TIMELINE

The two-century journey of Parkinson disease research

Serge Przedborski

Abstract | Since the first formal description of Parkinson disease (PD) two centuries ago, our understanding of this common neurodegenerative disorder has expanded at all levels of description, from the delineation of its clinical phenotype to the identification of its neuropathological features, neurochemical processes and genetic factors. Along the way, findings have led to novel hypotheses about how the disease develops and progresses, challenging our understanding of how neurodegenerative disorders wreak havoc on human health. In this Timeline article, I recount the fascinating 200-year journey of PD research.

James Parkinson, who was an English surgeon, apothecary, geologist, palaeontologist and political activist, published his thin monograph titled *An Essay on the Shaking Palsy*[1] exactly 200 years ago, in 1817, and this account represents the first description of Parkinson disease (PD) as a neurological disorder. Nowadays, individuals with PD live longer, healthier lives thanks to a wealth of discoveries, which have occurred in a step-wise manner and at ever-finer scales. Indeed, the initial clinical descriptions of PD led to studies of the neuropathological, functional neuroanatomical, neurophysiological and, more recently, cellular and molecular underpinnings of this disease. In this Timeline article, I recount key discoveries from this 200-year journey (FIG. 1) that form the basis of our understanding of, and pave the way towards more effective therapeutic strategies for, this disease.

Discovery of the shaking palsy

Ancient texts allude to PD-like clinical features[2], but the first description of PD as a neurological condition (as indicated above) is credited to James Parkinson. In his 1817 monograph, James Parkinson described a handful of patients who had a singular association of tremor at rest, slowness (bradykinesia) of or, in some cases, an absence of, voluntary movements (akinesia), stooped posture and festinating gait[1]. Beginning with Jean-Martin Charcot[3], approximately 50 years later, a succession of illustrious scientists contributed to the comprehensive description of the clinical range and anatomopathological basis of PD, which is now recognized as the second most common neurodegenerative disorder after Alzheimer disease. At least four fundamental concepts emerged from this body of work.

First, the fundamental features of what we call PD are now known to occur in more than 30 distinct conditions[4]. Thus, we now use the term parkinsonism to label any clinical condition with bradykinesia or akinesia and at least one of the following signs: muscle rigidity, resting tremor or postural instability. PD is the most common cause of parkinsonism, accounting for ~80% of cases[4].

Second, Charcot noted that some patients who were thought to have PD also showed atypical neurological signs, such as an erect rather than a stooped posture and a lack of tremor[3]. These observations led to the recognition of various PD-plus syndromes, such as multisystem atrophy and progressive supranuclear palsy, which, despite often initially being diagnosed as PD, are distinct conditions that have much bleaker prognoses. One important additional PD-plus syndrome, post-encephalitic parkinsonism, was common among patients who survived acute influenza infection during the epidemic of 1916–1918 (REF. 5). The parkinsonism in these patients was associated with a myriad of other manifestations, such as psychiatric symptoms, abnormal ocular movements, spasticity and brisk reflexes[6].

Third, recent clinical descriptions of PD have revealed non-motor features that are also a part of the disease, including cognitive impairment, psychiatric symptoms, autonomic dysfunction (such as constipation), pain and fatigue[7]. In some patients, these non-motor features can be more troublesome than the motor manifestations, and may even present years earlier[7]. Thus, this initial phase of research established our fundamental appreciation of PD as a disease that has diverse and wide-reaching pathological implications.

Last, growing attention has been paid to the prodromal phase of PD, which refers to the presence of clinical manifestations (for example, olfactory loss, rapid eye movement (REM) sleep behaviour disorders and even subtle motor dysfunctions) that may herald PD but that are insufficient to support this diagnosis. Although the field of prodromal PD is still in its infancy, intense research is underway to discover markers that can predict the conversion to PD[8]; this is fuelled by the perspective that such markers could then be used to initiate neuroprotective therapies even before the emergence of parkinsonism.

From anatomy to pathogenesis

In contrast to the rapid advances made towards the clinical delineation of PD and related conditions, its anatomopathological underpinnings remained enigmatic for quite a while. The initial reports of these underpinnings stated that the brains of individuals with PD showed no overt or consistent abnormalities. However, at the end of nineteenth century, Blocq and Marinescu[9] posited that a left-sided 5 Hz resting tremor in a 38-year-old patient was reminiscent of the symptoms of PD. They further noted that the patient's condition could have been caused by a tuberculous granuloma of the right cerebral peduncle that impinged on the ipsilateral substantia nigra (SN). This remarkable, serendipitous observation prompted Brissaud[10] to suggest that the SN may be the site of the lesion in PD. Two decades later, this idea gathered support from the work of Trétiakoff[11], who was the first to report neuropathological changes in

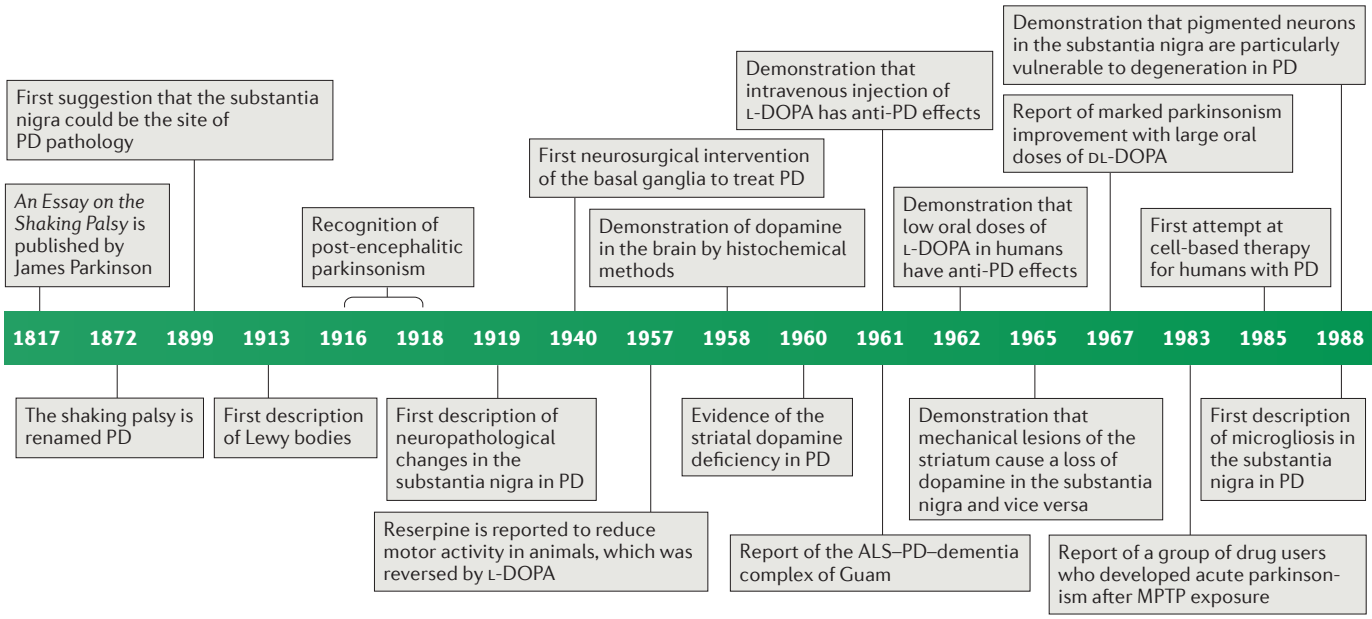


Figure 1 | **The 200 years of Parkinson disease research.** ALS, amyotrophic lateral sclerosis; *GBA*, glucosylceramidase; LAG3, lymphocyte-activation gene 3; L-DOPA, L-3,4-dihydroxyphenylanine; MPTP, 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine; PD, Parkinson disease; *SNCA*, α-synuclein.

the SN in patients with PD. Specifically, he observed macroscopic depigmentation of the SN, which is now known to be a result of the loss of SN neurons (which contain copious amounts of neuromelanin)[12], as well as the microscopic loss of neurons, which was associated with gliosis and Lewy bodies.

