have emphasized the role of increased oscillatory fluctuations of firing rates of neurons in the basal ganglia, thalamus, and cortex in the low beta-range of frequencies in humans and in slightly different (neighboring) frequency ranges in animals.[40-45] Oscillatory and nonoscillatory bursts of neuronal spiking are also increased throughout the basal ganglia, the ventral motor thalamus, and frontal motor areas of the cerebral cortex in the parkinsonian state.[46]

A related important change of neuronal activities in parkinsonism is a breakdown of the normal separation of the firing of individual neurons in the basal ganglia. The resulting neuronal synchrony has been directly documented in single-cell recordings with multiple electrodes[44,47,48] and is also implied by the finding of increased amplitudes of local field potentials (LFPs; summed electrical potentials at a brain location) in the beta-band range of frequencies (10–30 Hz) in the basal ganglia and cortex, in recordings from parkinsonian animals,[49-57] and from PD patients in whom implanted DBS electrodes were used for

recording purposes.[44,58-65] The increased beta-band activity is associated with a reduction in gamma-band oscillatory power.[44,65] In recent studies, it has been emphasized that an increase in the number and duration of beta-bursts in cortex or STN may be even more predictive of parkinsonism than the absolute level of beta-band activity.[66-68] The finding of increased low-frequency synchronization not only applies to the individual nodes of the basal ganglia/thalamocortical motor circuit, but similarly affects interactions *between* components of these circuits, as documented, for example, by the finding of substantial corticosubthalamic coherence in parkinsonian animals (e.g., see a previous work[51]) or in patients with PD (e.g., see previous works[69,70]).

Shifts in the spectral composition of cortical or basal ganglia LFP signals occur also in conjunction with levodopa-induced dyskinesias (LIDs). Recent reports have focused on narrow-band gamma oscillations (60–85 Hz) in the cerebral cortex and the STN during episodes of dyskinesia,[73] similar to the narrow-band ~70-Hz oscillations described to occur in L-dopa–treated parkinsonian patients at rest or during voluntary movement,[74] and, interestingly, to oscillations found in electrocorticography (ECoG) signals in patients with isolated dystonia (described in a dystonia-1 [DYT1]-negative and a DYT1-positive patient in a previous work[75]). This narrow-band gamma-band activity differs from the broad-band cortical gamma-band oscillations in these brain regions that accompany physiological movements, where oscillations in the 75- to 100-Hz range are associated with movement onset and oscillations in the 30- to 50-Hz range are present throughout ongoing movements.[76]

Overall, studies of spectral changes involving single-cell or LFP signals have demonstrated that most elements of the basal ganglia/thalamocortical circuitry are engaged in synchronized low-frequency oscillations in the parkinsonian state. This may work to the detriment of normal processing in the basal ganglia/thalamocortical circuits, which may depend on transient focal synchronization of activity at gamma frequency bands and which is suppressed or temporally/spatially misaligned in the parkinsonian state where beta oscillatory activities prevail.

An interesting recent series of studies has directly focused on these interactions between the beta- and gamma-band oscillations. In studies of ECoG and EEG signals from PD patients,[77] the amplitude of gamma-band oscillations was found to be abnormally coupled to the phase of ongoing beta-band oscillations in a process called phase-amplitude coupling (PAC). Together with beta-band power, and corticocortical and basal ganglia/cortical coherence, cortical PAC was associated with bradykinesia and rigidity[78] and lowered by therapeutically beneficial DBS in the STN or GPi.[79-81] As is true for other oscillatory activities (see above), increased *cortical* PAC is not specific for PD, but also occurs in patients with (isolated) dystonia[82] or essential tremor.[83]

Studies of *subcortical* PAC in parkinsonian patients have focused on LFP recordings from the STN and GPi. As in cortical recordings, PAC between beta- and gamma-bands is a sensitive marker of parkinsonism in STN LFPs[84-86] and is also found in cases of isolated dystonia.[59] Interestingly, it is not clear whether the situation is similar in the GPi. Thus, in a study of LFP PAC in GPi, Tsiokos and colleagues reported an inverse relationship between PAC and parkinsonian signs, suggesting that a high level of PAC could be a normal feature of GPi physiology.[87]

