Parkinson disease

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Abstract | Parkinson disease is the second-most common neurodegenerative disorder that affects 2–3% of the population ≥65 years of age. Neuronal loss in the substantia nigra, which causes striatal dopamine deficiency, and intracellular inclusions containing aggregates of α-synuclein are the neuropathological hallmarks of Parkinson disease. Multiple other cell types throughout the central and peripheral autonomic nervous system are also involved, probably from early disease onwards. Although clinical diagnosis relies on the presence of bradykinesia and other cardinal motor features, Parkinson disease is associated with many non-motor symptoms that add to overall disability. The underlying molecular pathogenesis involves multiple pathways and mechanisms: α-synuclein proteostasis, mitochondrial function, oxidative stress, calcium homeostasis, axonal transport and neuroinflammation. Recent research into diagnostic biomarkers has taken advantage of neuroimaging in which several modalities, including PET, single-photon emission CT (SPECT) and novel MRI techniques, have been shown to aid early and differential diagnosis. Treatment of Parkinson disease is anchored on pharmacological substitution of striatal dopamine, in addition to non-dopaminergic approaches to address both motor and non-motor symptoms and deep brain stimulation for those developing intractable L-DOPA-related motor complications. Experimental therapies have tried to restore striatal dopamine by gene-based and cell-based approaches, and most recently, aggregation and cellular transport of α-synuclein have become therapeutic targets. One of the greatest current challenges is to identify markers for prodromal disease stages, which would allow novel disease-modifying therapies to be started earlier.

Two hundred years after James Parkinson's seminal essay on 'the shaking palsy', most of his original clinical observations have stood the test of time. Beyond the perception of Parkinson disease as a disorder of movement, it has since become apparent that a multitude of non-motor features, such as cognitive impairment, autonomic dysfunction, disorders of sleep, depression and hyposmia (impaired smell), are part of the disease and add considerably to overall burden. Tremendous progress has been made in understanding the neuropathology of Parkinson disease and its progression throughout the nervous system, as well as the molecular and neurophysiological mechanisms and perturbations underlying the disease and its symptoms. Above all, highly efficacious therapies have become available, which are focused on pharmacological dopamine substitution (L-DOPA treatment), but with important refinements and ground-breaking expansions, such as the introduction of deep brain stimulation (DBS). These treatment advances have undoubtedly made Parkinson disease the first and still unparalleled example of a neurodegenerative disease that can be effectively managed, leading to sustained symptom control and quality of life (QOL) up to decades after disease onset. However, none of these treatments is curative and Parkinson disease remains a progressive disorder that eventually causes severe disability — not least by the increasing severity of treatment-resistant motor problems and non-motor symptoms. Thus, modifying disease progression and further delaying disability are the key unmet needs to be addressed by current and future research efforts. Of great future potential is the development of methods to identify individuals at risk and early manifestations that antedate the onset of the defining motor symptoms.

In this Primer, we describe the epidemiology of Parkinson disease, and review our current understanding of the underlying pathology and molecular pathogenesis as well as the perturbations of basal ganglia and cortical connectivity that underlie the cardinal motor features of this illness. We also summarize recent advances in clinical diagnostics, biomarker research and screening, and provide an overview of the natural history of Parkinson disease and the current, as well as future, therapies.

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Epidemiology

Worldwide incidence estimates of Parkinson disease range from 5 to >35 new cases per 100,000 individuals yearly[1], which probably reflects differences in the demographics of the populations studied or in study methods. In a population-based study in Minnesota (USA) with pathological validation of clinical diagnoses, the incidence of Parkinson disease was 21 cases per 100,000 person-years[2]. Parkinson disease is rare before 50 years of age[1], but the incidence increases 5–10-fold from the sixth to the ninth decade of life[1–3]. The global prevalence, conservatively estimated at 0.3% overall, likewise increases sharply with age to >3% in those >80 years of age[4] (FIG. 1).

Mortality is not increased in the first decade after disease onset, but increases thereafter, eventually doubling compared with the general population[5]. Improvement in health care has led to longer survival, which is associated with increasing prevalence of Parkinson disease over time in one 20-year study[6]. The number of people with Parkinson disease is expected to double between 2005 and 2030 (REF. 7). Years lived with disability and disability-adjusted life years due to Parkinson disease increased between 1990 and 2010, and a progressive increase in the personal, societal and economic burden associated with the disease is expected in the future as the world population ages[7–10].

Parkinson disease is twice as common in men than in women in most populations[3,11] (FIG. 1), although in a few populations, including one study from Japan, no difference or even a female excess was observed[12]. A protective effect of female sex hormones, a sex-associated genetic mechanism or sex-specific differences in exposure to environmental risk factors might explain this male preponderance, although disparities in health care could also contribute.