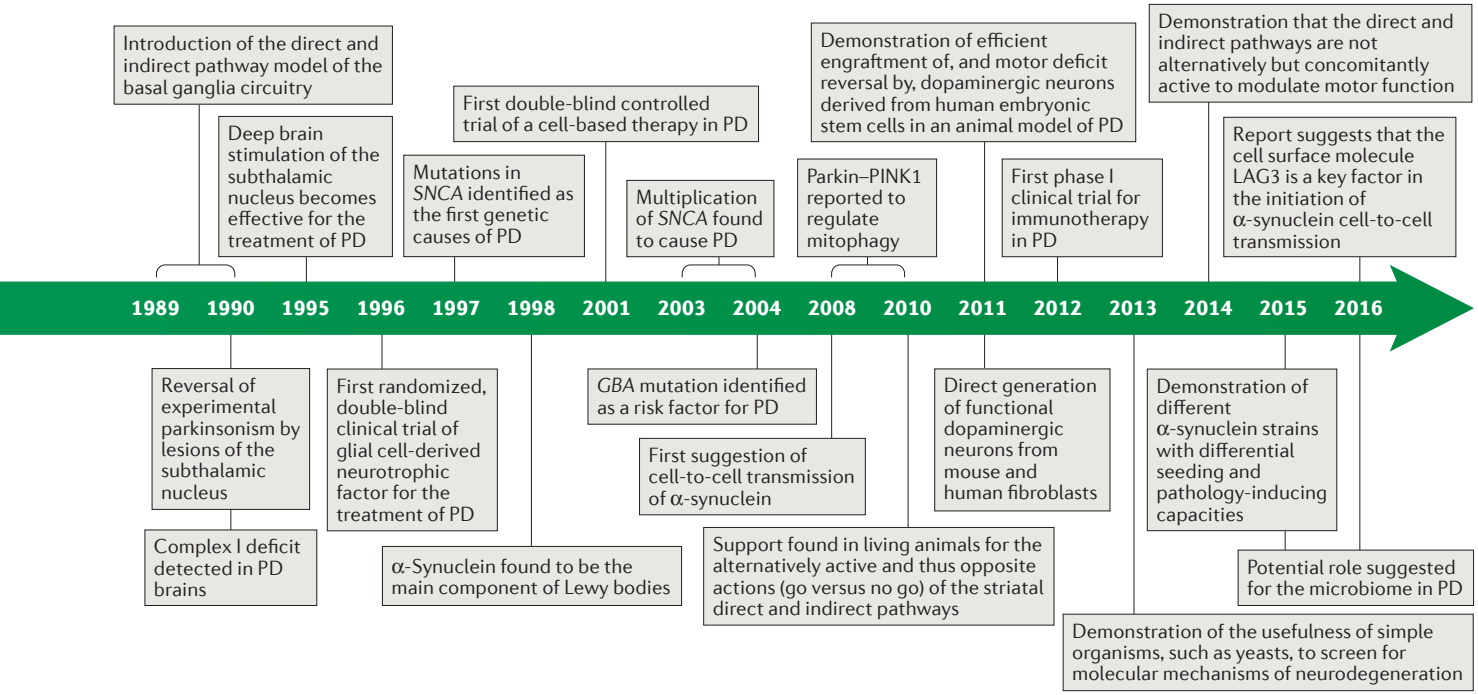
Lewy bodies had been described a few years earlier[13] and quickly became the focal point of neuropathological studies of PD. Of note, although we now know that Lewy bodies are found in a broad range of brain regions in patients with PD[14], these spherical eosinophilic intraneuronal inclusions were originally reported in the dorsal nucleus of the vagus nerve and the substantia innominate but, notably, there was no mention of them being found in the SN[13]. These initial observations led some to argue that the SN was not, in fact, the key brain region involved in PD pathology, but rather that the striatum was a more plausible locus, given the observed overt anatomical damage of the striatum in some diseases associated with parkinsonism[15]. A fierce, protracted debate ensued that was ultimately resolved by the elucidation of the dopaminergic nigrostriatal pathway.

The fact that the striatum and SN belong to the same neural pathway was not established until much later, after dopamine was implicated as a neurotransmitter intimately involved in the pathology of PD. The evidence of this link came from studies of mechanical unilateral lesions of the ventral midbrain that, in both rats and monkeys, caused depletion of striatal dopamine[16–19]. By building on the histofluorescence-based classification of brain monoamine neurons by Dahlström and Fuxe[20], Andén and collaborators[16] found that the unilateral removal of most of the striatum in adult rats was associated with first an increase and then, a few weeks later, a decrease in catecholamine-related fluorescence of neurons within the SN. These studies not only supported the existence of the dopaminergic nigrostriatal pathway but also demonstrated that the dorsolateral striatum — the part of the structure that is most affected in PD — was populated with nerve terminals from neurons the cell bodies of which were located in the SN.

Thereafter, more detailed neuropathological studies continued to contribute to our understanding of PD. For example, careful study of PD-related pathology within the SN identified a subregion, the pars compacta (SNpc), that is disproportionately affected by the disease[21,22], and a further study showed that there was a greater loss of pigmented neurons than their unpigmented counterparts in the SNpc[23]. This led to the hypothesis that neuromelanin confers a type of vulnerability, perhaps by promoting neurotoxic processes, such as oxidative stress[24]. Another study revealed a characteristic topology of PD-related neuron loss, concentrated in the ventrolateral and caudal portions of the SNpc[25]; this pattern is distinct from the dorsomedial-focused loss that is seen during ageing and suggested that distinct processes are involved in PD-related cell death. Last, although for a long time the neuropathology of PD has been epitomized by the loss of dopaminergic neurons in the SNpc, it is now well recognized that foci of neurodegeneration are not limited in the slightest to this brain structure[26].

A role for dopamine

The mid-1900s brought the beginning of what would be a fascinating saga regarding the neurochemical basis of PD. First, there was the demonstration, through both fluorescent-based biochemical methods and histochemical methods, that dopamine is present in the vertebrate brain[27,28]. The highest concentrations of dopamine were found in the striatum; a structure known to contain only low levels of noradrenaline[29–31]. These observations were taken as evidence that dopamine is an independent neurotransmitter, rather than merely a precursor of adrenaline and noradrenaline, as was previously thought. Concurrently, Carlsson and collaborators[32] published a landmark paper reporting the first evidence of a functional role for dopamine[32]. Specifically, they noted that the administration of L-3,4-dihydroxyphenylanine (L-DOPA), a dopamine precursor, to animals reversed the reductions in dopamine levels and in motor activity that were induced by reserpine (a monoamine depletor). These findings were taken by many at the time as evidence of a crucial role for dopamine signalling in the basal ganglia in motor control.



As parkinsonism is the prototypical example of a human disorder with motor defects (that is, reduced voluntary movements), the next question was whether dopamine was involved in PD pathology. The answer came almost simultaneously from two independent research teams who reported a substantial dopamine deficit in both the striatum[33,34] and the SN[33] in brains from patients who were dying from either post-encephalitic parkinsonism or PD. Following this series of neurochemical discoveries, several investigators tested L-DOPA in patients with PD and post-encephalitic parkinsonism, and after a period of trial and error, L-DOPA was found to be effective in alleviating the motor defects in these patients, and rapidly became the premier symptomatic agent for treating PD and related conditions (reviewed in REF. 35).

However, most patients who are chronically treated with L-DOPA develop disabling motor and psychiatric adverse effects, such as dyskinesia and hallucinations, which are at least partly attributable to the non-physiological pulsatile striatal receptor stimulation that is caused by the intermittent oral administration of this agent[36]. Therefore, since the 1970s, various therapeutic strategies have been developed to produce a more physiological striatal stimulation, including[37]: new formulations of L-DOPA (for example, slow-release formulations); novel routes of administration for this drug (for example, intestinal infusion); brain-permeant agonists with distinct affinity profiles for dopamine receptor subtypes that have been isolated and characterized[38]; focal dopamine delivery systems that use cell-based and viral vector-based therapies; and intracerebral injection and viral vector-based delivery of trophic factors, such as glia cell-derived neurotrophic factor or neurturin, to boost both the viability and the function of compromised dopaminergic neurons.

Animal models of PD, in particular rodents that are unilaterally lesioned with the neurotoxin 6-hydroxydopamine (6-OHDA), have been instrumental in confirming that many of these strategies are effective at reversing the motor abnormalities that are related to striatal dopamine deficits[4]. This reactive oxygen species-generating neurotoxic model of PD, which was the first to be associated with dopaminergic neuronal death in the SNpc[39], remains popular for preclinical assessment of the anti-parkinsonism properties of new drugs and the benefits of transplantation or gene therapy to repair the damaged pathway[4]. Indeed, this model is valuable because unilateral 6-OHDA lesions induce an asymmetric circling behaviour in animals, the magnitude of which depends on the extent of the nigrostriatal lesion and is quantifiable[40]. Among this trove of therapeutic strategies, the more than 30-year history of the transplantation of neural cells, including induced pluripotent stem cell-derived dopaminergic neurons, in PD[41] provides a clear illustration of the kind of technical prowess and amazing innovations that underpin the search for treatments for PD that have no adverse effects. However, none of these approaches compares to the post-L-DOPA breakthrough in the symptomatic management of PD achieved by stereotaxic ablative procedures, which were rapidly supplanted by deep brain stimulation (DBS), the importance of which was saluted by the attribution of the 2014 Lasker–DeBakey Clinical Medical Research Award to Mahlon R. DeLong and Alim Louis Benabid.