The development of parkinsonism in chronically MPTP-treated monkeys is also associated with PAC in LFPs recorded in the basal ganglia[49,88,89] or frontal cortex,[49,90] in this case involving the phase of theta-beta–range frequencies and the amplitude of gamma-range frequencies (150–400 Hz). The studies also showed that basal ganglia or cortical PAC is highly dependent on the state of vigilance of the animal.[49,90] As in patients with PD, beta-gamma PAC in MPTP-treated animals findings appear to be more predictive of parkinsonism than changes of spectral power in specific frequency ranges.[88,89]

The Question of Causality

Most of the aforementioned abnormalities of neuronal activity patterns have been identified in multiple basal ganglia nuclei, in the thalamus, and are beginning to be identified in the cerebral cortex, suggesting that they may affect processing throughout the entire cortico-basal ganglia/thalamocortical circuits. If true, this may reduce the ability of the basal ganglia/thalamocortical system to normally process information and could interfere or eliminate major functions of the affected basal ganglia, such as their ability to contribute to motor learning, or to facilitate movement. It is important to emphasize again that removal of basal ganglia processing by creation of lesions in the basal ganglia output nuclei reduces rather than increases parkinsonism,[91,92] suggesting that the oscillatory and abnormally synchronized activity in the cortico-basal ganglia/thalamocortical circuits does not simply disrupt processing of information in the basal ganglia, but that the abnormal basal ganglia activity actively disrupts information processing downstream from the basal ganglia. Specific constellations of rate and pattern changes in the basal ganglia/thalamocortical circuits may affect cortical processing in a manner that triggers bradykinesia or akinesia in the parkinsonian state. Other diseases may be associated with separate (but overlapping) combinations of abnormalities that bias cortical processing in other ways, manifesting, for example, as changes in muscle tone and posture as observed in dystonia.

It remains an open question which of the observed abnormalities in basal ganglia activity are causal for parkinsonism.[43,51,93,94] This was already mentioned in the discussion of firing rates, and the same uncertainty applies to the synchronized oscillatory activities that

were described above. In fact, several published experiments did not find a strong correlation between spectral changes and the degree of (early) parkinsonism. For example, the described increase in low-frequency synchronization is not always found in animals with behavioral parkinsonism,[89,90] or in humans with PD (e.g., see a previous work[95]). Some of the observed changes may thus be inconstant (see discussion of beta bursts above) or simply represent epiphenomena of a yet-to-be-discovered underlying disruptive process. Of course, the lack of a causal relationship of spectral (or other) changes to parkinsonism does not diminish their potential value as biomarkers for the severity of parkinsonism if they *can* be detected in a given case.

Beyond Akinesia and Bradykinesia

The pathophysiological considerations mentioned in the previous paragraphs relate primarily to the emergence of akinesia and bradykinesia. Our knowledge concerning the pathophysiology of other principal signs of parkinsonism (rigidity, tremor, and gait impairments) is more limited. A brief summary of the major themes of research pertaining to the emergence of rigidity and gait impairments in PD patients is presented here. Information on the pathophysiology of tremor is found in the next section.

Most studies of the mechanisms underlying *rigidity* come from the human literature. Many studies focus on alterations in spinal and brainstem reflex mechanisms.[96] A role of the stretch reflex system[97-100] and its facilitation in PD patients (see earlier works,[101,102] but see another work[103]) was originally favored, whereas later studies emphasized a role of changes of the latency and amplitude of long-latency reflexes (see earlier works,[104,105] but see another work[106]). Changes in the basal ganglia are likely also involved, given that the severity of rigidity correlates with the degree of striatal dopamine loss,[107,108] and with the power or stability of beta-band oscillations in the STN.[109,110] The involvement of the basal ganglia and related area of the ventral motor thalamus is also suggested by the fact that surgical interventions targeting these systems reduce rigidity.[111-114]

Although the polarity of changes is not entirely consistent between studies, imaging experiments have shown that frontal and parietal cortical activity are altered in rigid parkinsonian patients.[115,116] For example, in studies of default-mode network expression in resting-state functional MRI (fMRI) experiments, the connectivity of posterior cortical network components was found to be reduced whereas that of frontal cortical components of the network was pathologically increased.[117,118] An interpretational issue with these and similar studies is, of course, that rigidity does not develop in isolation. It is difficult to assign brain activity abnormalities specifically to this parkinsonian sign while others, such as bradykinesia or cognitive impairments, also emerge.

