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Review

Initial clinical manifestations of Parkinson's disease: features and pathophysiological mechanisms

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A dopaminergic deficiency in patients with Parkinson's disease (PD) causes abnormalities of movement, behaviour, learning, and emotions. The main motor features (ie, tremor, rigidity, and akinesia) are associated with a deficiency of dopamine in the posterior putamen and the motor circuit. Hypokinesia and bradykinesia might have a dual anatomo-functional basis: hypokinesia mediated by brainstem mechanisms and bradykinesia by cortical mechanisms. The classic pathophysiological model for PD (ie, hyperactivity in the globus pallidus pars interna and substantia nigra pars reticulata) does not explain rigidity and tremor, which might be caused by changes in primary motor cortex activity. Executive functions (ie, planning and problem solving) are also impaired in early PD, but are usually not clinically noticed. These impairments are associated with dopamine deficiency in the caudate nucleus and with dysfunction of the associative and other non-motor circuits. Apathy, anxiety, and depression are the main psychiatric manifestations in untreated PD, which might be caused by ventral striatum dopaminergic deficit and depletion of serotonin and norepinephrine. In this Review we discuss the motor, cognitive, and psychiatric manifestations associated with the dopaminergic deficiency in the early phase of the parkinsonian state and the different circuits implicated, and we propose distinct mechanisms to explain the wide clinical range of PD symptoms at the time of diagnosis.

Introduction

Parkinson's disease (PD) has typically been considered to be a motor disorder[1,2] secondary to basal ganglia dysfunction. The definition in the 1960s of the nigrostriatal dopaminergic pathway and the discovery of dopamine striatal loss provided one of the best established correlations between clinical features and biochemical pathology.[3] The main manifestations of PD—akinesia or bradykinesia, rigidity, and tremor—are now known to be directly related to dopaminergic striatal loss. Other clinical manifestations, albeit usually less noticeable, that are also seen at the time of diagnosis include sensory symptoms (eg, pain and tingling), hyposmia, sleep alterations, depression and anxiety, and abnormal executive, working memory-related functions.

The clinical manifestations of PD after diagnosis comprise a mixture of disease-related and treatment-induced manifestations. Motor and non-motor side-effects directly related to treatment such as dyskinesias or hallucinations, and other features arising after long-term disease progression (eg, gait problems and disequilibrium, autonomic failure, and dementia), are not covered in this Review. We discuss the pathophysiological mechanisms underlying the main clinical features of PD at the time of diagnosis and, therefore, when the clinical features are mainly affected by catecholaminergic (ie, mainly dopaminergic) deficits. We provide a differential explanation for the anatomo-functional basis of the major clinical manifestations of PD (ie, tremor, rigidity, akinesia, dysexecutive syndrome, and depression) to expand the views and concepts held by the classic pathophysiological model.

Key motor features: basic concepts

PD motor manifestations begin focally, typically in one limb segment, when dopamine concentrations fall below 60–70% in the contralateral striatum. The onset of motor features correlates with loss of dopamine in the posterior putamen (figure 1), corresponding to the motor region of the striatum. The main features of PD (ie, akinesia or bradykinesia, rigidity, and tremor) are therefore mainly related to dysfunction of the motor circuit (figure 2).

Reduced and slow movements

The term akinesia (strictly defined as "lack of movement") comprises many clinical features, which need to be differentiated for the discussion of underlying pathophysiological mechanisms. One type of akinesia, hypokinesia, consists of reduced frequency and amplitude of spontaneous movement, which is particularly noticeable in automatic movements. Typical manifestations are reduced blinking rate and facial expressions, absent or reduced arm swinging, and absence of associated movements during daily life activities such as rising from a chair and waving. All these hypokinetic features were collectively grouped under the descriptive term "poverty of movement" by Wilson[1] in his influential series on disorders of motility and tone. This term also included a tendency of patients to stand still and to have reduced gesticulation. The parkinsonian gait includes several hypokinetic features such as reduced stride length and decreased off-ground elevation of the feet, leading to short stepping and shuffling, which are associated with reduced arm swinging and predominance of flexor posture. Micrographia is a particular form of hypokinesia, in which a highly learned automatic motor task is not only characteristically reduced in amplitude but is also associated with slowness in the execution.

Bradykinesia is characterised by reduced speed when initiating and executing a single movement and progressive reduction of its amplitude, up to complete cessation[1,2] during repetitive simple movements.

Undertaking sequential or simultaneous movements is severely disrupted and frequently impeded, which has substantial effects on daily living.[5] Kinematic studies have consistently shown that both movement time for single movements and inter-onset latency for sequential movements are increased. Although all types of movements are slower in PD, there is some evidence that externally triggered movements are less impaired than those that are self-initiated; this is best exemplified by gait improvement when external cues are provided.[6]
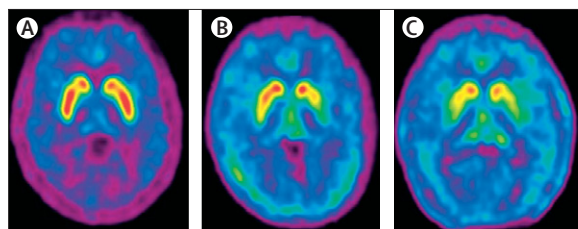

Figure 1: **¹⁸F-fluorodopa PET of a healthy individual (A) and a patient with Parkinson's disease at the time of diagnosis (B) and after 12 years of follow-up (C)**
¹⁸F-fluorodopa uptake is asymmetrically reduced in the early stages of disease, mostly localised to the posterior putamen. As the disease progresses, the anterior putamen and caudate are affected. Images provided by Carlos Juri and Javier Arbizu (Neurology and Neuroscience and Nuclear Medicine Departments, University of Navarra, Pamplona, Spain).