Even though more investigations remain to be carried out to completely expose the secrets of basal ganglia function (see below), dysfunction of the basal ganglia–thalamo–cortical circuit (FIG. 2) may explain some of the motor defects that are seen in PD. As early as the mid-1900s, researchers recognized that discrete lesions of the basal ganglia improve parkinsonism[42]. However, it was not until the seminal demonstration that parkinsonism can be abrogated in a monkey model of PD through the chemical destruction of the subthalamic nucleus (STN)[43] and the unravelling of the core functional neuroanatomy of the basal ganglia (FIG. 2), that the revolutionary strategy of targeting the STN or the globus pallidus internal segment (GPi) with DBS began to be applied to patients. This treatment often led to a degree of symptomatic improvement that had not been seen since the introduction

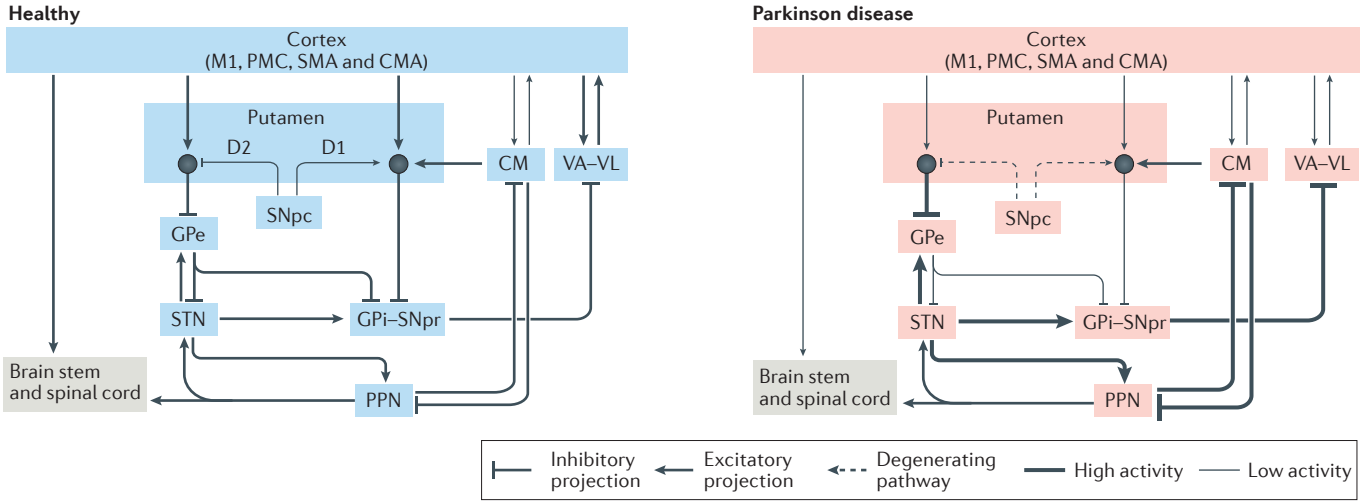


Figure 2 | **Direct and indirect pathways of the basal ganglia motor circuits in health and parkinsonism.** Under healthy conditions, substantia nigra pars compacta (SNpc) dopaminergic neurons activate the D1 dopamine receptor-expressing striatal projecting neurons of the direct pathway and inhibit the D2-expressing striatal projecting neurons of the indirect pathway. Once activated by the cortex and the SNpc, the direct pathway inhibits the globus pallidus internal segment (GPi)–substantia nigra pars reticulata (SNpr). Once the indirect pathway is activated by the cortex (and to a lesser extent inhibited by the SNpc), it inhibits the globus pallidus external segment (GPe), which inhibits the subthalamic nucleus (STN) and the GPi–SNpr. These inputs to the GPi–SNpr together cause a net decrease in inhibition to the thalamus. As the thalamus activates the motor cortex itself, it can be concluded that an increase in activity in the SNpc may promote motor activity. However, in Parkinson disease, degeneration of the SNpc will decrease the activation of the direct pathway and the inhibition of the indirect pathway. This striatal imbalance will cause an increase in STN-mediated activation and a decrease in GPe-mediated inhibition of the GPi–SNpr, which, in turn, will exert a much stronger inhibition of the thalamus, resulting in a lower activation of the motor cortex. Thus, the loss of SNpc input to the striatum leads to a decrease in motor activity. CM, centromedian nucleus; CMA, cingulate motor area; M1, primary motor cortex; PMC, pre-motor cortex; PPN, pedunculopontine nucleus; SMA, supplementary motor area; VA–VL, ventral anterior–ventral lateral nucleus. Adapted with permission from REF. 37, Macmillan Publishers Limited.

of L-DOPA[37]. DBS suppresses the excessive synchronized oscillation in nuclei of the basal ganglia[44] and reduces the phase-amplitude coupling in the motor cortex that is recorded in patients with PD[45], which suggests that the high-frequency current delivered to the STN or GPi by the DBS electrodes may produce symptomatic benefits by alleviating a PD-related pathological synchrony[44]. Currently, targets other than the STN or GPi, such as the pedunculopontine nucleus[37], and closed-loop devices[46] are being tested to produce even better and more personalized control of parkinsonism through DBS.

In parallel with the above studies, several investigators set out to elucidate how the basal ganglia mediate voluntary movement, by studying patients using various functional imaging modalities, such as positron emission tomography[47], as well as healthy animals and animal models of PD using a range of innovative approaches. Indeed, from the late 1970s onwards, novel behavioural paradigms and electrophysiological approaches have been combined with experimental tools, such as neurotoxins, viral neuronal tracers and optogenetics, to probe the functional anatomy of the basal ganglia in rodents and monkeys. Initially, the emphasis was placed on elucidating the molecular basis of the dopamine responsiveness of striatal neurons. These investigations led to the discovery that striatal neurons respond to dopamine through the activation of various dopamine receptors, mainly the D1 and D2 subtypes[48], and also revealed the subsequent engagement of signal transduction pathways involving dopamine- and cAMP-regulated neuronal phosphoprotein (DARPP-32; also known as PPP1R1B)[49]. Additional ground-breaking studies[50–52] revealed that the striatum (the main input nucleus of the basal ganglia) contains mostly GABAergic spiny neurons, which project either directly to the substantia nigra pars reticulata (SNr; the main output nucleus) or indirectly to the SNr through the globus pallidus external segment (GPe). One study[53] found that the majority of striatonigral neurons express substance P and the D1 dopamine receptor, whereas the majority of striatopallidal neurons express the peptide enkephalin and the D2 dopamine receptor, segregating D1 and D2 dopamine receptors between the striatal direct and indirect pathways. This finding has prompted the development of engineered mouse lines that, through the expression of Cre recombinase or channelrhodopsin under the control of either the D1 or the D2 dopamine receptor promoter, enable the specific modulation of the striatal direct or indirect pathway in living animals (as shown in REF. 54).

Furthermore, this remarkable neurochemical and anatomical segregation, coupled with electrophysiological and behavioural investigations (FIG. 2), led scientists to surmise that the direct striatal pathway probably facilitates movement (that is, it acts as a 'go' pathway), whereas the indirect striatal pathway suppresses movements (that is, it acts as a 'no go' pathway)[55]. This opponent model is consistent with some experiments in awake, moving animals[54], but alternative views have also been put forward. For example, some studies have argued that the direct and indirect pathways are not alternatively active but are concomitantly active during movement initiation and that they behave differently during the performance of a motor task[56], and that the pattern of coordinated activity across these two pathways, rather than the relative amount of activity, regulates movement initiation and execution[57]. In both of these models, disruption of dopamine-modulated basal ganglia circuits would be expected to result in the disruption of action initiation, which could explain the paucity of voluntary movements in PD.

Nevertheless, how does one explain the slowness of movement that is so characteristic of PD? A recent study in mice that were carrying out a task requiring substantial,

intentional variation in movement velocity showed that the activity of dorsal striatal neurons represented movement velocity in a graded manner[58]. In a mouse model of PD, animals that experience progressive dopamine depletion exhibit both a persistent reduction in movement velocity and a concomitant loss of the dorsal striatal representation of movement velocity[58]. Furthermore, dopaminergic signalling has been shown to control how the basal ganglia learn to modulate the velocity of movements[59,60]. Thus, the disruption of this velocity-controlling function of dopamine-modulated basal ganglia circuits could underlie the slowness of movement that is observed in patients with PD.

A mitochondrial cytopathy?

The discovery of evidence for a role for mitochondrial defects in PD was both surprising and serendipitous. In the late 1970s and early 1980s, several young people with drug addictions were found to have developed an acute syndrome that was almost indistinguishable from PD following the self-injection of 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP), which is a by-product of the synthesis of an opioid analogue[61,62]. The remarkable similarity between MPTP-induced parkinsonism and PD prompted researchers to investigate the mechanism of action of this neurotoxin. From 1984 onwards, a host of seminal papers established that MPTP-induced toxicity results from a complex, multistep process that culminates in the concentration of 1-methyl-4-phenylpyridinium ion, the active metabolite of MPTP, in the mitochondrial matrix and the subsequent inhibition of complex I of the electron transport chain (reviewed in REF. 4). These findings raised the question of whether a similar deficit might be involved in PD pathogenesis. Sure enough, a few years later, a study found that, in post-mortem brain tissue from patients with PD, the SN exhibited a marked decrease in complex I activity[63,64].

As PD is a chronic condition, acute exposure to a mitochondrial poison was unlikely to be responsible for this disease, but it was conceivable that a genetic mutation could have a similar effect on mitochondrial respiration. The initial reports of neurological disorders caused by mutations in complex I genes (reviewed in REF. 65) included evidence that some — for example, mutations in *NDUFV2* (NADH:ubiquinone oxidoreductase core subunit V2), which is transcribed in the nucleus — were associated with PD[66], and that accumulations of large-scale deletions of mitochondrial DNA were found in spared SNpc neurons in patients with PD[67,68]. Moreover, certain polymorphisms in genes that encode subunits of complex I might enhance susceptibility to PD, but only in specific subgroups of individuals[69,70]. As all mitochondrial DNA originates from the ovum, the mitochondrial cytopathy hypothesis predicts that PD should be maternally inherited. Currently, there is some epidemiological support for a maternal inheritance pattern, but only in a subset of patients with PD[71,72].