The incidence seems to vary within subgroups defined by race, ethnicity, genotype or environment. Parkinson disease might be less common in African Americans and Asians in the United States, but systematic race-specific incidence has not been investigated in other multiracial populations, and societal rather than biological causes might underlie these findings[3]. Geography and race are often related, and it might be difficult to determine the relative contribution of each to the risk of developing Parkinson disease. In Israel, the prevalence is high, possibly reflecting the higher prevalence of the incompletely penetrant genes associated with Parkinson disease (that is, *LRRK2* (which encodes leucine-rich repeat serine/threonine-protein kinase 2) and *GBA* (which encodes glucocerebrosidase)) in Ashkenazi Jews[13]. The prevalence of Parkinson disease is also high in Inuit, Alaska Native and Native American populations[14]. Lifestyle, including dietary exposure to persistent organic pollutants, or shared genetic factors could explain this pattern. The incidence is greater in men of Japanese and Okinawan descent living in Hawaii than in men living in Japan, supporting that environmental factors have a role[15]. Gene–environment interactions definitely modify the risk for sporadic Parkinson disease. For example, the incidence of Parkinson disease is significantly greater in individuals exposed to certain environmental factors, such as pesticides and traumatic brain injury, and lower in smokers or caffeine users[16].

Mechanisms/pathophysiology

Neuropathology

Characteristic features of Parkinson disease include neuronal loss in specific areas of the substantia nigra and widespread intracellular protein (α-synuclein) accumulation. Although neither the loss of pigmented dopaminergic neurons in the substantia nigra[17,18] nor the deposition of α-synuclein in neurons is specific for Parkinson disease, these two major neuropathologies are specific for a definitive diagnosis of idiopathic Parkinson disease when applied together (FIG. 2).

Gross macroscopic atrophy of the brain is not a feature of Parkinson disease, rather neuronal degeneration occurs in only certain types of neurons within particular brain regions. In early-stage disease, loss of dopaminergic neurons is restricted to the ventrolateral substantia nigra with relative sparing of other midbrain dopaminergic neurons[19,20] (FIG. 2a–d), but becomes more widespread by end-stage disease. The dramatic loss of these dopaminergic neurons even early in the disease suggests that the degeneration in this region starts before the onset of motor symptoms, which is supported by several recent clinicopathological studies[21,22].

The other required neuropathology is the abnormal deposition of α-synuclein in the cytoplasm of certain neurons in several different brain regions[23]. Lewy bodies, which are largely made up of aggregated α-synuclein, were the first to be described over a century ago. Following the development of refined histopathological methods, a broader range of α-synuclein aggregates have been described (FIG. 2e–g). The Lewy pathology initially occurs in cholinergic and monoaminergic brainstem neurons and in neurons in the olfactory system, but is also found in limbic and neocortical brain regions with disease progression (FIG. 2h). In patients with Alzheimer pathology, there is a different pattern of α-synuclein pathology that concentrates mainly in limbic brain regions[22].

Although heritable forms of Parkinson disease only represent 5–10% of all cases (TABLE 1), they have provided crucial clues to the mechanisms underlying the neuropathology of Parkinson disease. Some of the proteins encoded by genes associated with Parkinson disease are involved in a set of molecular pathways that, when perturbed, can trigger a neuropathology that resembles, or is indistinguishable from, sporadic Parkinson disease. In addition, large genome-wide association studies (GWAS) confirm that some of these genes are also affected in sporadic Parkinson disease[24]. Examples of these pathways are: α-synuclein proteostasis, mitochondrial function, oxidative stress, calcium homeostasis, axonal transport and neuroinflammation (FIG. 3).

α-Synuclein proteostasis

Intraneuronal protein aggregates that are largely made up of α-synuclein are found in all patients with Parkinson disease. The existence of point mutations and multiplications of *SNCA*, the gene encoding α-synuclein, that cause heritable forms of Parkinson disease strongly support the notion that α-synuclein is a key player in Parkinson disease (TABLE 1). Similarly, GWAS have revealed a single-nucleotide polymorphism associated with the *SNCA* locus that alters the risk for sporadic Parkinson disease and is associated with increased expression levels of α-synuclein[24,25]. A study in human neurons derived from induced pluripotent stem cells and post-mortem frontal cortex samples from patients with Parkinson disease supports the idea that a risk variant associated with Parkinson disease in a non-coding distal enhancer element of *SNCA* is coupled to increased α-synuclein expression[26].

The normal neuronal function of the 140 amino acid α-synuclein protein is not fully understood, but it occurs in the cytosol, possibly also in mitochondria and the nucleus, and probably has a role in synaptic vesicle dynamics, mitochondrial function, intracellular trafficking and might be a potential chaperone[25,27,28]. α-Synuclein acquires neurotoxic properties during a pathogenetic process in which soluble α-synuclein monomers initially form oligomers, then progressively combine to form small protofibrils and eventually large, insoluble α-synuclein fibrils (that is, the aggregates that make up Lewy pathology)[29,30]. The underlying triggers of accumulation and aggregation of α-synuclein can be manifold, for example, a relative overproduction of the protein, the presence of mutations that increase the likelihood for its misfolding and oligomerization or impairments in the molecular pathways that are charged with degrading native or misfolded α-synuclein.