Disorders of muscle tone

Rigidity is characterised by increased muscular tone to palpation at rest, reduced distension to passive movement, increased resistance to stretching, and facilitation of the shortening reaction. Both flexor and extensor muscular groups are involved but flexor muscles of the limbs are more affected in the early stages of disease progression.[7] Increased resistance is dependent on velocity and is more noticeable when the examined joint is stretched slowly;[7] fast displacement is associated with minimum or no rigidity. Joint elongation is typically increased by voluntary activation of other body parts (Froment's manoeuvre) and is commonly interrupted by so-called cog-wheel rigidity.[8]

Tremor

Tremor is typically characterised by 4–6 Hz activity at rest in the limbs with distal predominance. The fingers are most commonly affected, giving rise to the classic "pill-rolling" tremor. The jaw muscles and tongue can occasionally be involved but axial muscles (abdomen, back, and hip) and the neck are rarely affected. Tremor increases in amplitude, or can be triggered by manoeuvres such as voluntary movement of other body parts, arithmetic calculation, and stress. Levodopa and other dopaminergic drugs are less efficacious against
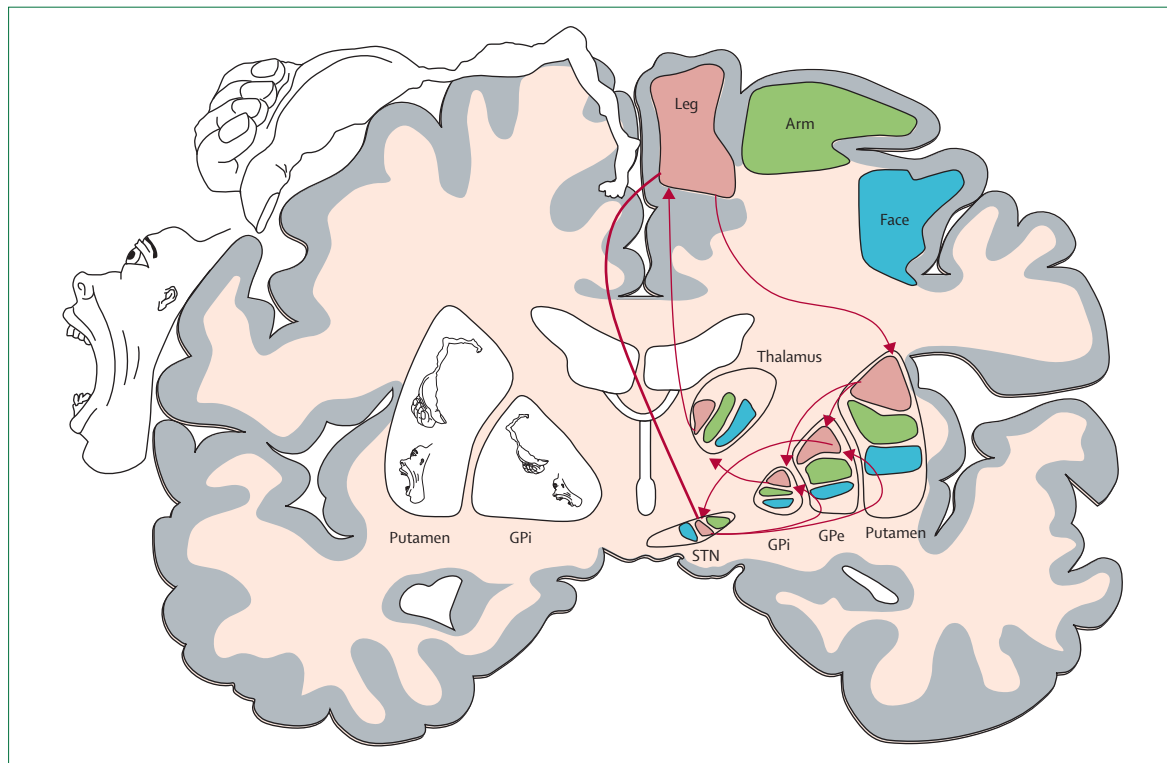

Figure 2: **The motor circuit and its somatotopic organisation**
The motor circuit (indicated by red arrows connecting the regions that modulate leg movements) is somatotopically organised throughout the loop, with the regions representing leg movements lying dorsal and medial, those representing face movements lying ventral and lateral, and those representing arm movements lying in-between. The somatotopic arrangement of the primary motor cortex is generally maintained in the striatopallidal and subthalamic nuclei. Figure reprinted from Obeso and colleagues.[4] GPe=globus pallidus pars externa. GPi=globus pallidus pars interna. STN=subthalamic nucleus.
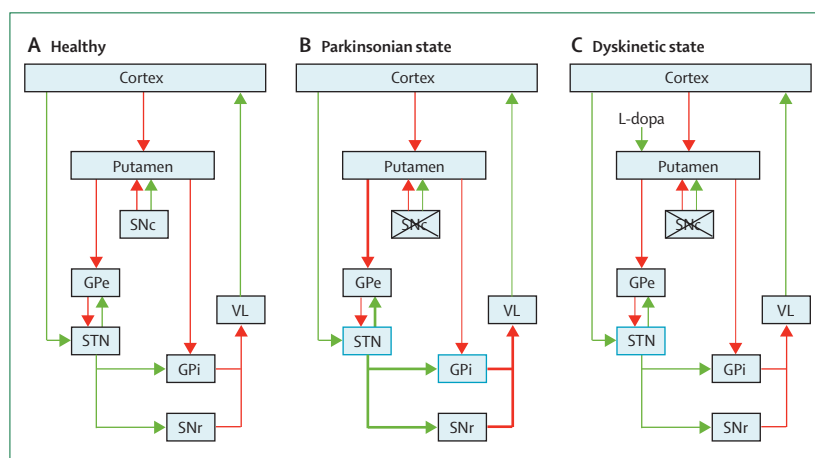
Figure 3: The classic pathophysiological model of the basal ganglia in healthy (A), parkinsonian (B), and dyskinetic (C) states