Thus far, there have been no cases of 'true' PD linked to a mitochondrial gene mutation. However, a point mutation (A1555G) in the 12S rRNA gene has been implicated in maternally inherited deafness associated with L-DOPA-responsive parkinsonism[73]. Similarly, a distinct heteroplasmic, maternally inherited 12S rRNA gene point mutation (T1095C) was found in another pedigree whose members presented with deafness, L-DOPA-responsive parkinsonism and neuropathy[74]. However, these mutations were not found in 20 cases of sporadic PD[74], which suggests that the 12S rRNA gene mutations are not likely to be a common cause of PD. Clearly, when parkinsonism is attributed to one of these rare mitochondrial DNA mutations, it is part of a multi-system clinical picture. This conclusion also holds true for patients who have mitochondrial DNA mutations secondary to defects in the proteins that are responsible for the integrity of the genome of this organelle, such as mitochondrial DNA polymerase-γ[75].

Quality-control deficits

By the mid-1990s, there were serious concerns regarding the hypothesis that a deficit in mitochondrial respiration was the primary mechanism of PD. One such concern was that mitochondrial diseases are typically paediatric conditions that have a short lifespan expectancy (<40 years), whereas many patients with PD live much longer than that[65]. However, the mitochondrial hypothesis continues to drive provocative lines of research. In the past decade, several genetic loci that have gene products that are associated with mitochondria have been linked to familial PD[65]. Interestingly, none has direct connections to mitochondrial respiration; rather, they seem to be involved in the quality-control mechanism that protects against defective mitochondria.

Evidence for the connection between PD and mitochondrial quality-control defects stems from studies of loss-of-function mutations in *PARK2*, which encodes parkin. Such mutations are known to cause a recessive-inherited form of parkinsonism[76]. In general, *PARK2* mutations are found in patients with PD who experience an early onset of symptoms (before the age of 30), particularly those with a family history that is consistent with recessive inheritance[77]. Attempts to recapitulate parkin loss of function in mice have not succeeded in producing a PD-like phenotype[78], although flies engineered so that they did not express this protein exhibited mitochondrial abnormalities[79,80]. It is still unclear exactly how *PARK2* mutations lead to dopaminergic neuron degeneration, but we now know that parkin normally functions as an E3 ubiquitin ligase[81,82]. One of the substrates of parkin is parkin-interacting substrate (PARIS; also known as ZNF746), which represses peroxisome proliferator-activated receptor-γ co-activator 1α (PGC1α)[83]. This suggests that parkin may indirectly regulate mitochondrial respiration, as PGC1α has a role in mitochondrial biogenesis[84]. However, the majority of the attention has been directed towards the observation that parkin, which is a primarily cytosolic protein, can translocate to dysfunctional mitochondria, where it participates in the destruction of these defective organelles[65].

Parkin participates in the macro-autophagy of defective mitochondria in a process that is dependent on the mitochondrial serine/threonine protein kinase PINK1 (REFS 85–87). *PINK1* mutations, similarly to those found in *PARK2,* are linked to a recessive form of PD that is probably caused by a loss of gene function[88]. In flies, the deletion of *pink1* recapitulates the same mitochondrial abnormalities that are observed in *parkin*-null flies, and the *pink1*-null phenotype can be rescued by parkin overexpression[89,90]. Thus, on the basis of both clinical similarities and genetic interactions, it seems that parkin and PINK1 operate in the same molecular pathway. Indeed, overexpression of parkin leads to a loss of mitochondria owing to an increase in mitophagy[91] — an effect that requires the presence of PINK1 (REF. 85).

A clear pathogenic scenario has emerged from these observations. Dysfunctional mitochondria spontaneously arise in postmitotic cells, such as neurons, and, under normal circumstances, are eliminated by the parkin–PINK1 quality-control mechanism. However, if *PARK2* and/or *PINK1* are mutated, defective mitochondria accumulate, ultimately causing neuronal dysfunction and cell death. Further strengthening the potential importance of a defect in mitochondrial quality control in PD, some reports show

that both vacuolar protein sorting-associated protein 13C (VPS13C) and F-box only protein 7 (FBXO7) interact with this parkin–PINK1 machinery, and mutations in *VPS13C* and *FBXO7* have been linked to familial forms of the disease[92,93].

A link between PD pathogenesis and a defect in another quality-control mechanism, namely, proteostasis, has arisen from work on the protein α-synuclein. Five missense mutations (A30P, E46K, H50Q, G51N and A53T) in the α-synuclein gene (*SNCA*) have been linked to a dominantly inherited form of PD[94–98]. The recognition that this presynaptic protein is abundant in Lewy bodies[99] prompted many researchers to suggest that α-synuclein-mediated neurotoxicity stems from a propensity to misfold and to form oligomers and protofibrils[100]. Interestingly, *SNCA* mutations have not been found in patients with sporadic PD[101], although the protein has been found in Lewy bodies in these individuals[102]. Moreover, the multiplication of *SNCA* also causes an autosomal dominant PD phenotype[103–105], which suggests that the cytotoxic effect of mutant α-synuclein is not a newly acquired property, but an enhancement of a native property that then causes disease pathology. Although how this gain of function results in PD phenotypes remains to be established, there is a growing enthusiasm for the idea that neurodegeneration in PD may arise from the failure of misfolded proteins, such as mutated α-synuclein, to be cleared in a timely manner. Indeed, it is thought that the mechanisms of protein quality control (that is, proteasome activity, chaperone activity and autophagy) may decrease in effectiveness with age and, consequently, cannot cope with the additional load of misfolded protein that is caused by either mutation or post-translation modification (for example, oxidative damage).

Genes versus the environment

It may come as a surprise that the possible heritability of PD was raised as early as the turn of the twentieth century by the British neurologist William Gowers[106]. This idea was subsequently supported by the finding that individuals whose first-degree relatives had PD were ~twofold more likely to develop this disease than those with no family history of PD[107]. However, there was also evidence for an environmental basis of PD, as clusters of parkinsonism were observed that seemed to be linked to various environmental scenarios. Specifically, there have been clusters linked to the influenza epidemic[5], the consumption of *Cycas micronesica* seeds by the indigenous peoples of Guam[108] and the self-injection of MPTP[61,62]. Numerous epidemiological studies have linked an increased risk of PD to the consumption of well water, living in rural areas, and exposure to herbicides and pesticides[109]. Coffee consumption and cigarette smoking have also been inversely associated with PD[110]. The accumulation of such findings supports the idea that environmental factors may contribute to susceptibility to PD, although no single factor has been identified as the sole culprit. In fact, it may be the case that a particular combination of toxins effectively promotes PD. Thiruchelvam and collaborators[111] note that the agricultural fungicide manganese ethylenebisdithiocarbamate has been implicated in some cases of PD-like syndromes and shows a striking geographic overlap with the widely used herbicide paraquat[4]. In this case, it may be the combination of paraquat and manganese ethylenebisdithiocarbamate, and possibly also rotenone[112], that is to blame for the PD-like condition.

The environmental hypothesis increased in popularity until the discovery in 1997 that the missense mutations in *SNCA* cause a rare form of familial PD. This finding triggered a true conceptual shift towards the idea that PD has a genetic basis. Subsequent discoveries also linked genetic mutations to familial forms of PD, with phenotypes inherited as either autosomal recessive or dominant traits[113]. Is there anything that can be said about the genetic basis of sporadic PD? Remarkably, mutations in *PARK2* and *LRRK2* (leucine rich repeat serine/threonine protein kinase 2) that are identical to those linked to familial PD have been found in some cases of sporadic PD, despite the apparent absence of family history[114,115]. Large-scale epidemiological studies have also revealed several pieces of evidence that support the genetic hypothesis, including single-nucleotide polymorphisms in *MAPT*, which encodes tau, that are associated with PD susceptibility[116], and specific apolipoprotein E genotypes and linkage with probably more than one gene on chromosome 1p that influence the age at onset of PD[117,118]. Furthermore, heterozygosity for mutations in the glucosylceramidase gene (*GBA*) was found to predispose individuals to PD[119], and it has been reported that the altered expression levels of several non-coding small RNA species (microRNAs) are of importance in PD[120].

Some genetic studies actually report findings that argue against a role for a genetic component in sporadic PD. For example, studies of monozygotic twins show a lack of concordance for the disease[121], although such studies need to be interpreted in light of the fact that twins may be clinically discordant for PD for up to 20 years[122]. Moreover, a genome-wide complex trait analysis[123] revealed that the heritable component of PD is at least 30%. Interestingly, the 28 risk loci that have been found[124] so far only account for ~15% of the heritable component, which suggests that there are numerous additional loci to be found. The correlate of this idea is that in PD there may be numerous common variants of small effect that may be necessary, but perhaps not sufficient, to bring about this complex phenotype. Could the legendary gene-versus-environment distinction be a false dichotomy and could they in fact work together?