The pathophysiological basis of *gait impairments* in parkinsonian patients is complex and likely multifactorial. A specific parkinsonian impairment that has garnered interest in recent years is freezing of gait (FOG). The phrase FOG is applied to sudden and unpredictable blocks in stepping, specifically occurring when the patient initiates gait or turns, and under certain situations, for instance when walking though narrow passages. The presence of FOG is disabling and significantly affects the quality of life.[119] Pathophysiologically relevant clinical observations are that FOG typically affects patients with long disease duration.[119-122] is at least partially corrected by L-dopa in many patients,[119,121] and is typically associated with changes in cognition, such as altered attention,[123] cognitive dysfunction,[124-127] or psychosis,[128] suggesting cortical involvement. In experiments in which patients were engaged in cognitive activities while walking, those suffering from FOG typically showed worse walking performance than those without FOG ("dual task interference"),[129] supporting the notion that FOG tends to arise in susceptible individuals when cognitive resources that are needed for maintenance of gait under parkinsonian conditions have to be shared with other activities. Volumetric and fMRI studies have demonstrated that specific frontal and parietal cortical regions are atrophic in patients with FOG,[130-135] and EEG studies have suggest that patients who suffer from FOG have high beta-band oscillatory activity in frontal regions EEG,[136] specifically increased during conditions that demand increased attention.[137]

Subcortical gait networks, including the striatum, GPi, thalamus, the mesencephalic locomotor region, and the cerebellum, are also involved in FOG.[126,132,133,136,138] Whereas STN- or GPi-DBS reduces FOG in some patients, others suffer from stimulation-induced freezing,[139] potentially depending on the choice of stimulation parameters.[140] In an interesting recording study comparing STN-DBS implanted PD patients with and without freezing, Storzer and colleagues discovered that pedaling movements that are (by themselves) not specifically affected by freezing bring out increased power in the low beta band in LFPs in the STN.[141]

It is believed that freezing can also occur in parkinsonian rodents[142-144] and monkeys.[145] The few available studies point to the involvement of components of the mesencephalic locomotor region/pedunculopontine nucleus (PPN).[142] Recordings in MPTP-treated, parkinsonian monkeys indicated a greater tendency of mesencephalic locomotor region neurons to discharge in bursts, which could be related to FOG.[146]

Neurochemically, FOG may be associated with changes in the norepinephrine[147] and/or cholinergic systems.[148] The former is supported by the finding that the catecholaminergic locus coeruleus appears to be damaged in parkinsonian monkeys that show FOG (compared to those without FOG),[149] by neuromelanin MRI findings in

parkinsonian patients with and without FOG,[150] and by the (empirically determined) effectiveness of medications that alters catecholamine release or levels in the brain, such as atomoxetine,[151,152] or L-threo-DOPS.[153-156] Cholinergic dysfunction is implicated by imaging studies that show cholinergic loss in cortical regions,[148,157] and in the striatum[157] of patients with FOG. Studies in rodents and monkeys have supported the notion that severe gait abnormalities may arise in situations where both the dopaminergic nigrostriatal system and cholinergic cells in the pedunculopontine nucleus (area) are destroyed.[144,158,159]

Evolving Topics

The ever-increasing pace of discovery in basal ganglia research has led to many exciting evolving topics in studies of the pathophysiology of parkinsonism. Only some examples of these can be reviewed here.

Heterogeneity of GPe Neurons

In traditional schemes of the basal ganglia, the GPe is depicted as a homogeneous structure in which neurons relay input from the striatum to STN, GPi, and SNr (Fig. 1). An important recent insight has changed this concept by showing that GPe neurons are, in fact, heterogeneous, belonging to at least two major classes, that is, "arkypallidal" neurons that project to the striatum and "prototypical" neurons, which project to the STN, GPi, and SNr. In rodents, molecular differences among GPe neurons have been used to genetically target and manipulate these neuron subtypes using optogenetic and pharmacogenetic techniques.[160-164] It is not clear whether and how these protein expression patterns translate to the primate GPe.