Cortical motor areas project glutamatergic axons to the putamen, which sends GABAergic projections to the GPi and the SNr by two pathways: the monosynaptic GABAergic "direct circuit"(putamen-GPi) and the trisynaptic (putamen-GPe-STN-GPi/SNr) "indirect circuit". Dopamine from the SNc facilitates putaminal neurons in the direct pathway and inhibits those in the indirect pathway. Activation of the direct pathway leads to reduced neuronal firing in the GPi/SNr and movement facilitation, while activation of the indirect pathway suppresses movements. The STN is also activated by an excitatory projection from the cortex ("hyperdirect" pathway), a connection that was not included in the original model. In Parkinson's disease (B), dopamine deficit leads to increased activity in the indirect circuit, in which STN hyperactivity is a key characteristic, and hypoactivity in the direct circuit. Together, these actions result in increased GPi/SNr output inhibition of the VL nucleus of the thalamus and reduced activation of cortical and brainstem motor regions. In the dyskinetic state (C), abnormal putaminal dopaminergic activation (L-dopa arrow) leads to hypoactivity in the indirect circuit and hyperactivity in the direct circuit, resulting in reduced inhibitory output activity from the basal ganglia. Green arrows indicate excitatory activity and red arrows indicate inhibitory activity. Figure modified from Obeso and colleagues.[12] GPe=globus pallidus pars externa. GPi=globus pallidus pars interna. SNc=substantia nigra pars compacta. SNr=substantia nigra pars reticulata. STN=subthalamic nucleus. VL=ventrolateral nucleus.

tremor than other key features of PD, an assumption generally accepted without clear explanation or formal assessment.

Pathophysiology of key motor features: the classic model

The classic pathophysiological model of the basal ganglia, which was elaborated in the 1980s,[9–11] triggered a large amount of experimental and clinical activity and led to the revitalisation of surgery for PD and other movement disorders. Figure 3 provides a summary of this original model in the healthy and pathological states, and the table summarises the main experimental findings that support this model. The initial model, based on cortico-basal ganglia-cortical loops and changes in neuronal firing rate in the globus pallidus pars interna (GPi) and the substantia nigra pars reticulata (SNr), is now recognised as limited and incapable of providing explanations for many clinical observations. The main clinical paradoxes of this model[13,14] are summarised in the panel.

However, there are several aspects that fit well with this model. The importance of hyperactivity of the subthalamic nucleus (STN) and GPi in the parkinsonian state has been substantiated by different functional approaches in patients with PD. An increased neuronal

firing rate in the "off" state is a typical finding in the STN,[15] which correlates with increased metabolic activation measured by PET of the putamen and the GPi.[16] Moreover, substantial amelioration of motor features and improvement of neurophysiological and PET metabolic markers have been documented after surgery (ie, pallidotomy, subthalamotomy, and deep brain stimulation).[17,18]

Pathophysiology of PD: expanding classic concepts

The basal ganglia networks are now known to be anatomically and physiologically subdivided into motor, oculomotor, associative, and limbic territories that are involved in functions such as learning, planning, working memory, and emotions[19,20] (figure 4). The dopaminergic system innervates all striatal regions, as well as other non-striatal basal ganglia nuclei and limbic and associative cortical areas.[21] Progressive loss of dopaminergic striatal innervation (figure 1) is associated with the emergence of executive dysfunction, learning problems, and mood disorders.[22,23] Loss of dopaminergic cortical input is also an early feature,[24] and cell loss in the raphe nuclei and locus coeruleus[25] might also have a role in the origin of non-motor manifestations. In this section we discuss the origin of the main movement, cognitive, and psychiatric manifestations commonly seen in early (ie, around diagnosis) phases of PD.

Motor features
Akinesia
Difficulty with movement has been generally considered the main manifestation of dysfunction of the basal ganglia.[1,2] The clinical characteristics of akinesia indicate that hypokinesia and bradykinesia are probably mediated by different pathophysiological mechanisms. Hypokinesia is closely associated with reduced rhythmic movements, which in turn depends on timing mechanisms. This timing is mediated by central pattern generators, which are neuronal circuits that fire synchronously without sensory input to produce rhythmic activity. Central pattern generators thus provide a pacemaker function to the nervous system. These generators are well typified in the spinal cord for locomotion in quadruped animals and in the brainstem for the respiratory centre.[26] Presumably, other highly rhythmic and automatic movements such as eye blinking and arm swinging also have a central pattern generator, although the precise anatomical basis is undefined.