The above discussion covers one example of the new kind of hypotheses that emerged from the remarkable contribution of genetics to PD research. Indeed, the fact that sporadic and familial forms of PD are phenotypically indistinguishable has raised the hypothesis that they may share common underlying mechanisms, despite having, perhaps, very different causes. In support of this view, a study found genes that had previously been linked to familial PD, such as *SNCA*, *LRRK2* and *VPS13C*, among the risk loci identified for sporadic PD[125]. Furthermore, the fact that familial PD can be caused by mutations in multiple distinct genes raises the possibility that the functions of the affected genes overlap or interact through common pathways. In addition, and perhaps most importantly, post-mortem brain tissue from patients with PD who had *PARK8* mutations exhibited a remarkable neuropathological heterogeneity[126], and α-synuclein can adopt different pathological conformations that cause different neurotoxic phenotypes[127]. These facts suggest that although the clinical phenotype-based classification scheme of neurodegenerative diseases is useful, it may be helpful, or perhaps essential, that we acknowledge that various neurodegenerative disorders may represent different expressions of common fundamental problems. Finally, mutations that cause PD are already expressed on the first day of life, whereas the manifestations of the disease emerge only in adults, leading to the provocative view that PD, rather than being labelled a neurodegenerative disease, might be a neurodevelopmental disorder, in which chronic but insidious deficits are masked by compensatory mechanisms that eventually fail with age. Collectively, the aforementioned new ideas — mostly driven by genetic findings — provide compelling evidence for an ongoing revolution in our understanding of the molecular pathophysiology of PD.

Progression of disease

Although the above discussion primarily focuses on cell-autonomous mechanisms of neurodegeneration in PD, the unique pathological progression of the disease suggests a role for non-cell autonomous mechanisms. Two such mechanisms have been put forward for PD. First, there is the idea that neuroinflammation, which involves a series of immune-mediated cascading events that are triggered by the loss of dopaminergic neurons, may facilitate further degeneration. In studies in animal models of PD, there is a large body of evidence indicating that glial cells, especially microglia, readily adopt a pro-inflammatory phenotype that is associated with the release of cytotoxic molecules and ensuing enhanced neurodegeneration[128]. However, thus far, there is only suggestive evidence linking PD to neuroinflammation. Indeed, the loss of dopaminergic neurons in post-mortem PD brains is associated with microgliosis and, to a lesser extent, astrocytosis[129–132]. Furthermore, activated microglial cells are predominantly found in proximity to free neuromelanin in the neuropil, and these cells sometimes cluster around remaining neurons, producing an image of neuronophagia[129]. Although tantalizing, none of these findings proves a causal role of neuroinflammation in PD pathogenesis. Nonetheless, the mere association of PD with indices of neuroinflammation has prompted preclinical and clinical immunotherapeutic trials using both passive and active immunization strategies, especially against α-synuclein[133], as potential new approaches to disease modification.

The second idea pertains to the hypothesis that there may be some mechanism by which protein pathology is 'transmitted' throughout the brain in PD. This view stems from two initial observations[134]: first, 10–15% of embryonic ventral midbrain neurons that survived for decades after being grafted in the striatum of patients with PD exhibited α-synuclein-positive inclusions that were reminiscent of Lewy bodies[41]; and, second, abnormal α-synuclein immunostaining in PD brains seemed to follow a stereotypical pattern of distribution[135]. These data have been seen by many as providing compelling impetus to the notion that misfolded α-synuclein can be transferred from an affected neuron to a previously healthy neuron through a 'prion-like' process. Indeed, preformed fibrils generated from full-length and truncated recombinant α-synuclein can enter primary neurons by endocytosis through binding to the surface motif lymphocyte-activation gene 3 (LAG3)[136], and can recruit soluble endogenous α-synuclein into insoluble inclusions that are suggestive of Lewy bodies[137]. This study also demonstrated that the accumulation of pathological α-synuclein can lead to decreases in synaptic protein levels, progressive impairments in neuronal excitability and connectivity, and, ultimately, neuronal death[137]. However, whether a similar pathogenic scenario occurs in patients with PD remains to be established[134].

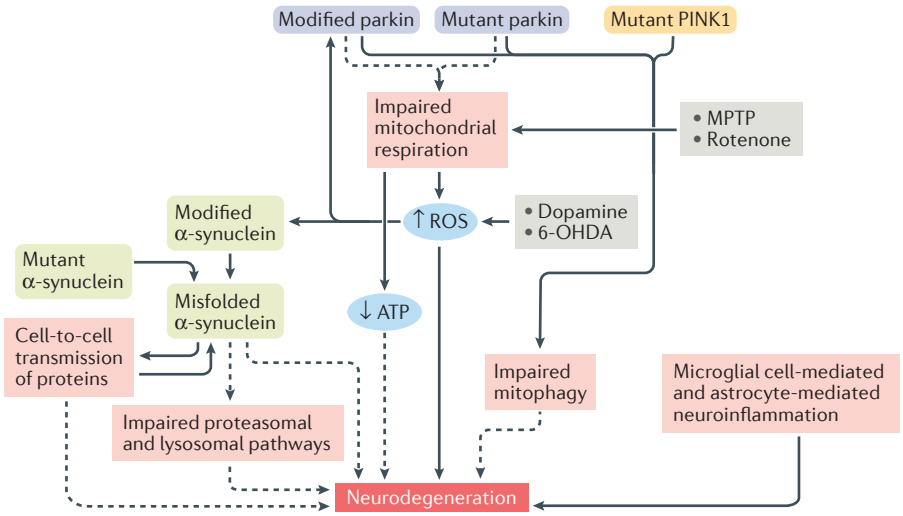


Figure 3 | **Potential pathogenic mechanisms involved in Parkinson disease.** Various mechanisms have been proposed to contribute to Parkinson disease (PD). This schematic only includes some of these mechanisms, primarily to highlight the emerging directions in PD research and the multifactorial nature of the envisioned neurodegenerative cascade. Solid arrows represent established processes, whereas dashed arrows signify hypothesized links. Quality-control mechanisms for proteins and organelles, such as the mitochondria, on becoming defective, may be crucial determinants of the PD disease process. Defects in protein quality-control mechanisms may be precipitated by the misfolding of proteins such as α-synuclein. Indeed, once misfolded, proteins may overload the ubiquitin-proteasome and lysosomal degradation pathways, thus hampering the ability of the cellular machinery to detect and degrade undesired proteins. Protein misfolding may result from gene mutations or post-translational modifications induced by, for example, reactive oxygen species (ROS). Of note, ROS by themselves can cause broad cellular damage, and hence can directly contribute to neurodegeneration, and can be generated through the oxidation of dopamine, by environmental toxins that behave similarly to 6-hydroxydopamine (6-OHDA), and by mitochondrial repair defects. Notably, proteins that are prone to misfolding, such as α-synuclein, seem to be capable of travelling from cell to cell, hence propagating protein misfolding and the disease process. Other mutant and modified proteins, such as parkin and PINK1, may lack their wild-type function. Defects in the function of one or both of these proteins would alter mitochondrial turnover by macro-autophagy (mitophagy), thus hampering the ability of the cellular machinery to detect and degrade dysfunctional mitochondria. Alterations in these two quality-control mechanisms may lead to the accumulation of unwanted proteins and mitochondria, which, by unknown mechanisms, may lead to neurodegeneration. Defective parkin can, in an indirect manner through peroxisome proliferator-activated receptor-γ co-activator 1α (PGC1α), affect mitochondrial respiration, which, through a distinct mechanism, is also the target of two known neurotoxins: 1-methyl-4 phenyl-1,2,5,6-tetrahydropyridine (MPTP) and rotenone. A defect in mitochondrial respiration can increase the level of ROS and decrease ATP production, and hence can lead to potentially pathogenic cellular oxidative stress and an energy crisis. Although these different cell-autonomous molecular alterations are taking place within degenerating neurons, neighbouring glial cells, especially astrocytes and microglia, may adopt a pro-inflammatory phenotype, which, through the production of a host of cytotoxic molecules, enhances the level of stress on compromised neurons that are present in their vicinity, thereby promoting degeneration.

Conclusions

Needless to say, the advances in our understanding of PD in the past 200 years have been remarkable, and PD research is still advancing rapidly on several fronts: circuit-level investigations, new experimental treatments, molecular studies, and human studies based on genetics, pathology and brain-imaging techniques. Unfortunately, despite major breakthroughs in our understanding of the disease, we still do not have an effective treatment. For the most part, research findings have forced us to expand our thinking in terms of the possible aetiologies and pathogenic and pathophysiological processes of PD (FIG. 3).