Prototypical GPe neurons powerfully influence the frequency and firing patterns of STN neurons[165-168] and, perhaps to a lesser degree, of GPi neurons.[169-171] Global activation of GPe activity in parkinsonian monkeys[172] induces pathological STN neuron activity and can ameliorate parkinsonian motor signs, but may produce dyskinetic movements.[169,173,174] Arkypallidal neurons, on the other hand, make abundant connections and strongly inhibit direct and indirect pathway striatal projection neurons and interneurons.[160,162,163,175-177] Although this may play a role in normal basal ganglia function(s), the role of these cells in parkinsonism is not known.[175,178] Recent optogenetic and pharmacogenetic studies in parkinsonian rodents have suggested that selective activation of arkypallidal neurons may be detrimental[160,179] whereas selective activation of prototypical neurons can produce antiparkinsonian effects.[164] It remains to be seen whether similarly specific manipulations can lead to antiparkinsonian effects in nonhuman primates or patients with PD, without the risk of inducing dyskinesias.

Role of Extrastriatal Dopamine Loss

There is ample evidence that dopaminergic midbrain neurons innervate not only the striatum, but also extrastriatal sites in basal ganglia, thalamus, and cortex.[180] The loss of dopamine at these sites in is also well documented to occur in parkinsonian animals[181] and in PD patients.[182-184]

In the primate GPe, D2-like receptors (D2LRs) are expressed on GABAergic striatopallidal inputs. Local activation of these receptors by injections of small amounts of D2LR agonists increases the firing of GPe neurons in monkeys, likely because of reduction of the GABAergic inhibition.[185] In the monkey STN, D1 and D2 receptors are found on preterminal axons and glutamatergic and GABAergic terminals and on postsynaptic D5 receptors.[186] Locally administered agonists at D1LRs lower STN firing rates, but increase bursting in these animals,[186] perhaps through a combination of effects on presynaptic D1- and postsynaptic D5-receptors, respectively.

In GPi and SNr, D1LRs are expressed on axons and terminals of the striatopallidal and striatonigral pathways. D2LRs are also found, on (presumptive) glutamatergic inputs. Local administration of D1LR or D2LR agonists into the GPi and SNr reduces firing in these nuclei.[185] The comparatively maintained pallidal and nigral dopamine levels in early parkinsonism may thus compensate for the striatal dopamine loss in early PD, helping to maintain GPi/SNr firing rates at levels close to normal.[187] In the fully parkinsonian state, the fraction of membrane-bound (active) D1LRs (among all D1LRs) at these sites increases.[188]

The basal ganglia–receiving portion of the ventral motor thalamus is also innervated by dopaminergic fibers,[189] arising from several dopaminergic cell groups in the midbrain.[190-192] There appears to be a substantial loss of the thalamic dopaminergic innervation in MPTP-induced parkinsonism in monkeys,[189] which could be related to the emergence of tremor (see also below).[193,194]

Activation of extrastriatal dopamine receptors may contribute to the antiparkinsonian efficacy of systemically administered dopamine receptor agonists, specifically to that of D2LR agonists such as ropinirole or pramipexole. Conceivably, activation of extrastriatal D2LRs by these agents could lower firing irregularities through actions in the STN, while reducing the overall basal ganglia output through actions in SNr and GPi.[195-197]

The expression of extrastriatal dopamine receptors is obviously not restricted to the motor areas of the basal ganglia, thalamus, and cortex. Activation of dopamine receptors at nonmotor sites may contribute to some of the frequent side effects of D2LR agonist therapies. For example, specific associations to changes in extrastriatal

dopamine levels (or receptor occupancy) were recently documented in the context of impulse control problems,[198,199] depression,[200] and dementia.[200-202]

Parkinsonism-Related Synaptic Plasticity

There is growing awareness of the fact that the effects of dopamine depletion in the basal ganglia/thalamocortical motor circuit does not simply lead to stable changes of neuronal activity or excitability in the affected circuitry. Instead, parkinsonism is associated with considerable morphological and functional plasticity at synapses within the basal ganglia, thalamus, and cortex. Thus, it had been known since the late 1980s that dopamine depletion causes loss or remodeling of glutamatergic synapses within the striatum.[203-208] Whereas some of these changes affect cortical inputs to the striatum,[209] thalamostriatal inputs are also involved, likely because of the overall loss of neurons in the intralaminar nuclei.[210-212] The loss of glutamatergic inputs to the striatum is associated with a coarsening of the remaining synapses and the formation of multisynaptic neuronal terminations.[209]