Dopamine and other catecholamines have a fundamental role in modulating the excitability of the central pattern generator and the perception of time.[27] Additionally, the substantia nigra and the basal ganglia connections with the supplementary motor area and the lateral premotor and dorsolateral prefrontal cortices are involved in time processing in animals and human beings.[28,29] Moreover, time estimation and rhythm

	Putamen	GPe	GPi	STN	SNr
Parkinsonian state	• Increased expression of D2 receptors, enkephalin, preproenkephalin (rat, monkey) • Decreased expression of D1 receptors, dynorphin, preprotachykinin and substance P (rat, monkey)	Decreased rate of neuronal firing (rat, monkey)	• Increased rate of neuronal firing (monkey, patients with PD) • Increased expression of CO-I and GAD (rat, monkey) • STN lesion reduces CO-I and GAD (monkey) and neuronal firing rate (monkey, rat)	• Increased rate of neuronal firing (rat, monkey, patients with PD) • Increased expression of CO-I (rat, monkey) • Decreased expression of 2-DG (monkey) • STN lesion improves parkinsonism (monkey, rat, patients with PD)	• Increased expression of CO-I and GAD (monkey, rat) • STN lesion reduces expression of CO-I and GAD (monkey)
Treatment with L-dopa or apomorphine	• Normalisation of expression of D1 and D2 receptor (rat, monkey) • Normalisation of expression of preprotachykinin and substance P (rat, monkey)	Normalisation of rate of neuronal firing (monkey)	• Decreased rate of neuronal firing (rat, monkey, patients with PD) • Decreased expression of CO-I and GAD (rat, monkey)	• Decreased rate of neuronal firing (rat, monkey, patients with PD) • Decreased expression of CO-I (monkey)	• Decreased expression of CO-I and GAD (monkey)

2-DG=2-deoxyglucose measured by autoradiography. 6-OHDA=6-hydroxydopamine. CO-I=cytochrome oxidase-I measured by in situ hybridisation. GAD=glutamic acid decarboxylase measured by in situ hybridisation. GPe=globus pallidus pars externa. GPi=globus pallidus pars interna. MPTP=1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. PD=Parkinson's disease. SNr=substantia nigra pars reticulata. STN=subthalamic nucleus.

Table: Summary of the main findings in the 6-OHDA rat and the MPTP monkey models of parkinsonism and in patients with PD

generation are abnormal in PD[27,30] and increased striatal expression of D2 receptors in rodents (PD model; table), is associated with impaired interval timing.[31] Extracellular neuronal recordings in non-human primate and rodent models of PD have also shown impairment in temporal processing of spatial information.[32] Therefore, hypokinesia in PD is probably mediated by disruption of central pattern generators and abnormal timing mechanisms. GPi and SNr project and activate several brainstem regions (ie, the pedunculopontine nucleus and the superior colliculus) that are functionally impaired in the parkinsonian state. The clinical features of hypokinesia suggest that excessive inhibition of brainstem circuits from the basal ganglia might have a major role in its pathophysiology. For example, a low blinking rate suggests direct inhibition of the central pattern generators, whereas increased excitability of the blink reflex and Meyerson's sign might be caused by SNr overinhibition of the superior colliculus and secondary disinhibition of the nucleus gigantocellularis.[33] Brainstem mechanisms are also likely to be engaged in the origin of postural disturbances and other motor signs such as dysphagia and dysarthria; however, these features typically occur later in the disease.

Bradykinesia can be understood as a failure of neuronal recruitment or "energisation".[34,35] Movement patterns are correctly selected but the parameters for undertaking the action in terms of speed and amplitude of the movement are incorrectly set,[36,37] despite preserved capability to choose the appropriate parameters.[35] Striatal medium spiny neurons receive many glutamatergic afferents (about 10 000 synaptic contacts per medium spiny neuron) and about 100 of these neurons converge into one GPi neuron.[38] This large input to output gradient requires that the basal ganglia is largely involved in selecting which neuronal signals are facilitated or not.[39,40] In the parkinsonian state,

Panel: Major clinical paradoxes and observations in Parkinson's disease that are not explained by the classic model

Origin of key features
Increased neuronal activity in the STN/GPi-SNr and the associated inhibition of the thalamocortical projection does not provide an explanation for the origin of tremor and rigidity in Parkinson's disease.

Pallidotomy abolishes dyskinesias
Levodopa-induced dyskinesias in patients with Parkinson's disease are eliminated by GPi lesions, which is incompatible with a model that associates excessive inhibition with the GPi/SNr and reduced basal ganglia efferent activity with dyskinesias.

No deficits after interrupting basal ganglia-cortical connections
Disruption of the motor circuit by surgical lesions (ie, thalamotomy or pallidotomy) does not aggravate bradykinesia in Parkinson's disease nor induces any new motor deficit.

GPi=globus pallidus pars interna. SNr=substantia nigra pars reticulata. STN=subthalamic nucleus.

activity in the motor circuit is disrupted at several fundamental levels. First, the proportion of striatal medium spiny neurons and GPi neurons responding to stimulation is increased and the inhibition to excitation ratio decreases substantially.[41] Second, selectivity of somatotopic neuronal responses to peripheral stimulation is blurred in cortical motor areas[42,43] and basal ganglia nuclei.[44] Third, corticostriatal activity is biased towards activation of striatal neurons in the indirect circuit,[45] which, in association with increased collateral inhibition from medium spiny neurons,[46] leads to globus pallidus pars externa (GPe) inhibition

and increased STN and GPi output (figure 3B). Fourth, striatal plasticity is impaired, so that synaptic changes induced by cortical afferent stimulation such as long-term depression or potentiation are eliminated.[47] Fifth, neuronal firing synchrony increases substantially within basal ganglia structures such as the STN and GPi[43,48] and also among different structures throughout the motor loop nuclei,[49,50] producing abnormal oscillatory activity. In patients with PD,[51] the "off" medication state is characterised by a net predominance of beta-band activity in the STN, which is substantially reduced in the "on" state[52] (figure 5). This activity propagates to the basal ganglia and thalamocortical projection, so that the entire motor circuit is synchronised at about 20 Hz.[50]