Indeed, a combination of environmental and genetic factors may determine who develops the disease. Moreover, its unique pattern of progression suggests some form of cell-to-cell transmission within the brain (FIG. 3), which, in turn, not only kills specific subsets of neurons, but also compromises specific neuronal circuits. Although unravelling this puzzle may be daunting at first glance, this complexity will hopefully provide multiple opportunities for the treatment, or even the prevention, of the debilitating effects of PD. I predict that the development of such treatments or preventive measures will depend on a sound understanding of the interactions among the various environmental, genetic, cellular, molecular and physiological mechanisms that are involved to reach an integrated view of the multifaceted nature of PD (FIG. 3) that must extend beyond the CNS, as implied by the potential role of the gut microbiome in PD neurodegeneration[138] and the demonstration that systemic administration of pathological α-synuclein can gain access to the brain[127]. At this juncture, it may be speculated that mitochondrial dysfunction, oxidative stress and the mishandling of damaged proteins and mitochondria are tightly interconnected pathogenic factors, that, in combination, drive the demise of specific subsets of neurons in PD (FIG. 3). Although these different alterations are taking place within degenerating neurons, neighbouring glial cells, especially astrocytes and microglia, may be mounting a neuroinflammatory response (FIG. 3), supporting the idea that PD may be caused by the conjunction of both cell-autonomous and non-cell-autonomous processes. Thus, although this hypothetical multifactorial pathogenic view of PD may be appealing, we must maintain the momentum of the progress made over the past 200 years, not only to confirm this vision, but also to understand why the proposed pathogenic cascade kills only specific types of neurons in PD.

Serge Przedborski is at the Departments of Neurology, Pathology, and Cell Biology, College of Physicians and Surgeons, Columbia University, New York, New York 10032, USA.
sp30@cumc.columbia.edu

doi:10.1038/nrn.2017.25
Published online 17 Mar 2017

1. Parkinson, J. *An Essay on the Shaking Palsy* (Whittingham and Rowland, 1817).
2. Goetz, C. G. The history of Parkinson's disease: early clinical descriptions and neurological therapies. *Cold Spring Harb. Perspect. Med.* **1**, a008862 (2011).
3. Charcot, J. M. in *Oeuvres Complètes (Tome 1). Leçons sur les Maladies du Système Nerveux* (eds Delahaye, A. & Lecrosnier, E.) 155–188 (in French) (Bureaux du Progrès Médical, 1872).
4. Dauer, W. & Przedborski, S. Parkinson's disease: mechanisms and models. *Neuron* **39**, 889–909 (2003).
5. Casals, J., Elizan, T. S. & Yahr, M. D. Postencephalitic parkinsonism — a review. *J. Neural Transm. (Vienna)* **105**, 645–676 (1998).
6. Economo, C. V. *Encephalitis Lethargica: its Sequelae and Treatment* (Oxford Univ. Press, 1931).
7. Kalia, L. V. & Lang, A. E. Parkinson's disease. *Lancet* **386**, 896–912 (2015).
8. Postuma, R. B. & Berg, D. Advances in markers of prodromal Parkinson disease. *Nat. Rev. Neurol.* **12**, 622–634 (2016).
9. Blocq, C. & Marinescu, G. Sur un cas de tremblement parkinsonien hémiplégique symptomatique d'une tumeur du pédoncule cérébral. *C. R. Cos. Biol.* **45**, 105–111 (in French) (1893).
10. Brissaud, E. *Leçons sur les Maladies Nerveuses* Vol. 2 (in French) (Masson, 1899).
11. Trétiakoff, C. *Contribution à l'étude de l'anatomie pathologique du locus niger de Soemmering avec quelques deductions relatives a la pathogenie des troubles du tonus musculaire et de la maladie de Parkinson* (in French) (Université de Paris, 1919).
12. Marsden, C. D. Neuromelanin and Parkinson's disease. *J. Neural Transm. Suppl.* **19**, 121–141 (1983).
13. Lewy, F. Zur pathologischen Anatomie der Paralysis agitans. *Dtsch. Z. Nervenheilk* **50**, 50–55 (in German) (1913).
14. Shults, C. W. Lewy bodies. *Proc. Natl Acad. Sci. USA* **103**, 1661–1668 (2006).
15. Wilson, S. A. K. Progressive lenticular degeneration: a familial nervous disease associated with cirrhosis of the liver. *Brain* **34**, 295–509 (1912).
16. Anden, N. E., Dahlstroem, A., Fuxe, K. & Larsson, K. Further evidence for the presence of nigro-neostriatal dopamine neurons in the rat. *Am. J. Anat.* **116**, 329–333 (1965).
17. Anden, N. E. *et al.* Demonstration and mapping out of nigro-neostriatal dopamine neurons. *Life Sci.* **3**, 523–530 (1964).
18. Poirier, L. J. & Sourkes, T. L. Influence of the substantia nigra on the catecholamine content of the striatum. *Brain* **88**, 181–192 (1965).
19. Goldstein, M., Anagnoste, B., Owen, W. S. & Battista, A. F. The effects of ventromedial tegmental lesions on the biosynthesis of catecholamines in the striatum. *Life Sci.* **5**, 2171–2176 (1966).
20. Dahlström, A. & Fuxe, K. Evidence for the existence of monoamine-containing neurons in the central nervous system. I. Demonstration of monoamines in the cell bodies of brain stem neurons. *Acta Physiol. Scand. Suppl.* **232**, 1–55 (1964).
21. Hassler, R. Zur Pathologie der Paralysis agitans und des postenzephalitischen Parkinsonismus. *J. Psychol. Neurol.* **48**, 387–476 (in German) (1938).
22. Greenfield, J. G. & Bosanquet, F. D. The brain-stem lesions in Parkinsonism. *J. Neurol. Neurosurg. Psychiatry* **16**, 213–226 (1953).
23. Hirsch, E., Graybiel, A. M. & Agid, Y. A. Melanized dopaminergic neurons are differentially susceptible to degeneration in Parkinson's disease. *Nature* **334**, 345–348 (1988).
24. Fahn, S. & Cohen, G. The oxidant stress hypothesis in Parkinson's disease: evidence supporting it. *Ann. Neurol.* **32**, 804–812 (1992).
25. Fearnley, J. M. & Lees, A. J. Ageing and Parkinson's disease: substantia nigra regional selectivity. *Brain* **114**, 2283–2301 (1991).
26. Braak, H. *et al.* Nigral and extranigral pathology in Parkinson's disease. *J. Neural Transm. Suppl.* **46**, 15–31 (1995).
27. Montagu, K. A. Catechol compounds in rat tissues and in brains of different animals. *Nature* **180**, 244–245 (1957).
28. Carlsson, A., Lindquist, M., Magnusson, T. & Waldeck, B. On the presence of 3-hydroxytyramine in brain. *Science* **127**, 471–471 (1958).
29. Bertler, A. & Rosengren, E. Occurrence and distribution of dopamine in brain and other tissues. *Experientia* **15**, 10–11 (1959).
30. Sano, I. *et al.* Distribution of catechol compounds in human brain. *Biochim. Biophys. Acta* **32**, 586–587 (1959).
31. Carlsson, A. The occurrence, distribution and physiological role of catecholamines in the nervous system. *Pharmacol. Rev.* **11**, 490–493 (1959).
32. Carlsson, A., Lindqvist, M. & Magnusson, T. 3,4-Dihydroxyphenylalanine and 5-hydroxytryptophan as reserpine antagonists. *Nature* **180**, 1200 (1957).
33. Sano, I. Biochemistry of the extrapyramidal system. *Shinkei Kennkyu No Shinpo* **5**, 42–48 (in Japanese) (1960).
34. Ehringer, H. & Hornykiewicz, O. Verteilung von noradrenalin und dopamin (3-hydroxytyramin) im gehirn des menschen und ihr verhalten bei erkrankungen des extrapyramidalen systems. *Klin. Wochenschr.* **38**, 1236–1239 (in German) (1960).
35. Fahn, S. The medical treatment of Parkinson disease from James Parkinson to George Cotzias. *Mov. Disord.* **30**, 4–18 (2015).
36. Olanow, C. W., Obeso, J. A. & Stocchi, F. Drug insight: continuous dopaminergic stimulation in the treatment of Parkinson's disease. *Nat. Clin. Pract. Neurol.* **2**, 382–392 (2006).
37. Smith, Y., Wichmann, T., Factor, S. A. & DeLong, M. R. Parkinson's disease therapeutics: new developments and challenges since the introduction of levodopa. *Neuropsychopharmacology* **37**, 213–246 (2012).
38. Missale, C., Nash, S. R., Robinson, S. W., Jaber, M. & Caron, M. G. Dopamine receptors: from structure to function. *Physiol. Rev.* **78**, 189–225 (1998).
39. Hokfelt, T. & Ungerstedt, U. Specificity of 6-hydroxydopamine induced degeneration of central monoamine neurones: an electron and fluorescence microscopic study with special reference to intracerebral injection on the nigro-striatal dopamine system. *Brain Res.* **60**, 269–297 (1973).
40. Ungerstedt, U. & Arbuthnott, G. Quantitative recording of rotational behaviour in rats after 6-hydroxydopamine lesions of the nigrostriatal dopamine system. *Brain Res.* **24**, 485–493 (1970).
41. Barker, R. A., Drouin-Ouellet, J. & Parmar, M. Cell-based therapies for Parkinson disease-past insights and future potential. *Nat. Rev. Neurol.* **11**, 492–503 (2015).
42. Meyers, R. The modification of alternating tremors, rigidity and festination by surgery of the basal ganglia. *Res. Publ. Assoc. Res. Nerv. Ment. Dis.* **21**, 602–665 (1942).
43. Bergman, H., Wichmann, T. & DeLong, M. R. Reversal of experimental parkinsonism by lesions of the subthalamic nucleus. *Science* **249**, 1436–1438 (1990).
44. Hammond, C., Bergman, H. & Brown, P. Pathological synchronization in Parkinson's disease: networks, models and treatments. *Trends Neurosci.* **30**, 357–364 (2007).
45. de Hemptinne, C. *et al.* Therapeutic deep brain stimulation reduces cortical phase-amplitude coupling in Parkinson's disease. *Nat. Neurosci.* **18**, 779–786 (2015).
46. Rosin, B. *et al.* Closed-loop deep brain stimulation is superior in ameliorating parkinsonism. *Neuron* **72**, 370–384 (2011).
47. Niethammer, M., Feigin, A. & Eidelberg, D. Functional neuroimaging in Parkinson's disease. *Cold Spring Harb. Perspect. Med.* **2**, a009274 (2012).
48. Gingrich, J. A. & Caron, M. G. Recent advances in the molecular biology of dopamine receptors. *Annu. Rev. Neurosci.* **16**, 299–321 (1993).
49. Walaas, S. I., Aswad, D. W. & Greengard, P. A dopamine- and cyclic AMP-regulated phosphoprotein enriched in dopamine-innervated brain regions. *Nature* **301**, 69–71 (1983).
50. DeLong, M. R. Primate models of movement disorders of basal ganglia origin. *Trends Neurosci.* **13**, 281–285 (1990).
51. Albin, R. L., Young, A. B. & Penney, J. B. The functional anatomy of basal ganglia disorders. *Trends Neurosci.* **12**, 366–375 (1989).
52. Crossman, A. R. Neural mechanisms in disorders of movement. *Comp. Biochem. Physiol. A Comp. Physiol.* **93**, 141–149 (1989).
53. Gerfen, C. R. *et al.* D1 and D2 dopamine receptor-regulated gene expression of striatonigral and striatopallidal neurons. *Science* **250**, 1429–1432 (1990).
54. Kravitz, A. V. *et al.* Regulation of parkinsonian motor behaviours by optogenetic control of basal ganglia circuitry. *Nature* **466**, 622–626 (2010).
55. Mink, J. W. in *Fundamental Neuroscience* Ch. 30 (eds Squire, L. R. *et al.*) 653–676 (Academic Press, 2013).
56. Jin, X., Tecuapetla, F. & Costa, R. M. Basal ganglia subcircuits distinctively encode the parsing and concatenation of action sequences. *Nat. Neurosci.* **17**, 423–430 (2014).
57. Tecuapetla, F., Jin, X., Lima, S. Q. & Costa, R. M. Complementary contributions of striatal projection pathways to action initiation and execution. *Cell* **166**, 703–715 (2016).
58. Panigrahi, B. *et al.* Dopamine is required for the neural representation and control of movement vigor. *Cell* **162**, 1418–1430 (2015).