More recently, glutamatergic plasticity was also shown to occur in the STN in parkinsonian rodents, nonhuman primates, and patients.[31,213,214] The remodeling of glutamatergic transmission in the STN involves N-methyl-D-aspartate receptor activation and appears to trigger subsequent remodeling of the GABAergic synapses of the pallidosubthalamic projection.[31,215,216] The emergence of these changes may set the stage for the presence of dopamine-treatment–resistant features of parkinsonism, triggered by loss of dopamine loss in the striatum.[31] The specific physiological causes and consequences of these morphological changes are a very active area of research, as is the question whether these changes represent homeostatic or maladaptive plasticity.

Finally, glutamatergic plasticity also occurs in the cerebral cortex.[217,218] In the motor cortex, there is a prominent dropout of the thalamic (glutamatergic) innervation of layer 5, which could be caused by the loss of neurons in the thalamic intralaminar nucleus and their cortical projections.[218] The behavioral effects of these (substantial) changes remain uncertain at this time.

Role(s) of the Cerebellum

A role of the cerebellum in the expression of parkinsonism has long been suspected,[219] and several studies have indeed identified morphological or biochemical changes in the cerebellum, ranging from low levels of alpha-synuclein aggregates[220,221] in the deep cerebellar nuclei, to a reduction of dopamine D1 and D3 receptor expression,[222] or reduced norepinephrine levels.[223] However, many researchers interpret the involvement of the cerebellum and its outflow pathways in parkinsonism as an indirect process, triggered through primary pathology in the striatum or midbrain.[224-226] This view has recently received additional attention because of the identification of anatomical pathways that link the basal ganglia to the cerebellum, so that dopamine loss in the basal ganglia could lead to changes in the function of cerebellar circuits (see Fig. 1 and previous publications[227-230]).

According to imaging studies, the cerebellar hemispheres are overactive in PD patients.[231-233] This may indicate compensatory effects of the cerebellum for the "lost" basal ganglia functions,[234,235] although it remains uncertain what level or type of "compensation" could specifically be provided in this case.

Dysfunction of the cerebellum and/or of its output pathways has likely a more direct role in the generation of parkinsonian tremor. This is supported by the fact that DBS of the thalamic cerebellar-receiving territory effectively treats parkinsonian tremor (e.g., see previous works[236,237]), while reducing the activity of the ipsilateral cerebellum, as measured by PET.[238] The pathophysiology of parkinsonian tremor thus likely differs from that of bradykinesia or akinesia (which do not respond to such interventions). Imaging and modeling studies have suggested that dopaminergic denervation of the cerebellar receiving territory of the thalamus may contribute to tremor, and that dopaminergic drugs could act directly in the thalamus in such patients.[193] STN-DBS also affects cerebellar function,[239,240] perhaps through the pathways shown in Figure 1, which may account for some of its antiparkinsonian effects,[240] specifically its effects on parkinsonian tremor.[241] Although there is mounting evidence that parkinsonian tremor involves the cerebello-thalamocortical system in some way, details of the pathophysiology of parkinsonian tremor remain entirely speculative. For example, the fundamental question regarding the circuit origin of the oscillatory activity that eventually manifests as tremor remains unanswered.

Subtle changes in sensory processing (such as altered responses to sensory uncertainty) in PD may attest to potential additional roles of the cerebellum in other parkinsonian symptoms, such as bradykinesia.[242] MRI studies demonstrating an attenuation of the modulation of corticocortical interactions by cerebellar inputs in the parkinsonian state[243] may further support this concept. Finally, the cerebellum has also been implicated in the development of LIDs.[244-247]