Accordingly, bradykinesia can be seen as a defect of the motor circuit to generate a phasic and time-locked inhibition of GPi neurons and to achieve substantial desynchronisation in the beta band to facilitate recruitment of cortical motoneurons appropriately adjusted for the intended movement.[41,53–55] This activity is not only due to reduced activation of medium spiny neurons in the direct circuit,[56] but also to the combination of functionally hypoactive GPe with hyperactive STN and GPi, which reduces the probability that a cortical signal will be facilitated via the STN-GPe-GPi loop.[56,57] Increased responsiveness of the STN-GPi might also increase movement-related activity through the hyperdirect pathway and contributes to progressive attenuation of repetitive and sequential movements and micrographia. A similar explanation might account for the prolonged latency between sequential time-locked simple movements that are automatically undertaken (ie, shaking hands or saluting at a distance). When the sequence involves different movements and body parts, there is a higher demand on serial striatal input-output and GPe-STN-GPi modulation, accounting for the greater slowness and increased errors in execution compared with single (one joint) movements.

Rigidity

The clinical features of rigidity suggest a complex pathophysiological origin for this key feature. Thus, increased muscle tone at rest and augmented resistance to passive displacement of the joint readily evoke different mechanisms. On the one hand, there must be facilitation of spinal cord motoneuron activity, probably related to increased supraspinal driving or facilitation. On the other hand, a fundamental role for the stretch reflex must be considered. Classic physiological studies have shown that rigidity is abolished by dorsal root sectioning or by local dural injection of anaesthetics supporting a reflexive origin.[58] The latter finding led to many studies of spinal cord excitability in the 1960s and 1970s. These studies showed that spinal motoneuron responsiveness to afferents from muscle spindles (type Ia fibres), which sustains the clinically applied tendon jerk, is unaltered in PD but the inhibition normally evoked from tendon organs (type Ib fibres) is reduced,[59] whereas interneurons activated by secondary muscle afferents (type II fibres) are hyperactive. These findings suggest a shifting of spinal cord motoneurons towards increased activity in response to peripheral stimulation.

The importance of supraspinal mechanisms in rigidity has also received much attention. Slow and sustained muscle stretching (giving rise to the tonic stretch reflex) is increased in patients with PD.[7] Furthermore, brief and rapid phasic muscle stretching of the limbs evokes a typical spinal reflex (latency about 20 ms) and a long-latency response (about 40 ms). The long-latency stretch reflex is mediated through the primary motor cortex and is increased in patients with PD. However, this stretch reflex is larger in distal muscles than in proximal muscles of the upper limb, whereas rigidity is also present proximally and in the axial musculature. The correlation of this reflex with clinical rigidity is not clear.[60]

The importance of cortical mechanisms is reinforced by findings of increased primary motor cortex excitability as detected by magnetic cortical stimulation.[61,62] Stimulation of the premotor cortex in patients with PD in the "off" medication state did not increase motor cortex excitability, an effect that was present in healthy controls and in the same patients with PD when "on" medication.[63] These results are similar to findings in monkeys treated with MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) in which primary motor cortex neurons responded more vigorously and with less specificity to passive limb movements, although the firing rate at rest was not modified.[43,53]
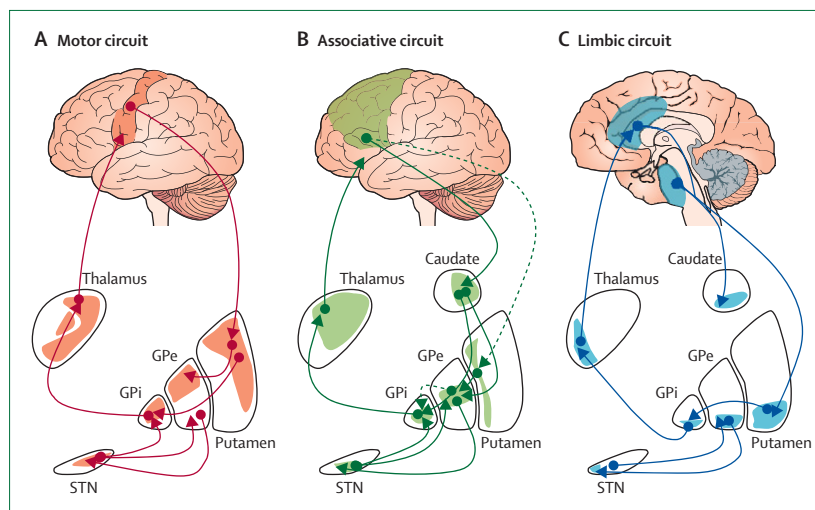

Figure 4: Functional organisation of the basal ganglia
The basal ganglia are divided into motor (A), associative (B), and limbic (C) subregions, which are topographically segregated, as highlighted by areas coloured in red (motor cortex), green (prefrontal cortex), and blue (anterior cingulate cortex). Figure reprinted from Obeso and colleagues.[4] GPe=globus pallidus pars externa. GPi=globus pallidus pars interna. STN=subthalamic nucleus.

Surgery of the basal ganglia and motor thalamus has a clear antirigidity effect, indicating a direct role of the motor circuit in the origin of rigidity. How dopamine deficiency and increased basal ganglia output activity are associated with primary motor cortex excitability and rigidity is not understood. There might be several possible and not mutually exclusive mechanisms. For example, changes in GABA and cholinergic interneurons lead to reduce intrastriatal inhibition in the indirect circuit, which could facilitate responses to peripheral stimulation. Neuronal responsiveness of the STN and GPi to peripheral stimulation is increased in the parkinsonian state, suggesting that responses to normal muscle afferent impulses could facilitate cortically mediated responses. Hyperactivity of area 4 (the primary motor cortex) plus increased gain in the cortico-STN-GPi microcircuit and the loss of somatotopic specificity could explain Froment's sign. However, neuronal discharges in the STN and GPi should lead to cortical inhibition or absence of facilitation, which does not explain the excessive response to stretching that characterises rigidity and the increased muscle tone at rest. Thus, rigidity is not explained by the classic model of basal ganglia pathophysiology. The origin of rigidity in PD would be easier to understand if basal ganglia output to the thalamus was not only inhibitory. Additionally, rigidity probably involves disinhibition of brainstem mechanisms (ie, reticulospinal projections[64] mediating muscle tone and posture).