59. Yttri, E. A. & Dudman, J. T. Opponent and bidirectional control of movement velocity in the basal ganglia. *Nature* **533**, 402–406 (2016).
60. Mazzoni, P., Hristova, A. & Krakauer, J. W. Why don't we move faster? Parkinson's disease, movement vigor, and implicit motivation. *J. Neurosci.* **27**, 7105–7116 (2007).
61. Langston, J. W., Ballard, P. & Irwin, I. Chronic parkinsonism in humans due to a product of meperidine-analog synthesis. *Science* **219**, 979–980 (1983).
62. Davis, G. C. *et al.* Chronic parkinsonism secondary to intravenous-injection of meperidine analogs. *Psychiatry Res.* **1**, 249–254 (1979).
63. Schapira, A. H. *et al.* Mitochondrial complex I deficiency in Parkinson's disease. *J. Neurochem.* **54**, 823–827 (1990).
64. Schapira, A. H. *et al.* Anatomic and disease specificity of NADH CoQ1 reductase (complex I) deficiency in Parkinson's disease. *J. Neurochem.* **55**, 2142–2145 (1990).
65. Schon, E. A. & Przedborski, S. Mitochondria: the next (neurode)generation. *Neuron* **70**, 1033–1053 (2011).
66. Nishioka, K. *et al.* Genetic variation of the mitochondrial complex I subunit NDUFV2 and Parkinson's disease. *Parkinsonism Relat. Disord.* **16**, 686–687 (2010).
67. Kraytsberg, Y. *et al.* Mitochondrial DNA deletions are abundant and cause functional impairment in aged human substantia nigra neurons. *Nat. Genet.* **38**, 518–520 (2006).
68. Bender, A. *et al.* High levels of mitochondrial DNA deletions in substantia nigra neurons in aging and Parkinson disease. *Nat. Genet.* **38**, 515–517 (2006).
69. Kosel, S. *et al.* Novel mutations of mitochondrial complex I in pathologically proven Parkinson disease. *Neurogenetics* **1**, 197–204 (1998).
70. van der Walt, J. M. *et al.* Mitochondrial polymorphisms significantly reduce the risk of Parkinson disease. *Am. J. Hum. Genet.* **72**, 804–811 (2003).
71. Wooten, G. F. *et al.* Maternal inheritance in Parkinson's disease. *Ann. Neurol.* **41**, 265–268 (1997).
72. Swerdlow, R. H. *et al.* Matrilineal inheritance of complex I dysfunction in a multigenerational Parkinson's disease family. *Ann. Neurol.* **44**, 873–881 (1998).
73. Shoffner, J. M., Brown, M. & Huoponen, K. A mitochondrial DNA (mtDNA) mutation associated with maternally inherited deafness and Parkinson's disease (PD). *Neurology* **46**, (2 Suppl.) A331 (1996).
74. Thyagarajan, D. *et al.* A novel mitochondrial 12SrRNA point mutation in parkinsonism, deafness, and neuropathy. *Ann. Neurol.* **48**, 730–736 (2000).
75. Luoma, P. *et al.* Parkinsonism, premature menopause, and mitochondrial DNA polymerase gamma mutations: clinical and molecular genetic study. *Lancet* **364**, 875–882 (2004).
76. Kitada, T. *et al.* Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism. *Nature* **392**, 605–608 (1998).
77. Mizuno, Y., Hattori, N., Mori, H., Suzuki, T. & Tanaka, K. Parkin and Parkinson's disease. *Curr. Opin. Neurol.* **14**, 477–482 (2001).
78. Goldberg, M. S. *et al.* Parkin-deficient mice exhibit nigrostriatal deficits but not loss of dopaminergic neurons. *J. Biol. Chem.* **278**, 43628–43635 (2003).
79. Palacino, J. J. *et al.* Mitochondrial dysfunction and oxidative damage in parkin-deficient mice. *J. Biol. Chem.* **279**, 18614–18622 (2004).
80. Greene, J. C. *et al.* Mitochondrial pathology and apoptotic muscle degeneration in *Drosophila* parkin mutants. *Proc. Natl Acad. Sci. USA* **100**, 4078–4083 (2003).
81. Shimura, H. *et al.* Familial Parkinson disease gene product, parkin, is a ubiquitin-protein ligase. *Nat. Genet.* **25**, 302–305 (2000).
82. Zhang, Y. *et al.* Parkin functions as an E2-dependent ubiquitin- protein ligase and promotes the degradation of the synaptic vesicle-associated protein, CDCrel-1. *Proc. Natl Acad. Sci. USA* **97**, 13354–13359 (2000).
83. Shin, J. H. *et al.* PARIS (ZNF746) repression of PGC-1alpha contributes to neurodegeneration in Parkinson's disease. *Cell* **144**, 689–702 (2011).
84. Austin, S. & St-Pierre, J. PGC1alpha and mitochondrial metabolism — emerging concepts and relevance in ageing and neurodegenerative disorders. *J. Cell Sci.* **125**, 4963–4971 (2012).
85. Vives-Bauza, C. *et al.* PINK1-dependent recruitment of Parkin to mitochondria in mitophagy. *Proc. Natl Acad. Sci. USA* **107**, 378–383 (2010).
86. Geisler, S. *et al.* PINK1/Parkin-mediated mitophagy is dependent on VDAC1 and p62/SQSTM1. *Nat. Cell Biol.* **12**, 119–131 (2010).
87. Narendra, D. P. *et al.* PINK1 is selectively stabilized on impaired mitochondria to activate Parkin. *PLoS Biol.* **8**, e1000298 (2010).
88. Valente, E. M. *et al.* Hereditary early-onset Parkinson's disease caused by mutations in PINK1. *Science* **304**, 1158–1160 (2004).
89. Clark, I. E. *et al. Drosophila* pink1 is required for mitochondrial function and interacts genetically with parkin. *Nature* **441**, 1162–1166 (2006).
90. Park, J. *et al.* Mitochondrial dysfunction in *Drosophila* PINK1 mutants is complemented by parkin. *Nature* **441**, 1157–1161 (2006).
91. Narendra, D., Tanaka, A., Suen, D. F. & Youle, R. J. Parkin is recruited selectively to impaired mitochondria and promotes their autophagy. *J. Cell Biol.* **183**, 795–803 (2008).
92. Burchell, V. S. *et al.* The Parkinson's disease-linked proteins Fbxo7 and Parkin interact to mediate mitophagy. *Nat. Neurosci.* **16**, 1257–1265 (2013).
93. Lesage, S. *et al.* Loss of VPS13C function in autosomal-recessive parkinsonism causes mitochondrial dysfunction and increases PINK1/Parkin-dependent mitophagy. *Am. J. Hum. Genet.* **98**, 500–513 (2016).
94. Polymeropoulos, M. H. *et al.* Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. *Science* **276**, 2045–2047 (1997).
95. Kruger, R. *et al.* Ala30Pro mutation in the gene encoding alpha-synuclein in Parkinson's disease. *Nat. Genet.* **18**, 106–108 (1998).
96. Zarranz, J. J. *et al.* The new mutation, E46K, of alpha-synuclein causes Parkinson and Lewy body dementia. *Ann. Neurol.* **55**, 164–173 (2004).
97. Lesage, S. *et al.* G51D alpha-synuclein mutation causes a novel Parkinsonian-pyramidal syndrome. *Ann. Neurol.* **73**, 459–471 (2013).
98. Proukakis, C. *et al.* A novel alpha-synuclein missense mutation in Parkinson disease. *Neurology* **80**, 1062–1064 (2013).
99. Spillantini, M. G. *et al.* Alpha-synuclein in Lewy bodies. *Nature* **388**, 839–840 (1997).
100. Lashuel, H. A., Overk, C. R., Oueslati, A. & Masliah, E. The many faces of alpha-synuclein: from structure and toxicity to therapeutic target. *Nat. Rev. Neurosci.* **14**, 38–48 (2013).