Role of Brainstem Nuclei

Traditional pathophysiology schemes strongly emphasize the role of the transthalamic route of transmission of basal ganglia output to the cerebral cortex as the main route for mediating parkinsonism (Fig. 1). However, parkinsonism is associated with relatively minor changes in firing in the basal ganglia receiving portion of the thalamus.[248-252] Whereas traditional models predict that interventions aimed at the basal ganglia–receiving portion of the ventral motor thalamus "should" impact

bradykinesia or akinesia, these predictions have not been confirmed in parkinsonian animals or human patients with the disease (e.g., see an earlier work).[35] These findings suggest that the branching GPi projections to brainstem nuclei, such as the PPN,[253,254] may be more important for the development of bradykinesia or akinesia than traditionally assumed. PPN dysfunction is usually blamed for dopamine-insensitive gait and balance problems in PD (e.g., see previous works[159,255]), but experiments in primates and rodents have suggested that lesions of the PPN (area) can elicit at least transient hypokinesia, and that stimulation of this site in parkinsonian animals appears to have beneficial effects.[256-268] In distinction from the parkinsonism-associated oscillations in the basal ganglia/thalamocortical circuits, parkinsonism is accompanied by increased alpha-band oscillations in the PPN in PD patients, modulated by movement and gait performance,[269-271] and emphasized in the ON-state.[272-274] Interestingly, beta-band synchronization, which is proparkinsonian in the basal ganglia and cortex, appears to be associated with reversal of parkinsonism in the PPN.[275]

It deserves mentioning that many of the recording and interventional studies targeting the PPN area are difficult to interpret because of the fact that this nucleus and the surrounding area are anatomically and functionally highly heterogeneous. To better understand the involvement of this nucleus in parkinsonian pathophysiology, it will be especially important to explore the anatomical connectivity of the specific PPN neurons that are targeted by basal ganglia output.

Conclusion

Studies of the consequences of dopamine loss in the basal ganglia have a long history, and substantial progress has been made. The studies reviewed here have identified some of the major abnormalities by which PD manifests itself at the single-cell or network level within the basal ganglia/thalamocortical circuitry. It is clear, however, that much work needs to be done to better define the anatomical network(s) that are affected by dopamine loss and account for the clinical manifestations of PD, and the mechanisms that bring about these changes.

Simplified models of the basal ganglia, and of the changes in activity that are caused by parkinsonism (such as the "rate model"), have directed our thinking of the pathophysiology of akinesia and bradykinesia. As a guide to therapy development, these traditional models have benefitted many thousands of patients with PD, by having a significant impact on the use of DBS approaches in the treatment of parkinsonism and by providing the backdrop for the development and testing of new medications. An important recent use of the knowledge gained from the studies mentioned in this review has been the generation of biomarkers that scale with the severity of parkinsonism and can be used to regulate the strength or activity of DBS devices. Thus, studies in monkeys showed that pathologically increased cortical beta-band oscillatory activity can be used as control signal for intermittent "closed loop" regulation of pallidal stimulation in monkeys,[276] and subsequent studies in parkinsonian patients demonstrated that beta oscillations[277] or beta-burst durations[67] of signals recorded in the basal ganglia may serve the same purpose, allowing discontinuous DBS, focused on periods of time of significant parkinsonism. Recently, the strength of the dyskinesia-associated cortical gamma-band peaks was used as a signal to limit ongoing DBS,[278] and cortical PAC has been discussed as a potentially useful additional control signal for the same purpose.[77]

Developing knowledge of parkinsonism-associated activity changes in the basal ganglia and their output pathways goes hand in hand with developing more detailed and precise anatomic insights. Future experimental exploration of the pathophysiology of PD will therefore continue to focus on parallel lines of studies of functional abnormalities, and of the anatomical connections whose activity and morphology may explain them.

It is also remarkable that most of our knowledge of the pathophysiology of parkinsonism was acquired through studies of neuronal activity at rest—when, strictly speaking, neither bradykinesia nor akinesia are present. Although technically more complicated, it will be important to put increasing emphasis on the study of perimovement activities in parkinsonian subjects, as has already been achieved in some studies in rodents,[279] nonhuman primates,[280,281] and patients with PD (e.g., see previous works[282-284]).

Models such as the "rate" model are now clearly outdated, but new convincing and testable models that take into account the multitude of oscillatory and non-oscillatory changes in the basal ganglia, the anatomical loci and connections that were newly identified to be pathophysiologically relevant, or the effects of synaptic plasticity remain elusive. To develop such models and carry out experiments designed to identify those abnormalities that are causal rather than secondary continues to have very high priority. ●

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