Tremor

Rhythmic and synchronous neuronal firing recorded in the STN and the GPi correlates with tremor in the limbs in both monkeys treated with MPTP and in patients with PD.[65] Surgery of the STN can readily stop parkinsonian tremor. This tremor is inhibited at the onset of a voluntary muscle contraction involving the same body part and by cortical magnetic stimulation, and disappears after stroke causing hemiparaesis, all of which indicate that the pyramidal tract is the final output pathway mediating tremor. However, rhythmic firing is better recorded and tremor stopped in the ventralis intermedius nucleus (Vim) of the thalamus.[66] The Vim is outside the basal ganglia projection territory; it receives propioceptive (type Ia) afferents from muscle spindles and projects to the primary somatosensory cortex and motor cortex (area 3a). In monkeys treated with MPTP, 5 Hz stimulation of the GPi is not capable of recruiting and driving motor cortex activity, revealing a filtering characteristic of low frequency activity in the motor circuit.[67] This finding means that rhythmic activity in the basal ganglia is unlikely to drive cortical-spinal motor activity to generate tremor. The origin of tremor in PD is therefore a pathophysiological puzzle. Specifically, the mechanistic link between dopamine deficiency and abnormal oscillatory activity in an extensive motor network that involves the basal
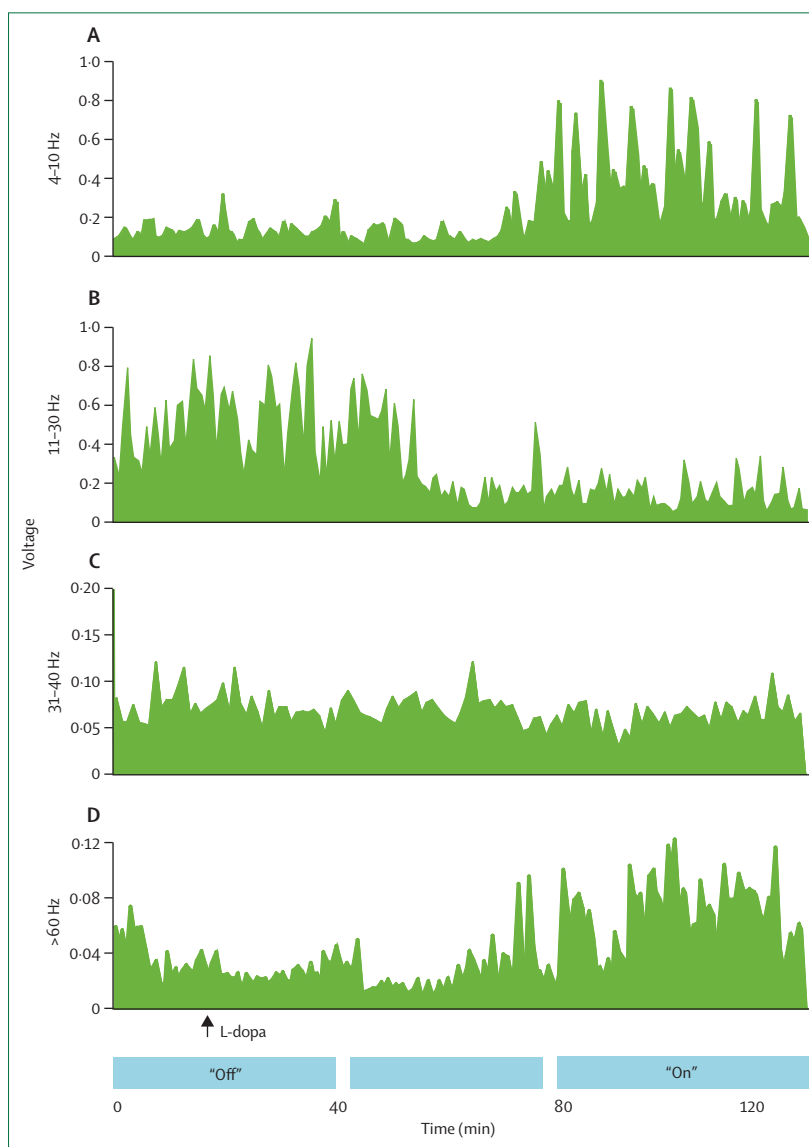

Figure 5: **Oscillatory activity recorded by local field potentials in the subthalamic nucleus in a patient with Parkinson's disease**
In the "off" state there is a net predominance of activity in the beta band (11–30 Hz), which is substantially reduced when the effect of levodopa starts and activity in the gamma band (>60 Hz) emerges. Figure reprinted from Alonso-Frech and colleagues.[52]

ganglia, the cerebellar, the thalamus and the motor cortex needs to be understood. We suggest two main possible mechanisms.