101. Munoz, E. *et al.* Identification of Spanish familial Parkinson's disease and screening for the Ala53Thr mutation of the alpha-synuclein gene in early onset patients. *Neurosci. Lett.* **235**, 57–60 (1997).
102. Spillantini, M. G., Crowther, R. A., Jakes, R., Hasegawa, M. & Goedert, M. Alpha-synuclein in filamentous inclusions of Lewy bodies from Parkinson's disease and dementia with Lewy bodies. *Proc. Natl Acad. Sci. USA* **95**, 6469–6473 (1998).
103. Singleton, A. B. *et al.* Alpha-synuclein locus triplication causes Parkinson's disease. *Science* **302**, 841 (2003).
104. Chartier-Harlin, M. C. *et al.* Alpha-synuclein locus duplication as a cause of familial Parkinson's disease. *Lancet* **364**, 1167–1169 (2004).
105. Ibanez, P. *et al.* Causal relation between alpha-synuclein gene duplication and familial Parkinson's disease. *Lancet* **364**, 1169–1171 (2004).
106. Gowers, W. R. (ed) *A Manual of Diseases of the Nervous System* 2nd edn (Blakiston, 1888).
107. Marder, K. *et al.* Risk of Parkinson's disease among first-degree relatives: a community-based study. *Neurology* **47**, 155–160 (1996).
108. Chen, K.-M. & Chase, T. N. in *Handbook of Clinical Neurology. Extrapyramidal disorders* Vol. 49 (eds Vinken, P. J., Bruyn, G. W. & Klawans, H. L.) 167–183 (Elsevier, 1986).
109. Tanner, C., Goldman, S. M. & Ross, G. W. in *Parkinson's Disease and Movement Disorders* Ch. 7 (eds Jankovic, J. & Tolosa, E.) 90–103 (Lippincott Williams & Wilkins, 2002).
110. Hernan, M. A., Takkouche, B., Caamano-Isorna, F. & Gestal-Otero, J. J. A meta-analysis of coffee drinking, cigarette smoking, and the risk of Parkinson's disease. *Ann. Neurol.* **52**, 276–284 (2002).
111. Thiruchelvam, M., Brockel, B. J., Richfield, E. K., Baggs, R. B. & Cory-Slechta, D. A. Potentiated and preferential effects of combined paraquat and maneb on nigrostriatal dopamine systems: environmental risk factors for Parkinson's disease? *Brain Res.* **873**, 225–234 (2000).
112. Betarbet, R. *et al.* Chronic systemic pesticide exposure reproduces features of Parkinson's disease. *Nat. Neurosci.* **3**, 1301–1306 (2000).
113. Trinh, J. & Farrer, M. Advances in the genetics of Parkinson disease. *Nat. Rev. Neurol.* **9**, 445–454 (2013).
114. Lucking, C. B. *et al.* Association between early-onset Parkinson's disease and mutations in the parkin gene. *N. Engl. J. Med.* **342**, 1560–1567 (2000).
115. Gilks, W. P. *et al.* A common LRRK2 mutation in idiopathic Parkinson's disease. *Lancet* **365**, 415–416 (2005).
116. Martin, E. R. *et al.* Association of single-nucleotide polymorphisms of the tau gene with late-onset Parkinson disease. *JAMA* **286**, 2245–2250 (2001).
117. Zareparsi, S. *et al.* Age at onset of Parkinson disease and apolipoprotein E genotypes. *Am. J. Med. Genet.* **107**, 156–161 (2002).
118. Li, Y. J. *et al.* Age at onset in two common neurodegenerative diseases is genetically controlled. *Am. J. Hum. Genet.* **70**, 985–993 (2002).
119. Aharon-Peretz, J., Rosenbaum, H. & Gershoni-Baruch, R. Mutations in the glucocerebrosidase gene and Parkinson's disease in Ashkenazi Jews. *N. Engl. J. Med.* **351**, 1972–1977 (2004).
120. Heman-Ackah, S. M., Hallegger, M., Rao, M. S. & Wood, M. J. RISC in PD: the impact of microRNAs in Parkinson's disease cellular and molecular pathogenesis. *Front. Mol. Neurosci.* **6**, 40 (2013).
121. Tanner, C. M. *et al.* Rotenone, paraquat, and Parkinson's disease. *Environ. Health Perspect.* **119**, 866–872 (2011).
122. Dickson, D. *et al.* Pathology of PD in monozygotic twins with a 20-year discordance interval. *Neurology* **56**, 981–982 (2001).
123. Keller, M. F. *et al.* Using genome-wide complex trait analysis to quantify 'missing heritability' in Parkinson's disease. *Hum. Mol. Genet.* **21**, 4996–5009 (2012).
124. Wood, A. R. *et al.* Imputation of variants from the 1000 Genomes Project modestly improves known associations and can identify low-frequency variant-phenotype associations undetected by HapMap based imputation. *PLoS ONE* **8**, e64343 (2013).
125. Nalls, M. A. *et al.* Large-scale meta-analysis of genome-wide association data identifies six new risk loci for Parkinson's disease. *Nat. Genet.* **46**, 989–993 (2014).
126. Zimprich, A. *et al.* Mutations in LRRK2 cause autosomal-dominant parkinsonism with pleomorphic pathology. *Neuron* **44**, 601–607 (2004).
127. Peelaerts, W. *et al.* Alpha-synuclein strains cause distinct synucleinopathies after local and systemic administration. *Nature* **522**, 340–344 (2015).
128. Przedborski, S. in *Handbook of Clinical Neurology. Parkinson's Disease and Related Disoders* Ch. 26 (eds Koller, W. C. & Melamed, E.) 535–551 (Elsevier, 2007).
129. McGeer, P. L., Itagaki, S., Boyes, B. E. & McGeer, E. G. Reactive microglia are positive for HLA-DR in the substantia nigra of Parkinson's and Alzheimer's disease brains. *Neurology* **38**,1285–1291 (1988).
130. Forno, L. S., DeLanney, L. E., Irwin, I., Di Monte, D. & Langston, J. W. Astrocytes and Parkinson's disease. *Prog. Brain Res.* **94**, 429–436 (1992).
131. Banati, R. B., Daniel, S. E. & Blunt, S. B. Glial pathology but absence of apoptotic nigral neurons in long-standing Parkinson's disease. *Mov. Disord.* **13**, 221–227 (1998).
132. Mirza, B., Hadberg, H., Thomsen, P. & Moos, T. The absence of reactive astrocytosis is indicative of a unique inflammatory process in Parkinson's disease. *Neuroscience* **95**, 425–432 (2000).
133. Valera, E., Spencer, B. & Masliah, E. Immunotherapeutic approaches targeting amyloid-beta, alpha-synuclein, and tau for the treatment of neurodegenerative disorders. *Neurotherapeutics* **13**, 179–189 (2016).
134. Walsh, D. M. & Selkoe, D. J. A critical appraisal of the pathogenic protein spread hypothesis of neurodegeneration. *Nat. Rev. Neurosci.* **17**, 251–260 (2016).
135. Braak, H. *et al.* Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol. Aging* **24**, 197–211 (2003).
136. Mao, X. *et al.* Pathological alpha-synuclein transmission initiated by binding lymphocyte-activation gene 3. *Science* **353**, aah3374 (2016).
137. Volpicelli-Daley, L. A. *et al.* Exogenous alpha-synuclein fibrils induce Lewy body pathology leading to synaptic dysfunction and neuron death. *Neuron* **72**, 57–71 (2011).
138. Sharon, G., Sampson, T. R., Geschwind, D. H. & Mazmanian, S. K. The central nervous system and the gut microbiome. *Cell* **167**, 915–932 (2016).

Acknowledgements
The author is supported by the US National Institutes of Health (NIH)/NIDS awards NS099862 and NS072428, DOD Award 13-1-0416 and from Target-ALS and the Project-ALS.

Competing interests statement
The author declares no competing interests.