First, basal ganglia could be directly involved. In this potential mechanism, increased basal ganglia output leads to increased excitability of the primary motor cortex and increased sensitivity to stretching and synchronous basal ganglia firing, thus facilitating the onset of oscillations around the motor loop. Muscle stretching evokes neuronal responses in the STN of patients with PD, which show a pronounced tendency to oscillate at tremor frequency. The latency of about 60–100 ms of

these responses and total movement time of each tremor beat of 150–200 ms fit with a loop through the basal ganglia at 5 Hz. Loss of direct dopaminergic control of the microcircuity network formed by the STN-GPe/GPi interconnections could play a part in this regard.[68]

Second, the neuronal network underlying tremor might not primarily lie in the basal ganglia. This possibility is supported by the high association between the Vim and cerebellar activation and tremor and by the exquisite sensitivity of Vim manipulations to cessation of tremor. Dopaminergic projections to the thalamus are known to be present in monkeys and human beings,[69] and the STN-GPi form a loop with the centromedian thalamic nuclei,[70] which in turn is reciprocally connected to the primary motor cortex. Extrastriatal dopamine denervation, or loss of other transmitters, could facilitate synchronous 5 Hz activity within the thalamus and basal ganglia. The possibility therefore arises that loss of catecholaminergic neurons required for tremor in PD might have a different pattern to that underlying the akinetic-rigid presentation. ^{18}F-fluorodopa PET striatal uptake does not correlate with tremor severity[71] and resting tremor is not associated with striatal lesions. However, a specific pattern of neurodegeneration accounting for tremor and differentiating predominant tremor from akinetic-rigid forms of PD has not been yet found.[72]

Key motor features of PD: conclusions and suggestions
Two main characteristics of parkinsonian motor features are the greater difficulty in moving with self-initiated than with externally triggered movements and the abnormal activation of specific body parts. Movements of the limbs or gait improve when initiated in response to external cues, and bradykinesia is made worse when more than one body part is activated simultaneously; both rigidity and tremor are also increased or are induced by movements of other body parts. These features fit well with the concept that the basal ganglia have a fundamental role in modulating activity of premotor areas (supplementary motor area, pre-supplementary motor area, and dorsolateral prefrontal cortex) that deal with selection of self-initiated actions.[39,40,55] However, analysis of the main motor manifestations of PD suggests a more complex pathophysiological origin. Thus, key features of hypokinesia such as absence of spontaneous movement or reduced blink rate are unlikely to share mechanisms with bradykinetic manifestations such as reduced amplitude and slowness of the limbs or simultaneous manual movements. We suggest that hypokinesia is related to overinhibition of the brainstem central pattern generator, whereas bradykinesia is related to perturbed activation or inhibition of the basal ganglia-thalamocortical pathway. The primary motor cortex is impaired in a complex way in the parkinsonian state and there is a functional uncoupling of premotor areas and primary motor area. This impairment could be due to a

preferential involvement of area 4 activity in the origin of rigidity (and possibly tremor), whereas hypoactivation of premotor areas could underlie bradykinesia. Recent data indicate that bradykinesia itself encompasses several mechanisms, with amplitude and speed of movement probably mediated by different mechanisms,[37] which suggest differential involvement of cortical motor areas. Additionally, the role of basal ganglia output on to the brainstem deserves greater attention. Several features of akinesia and rigidity probably involve a brainstem mechanism. It is difficult to explain the key motor features of PD on the basis of a common pathophysiological mechanism. Moreover, current data on the anatomo-functional organisation of the basal ganglia can not comprehensively explain the range of motor manifestations associated with dopamine depletion in PD.

Cognitive manifestations
Cognitive deficits in PD range from "frontal" executive dysfunction, which can be present in a mild form from early stages, to frank dementia in late stages. Here, we concentrate on disorders of executive function, which can be recognised as early features of PD.

Executive dysfunction
Executive function refers to processes involved in the higher-order control of behaviour, such as strategic planning and problem solving, maintaining and shifting attention, and behavioural regulation: the ability to initiate, execute, inhibit, and monitor a sequence of actions. Depending on sample characteristics and criteria used, cognitive deficits are present in early PD in 20–40% of patients[73–75] but are often overshadowed by motor features.

The finding that patients with PD show deficits compared with matched controls on several standardised neuropsychological tests of executive function such as the Wisconsin card sorting test, verbal fluency, and the Stroop test has been well documented.[76] Patients with PD also show impaired performance on other tests of executive function that require planning and problem solving[76,77] or shifting of attentional set,[77,78] on tasks requiring suppression of prepotent or habitual responses,[76,79] and in task situations that require sharing of attentional resources for concurrent performance of two tasks.[80,81] Such impairment becomes more evident when patients have to rely on internal control of attention relative to when external cues are available to guide behaviour,[82] in a way that is similar to what occurs with movement. Other deficits of cognitive function, such as impairment of visuospatial function, can also occur in PD,[83] but language is generally intact in early PD.[73–75] Memory impairment in early PD could be largely due to effortful retrieval, as cueing improves recall and recognition memory is usually not impaired,[76,84] although deficits in recognition memory have been found in other

studies (reviewed elsewhere[85]). Patients with PD have impaired implicit learning on both cognitive and motor tasks, such as the weather prediction task[86] and the serial reaction time task.[87]

Generally, many aspects of the dysexecutive syndrome improve with dopaminergic treatment.[88,89] However, dopaminergic medication has a detrimental effect on other aspects of cognition, such as reversal or conditional associative learning. These deficits have been attributed to a dopamine overdose effect in the frontostriatal circuits through the ventral striatum (orbitofrontal, anterior cingulate, and inferotemporal circuits). This effect could be because there is not substantial dopamine depletion in these circuits in the early stages of PD.[90,91]

Pathophysiology of executive dysfunction

Reduced ^{18}F-fluorodopa uptake in the caudate has been associated with executive dysfunction in patients with PD in some[92,93] but not all studies,[94] thus implicating nigrostriatal dopamine depletion in these cognitive deficits. The mesocortical dopamine system is also affected,[95] although prefrontal overactivity, particularly in the anterior cingulate, has been found at early stages of the disease.[96] Imaging studies have shown that executive deficits and working memory impairment in patients with PD are associated with dysfunction in the basal ganglia,[23,79,97,98] the dorsolateral prefrontal cortex,[79,99] or the caudate and prefrontal cortex,[100] thus implicating both the nigrostriatal and the mesocortical pathways in these deficits. However, a recent ^{11}C-raclopride study of spatial working memory concluded that executive dysfunction in patients with early PD is associated with impaired nigrostriatal function and that mesocortical dopaminergic function is well preserved in early PD.[22] Similarly, data from several studies in monkeys with minimum motor deficits after low and slow MPTP exposure have shown deficits in executive function and attention,[101] which were best explained by a nigrostriatal lesion.[102]

These findings suggest that dysfunction of cortico-basal ganglia associative areas secondary to dopamine depletion might have an important role in early executive problems in patients with PD. However, the relative contribution of the nigrostriatal and mesocortical dopamine depletion to executive dysfunction probably varies during the course of the illness and also depends on the nature of the specific executive process under investigation. Evidence also implicates other neurotransmitters such as acetylcholine in the cognitive manifestations of PD.[88,103–105]

Psychiatric manifestations

A premorbid personality has been described in several studies.[106,107] The typical personality of patients with PD is mainly characterised by emotional and attitudinal inflexibility, introversion, and a depressive tendency, which can precede the development of motor abnormalities by many years.

Psychiatric symptoms might appear at any time, usually worsen as the disease progresses, and occur frequently in patients with PD but without dementia.[108] Depression, anxiety, and apathy are the most prevalent symptoms. Apart from these features, most psychiatric symptoms that develop in the course of PD are seen in patients with advanced PD and are associated with complications derived from chronic dopaminergic treatments.[109]

Psychiatric problems in patients with early PD

In untreated patients with early PD, depression (37%), apathy (27%), sleep disturbances (18%), and anxiety (17%) are the most common neuropsychiatric symptoms.[110] Patients with PD who have never been treated also have deficits on reward processing and novelty seeking, which can be reversed by dopamine agonist therapy.[106,111]

Longitudinal studies assessing the predominant clinical psychiatric manifestations during disease progression are scarce.[112] Depression occurs in about 40–50% of patients with PD throughout the course of the disease,[113] but this symptom is commonly underdiagnosed and undertreated, despite being a predictor of poor quality of life.[114] Guilt and self-blame are less frequently reported. Suicidal ideation is not uncommon, but suicidal behaviour is rare. Depression is manifested as pessimism and feelings of hopelessness, can be associated with apathy and anxiety, and can occasionally be difficult to discern from symptoms such as bradyphrenia, fatigue, and sleep disturbances. Apathy is a generalised lack of motivation accounting for a decrease in goal-orientated activities, loss of interest, and blunted emotional experience. Apathy is seen in 17–70% of patients with PD,[115,116] and frequently coexists with depression or dementia, although it can occur as the sole major manifestation[116] or can be associated with executive dysfunction.[117]

Generalised anxiety, panic attacks, and social phobias are common in PD.[118] About 40% of patients have anxiety,[119,120] although a recent series reported a prevalence of 69% (930 of 1351).[108] The symptoms include apprehensiveness, nervousness, irritability, and feelings of impending disaster as well as palpitations, hyperventilation, and insomnia. Panic disorder is the most common anxiety disorder in PD.

Pathophysiological basis of psychiatric manifestations

The pathophysiological basis of the non-drug-induced psychiatric manifestations in PD is poorly understood. Depression and apathy have been linked to ventral striatum and mesolimbic dopaminergic denervation.[121,122] Involvement of norepinephrinergic[122] and serotoninergic metabolism has also been suspected.[123] As apathy, anxiety, and depression precede disease onset in 30% of recently diagnosed patients,[124] and there is no evidence of generalised catecholaminergic cell loss in patients with early PD, these manifestations could be associated

with dopaminergic striatal deficit. Thus, dopaminergic treatments are usually beneficial[125] and lead to a period of restored behaviour and mood. However, the available data do not allow any firm conclusion regarding the relative role of catecholamines in the origin of depression and other early psychiatric manifestations. In patients with more advanced disease, depression, acute sadness, or dysphoria might be associated with "off-drug" fluctuations,[126] which could be seen as the opposite of the hyperdopaminergic behaviours (ie, impulse control disorders[109]) induced by dopaminergic drugs. Additionally, apathy improves with dopaminergic treatment.[127]

Conclusions

The basal ganglia networks involve complex sets of cortical and subcortical connections involved in motor control, cognitive functions, and emotional processing, probably through a common pathway, whereas the nigrostriatal dopaminergic system modulates input and the glutamatergic subthalamic projection regulates output. The wide clinical range of symptoms in patients with PD, even in early stages, could be due to dysfunction in distinct cortico-basal ganglia loops. The classic pathophysiological model of the basal ganglia does not explain the origin of rigidity and tremor or the constellation of features comprising akinesia. Moreover, there is insufficient understanding of the mechanisms underlying executive dysfunction and psychiatric features. The effect of deficits in neurotransmitters other than dopamine, albeit known for many years, has not been adequately incorporated in the pathophysiology of PD. What is now required is a new holistic model dealing with the broadened clinical manifestations in early and later stages. The role of compensatory mechanisms would be an important feature to consider and incorporate into future models.

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