A progressive, age-related decline in proteolytic defence mechanisms in the ageing brain might play an important part in the accumulation of α-synuclein[31,32] (FIG. 3).

α-Synuclein degradation. Intracellular homeostasis of α-synuclein is maintained by the actions of the ubiquitin–proteasome system and the lysosomal autophagy system (LAS). The relative importance of the ubiquitin–proteasome system and LAS for intracellular α-synuclein proteolysis in neurons is debated and LAS seems to be more important than the ubiquitin–proteasome system to clear oligomeric assemblies[32]. With respect to LAS, both chaperone-mediated autophagy and macroautophagy are suggested to mediate α-synuclein degradation[32,33]. Chaperone-mediated autophagy involves specific chaperones that target certain proteins to lysosomes, whereas macroautophagy entails the formation of autophagosomes that are directed to perinuclear lysosomes. Inhibition of either system leads to increased levels of α-synuclein, and evidence for some compensatory crosstalk between the systems exists[34]. Additional proteases, which are not part of the ubiquitin–proteasome system and LAS, can also cleave α-synuclein in the extracellular space[32].

Several lines of evidence suggest that impairment of these degradation systems could contribute to α-synuclein accumulation. Increasing age — the greatest risk factor for Parkinson disease — is associated with reduced LAS and ubiquitin–proteasome system functions[31], which is consistent with observations of

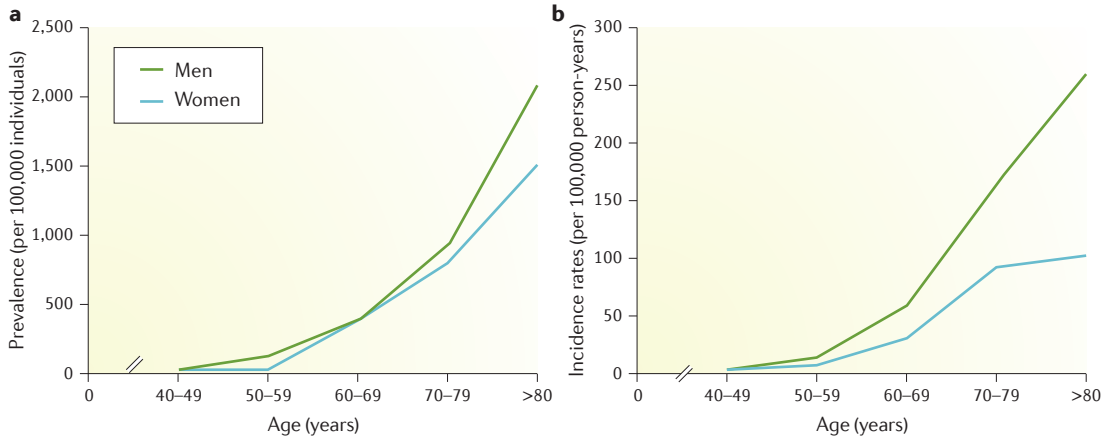

Figure 1 | **Incidence and prevalence of Parkinson disease. a** | Prevalence of Parkinson disease in men and women per 100,000 individuals. **b** | Incidence rate of Parkinson disease per 100,000 person-years. Data are derived from two recent meta-analyses, which used crude rates without adjustments for demographic differences or methodological differences between studies[4,235].

increased levels of α-synuclein in nigral dopaminergic neurons during normal ageing[35]. Pharmacological stimulation of macroautophagy reduces the levels of intracellular α-synuclein in experimental models[36,37]. In the substantia nigra of patients and experimental models of Parkinson disease, lysosomal enzyme levels are reduced, particularly in neurons containing α-synuclein inclusions[38], markers of chaperone-mediated autophagy are decreased[39] and autophagosomes accumulate[40]. Additional observations support the idea that altered proteostasis profoundly influences neuronal accumulation of α-synuclein. For example, α-synuclein oligomers inhibit the ubiquitin–proteasome system[41], accumulating α-synuclein can inhibit macroautophagy[42,43] and different forms of α-synuclein (wild type, mutant or post-translationally modified) can reduce chaperone-mediated autophagy function[34,44]. Collectively, these observations suggest a vicious cycle involving the accumulation of α-synuclein due to disrupted proteostasis, which in turn leads to defective α-synuclein degradation.

Several mutations associated with genetic forms of Parkinson disease are associated with reduced LAS function. The G2019S mutation in the gene encoding LRRK2 is associated with impaired LAS and increased aggregation of α-synuclein in dopaminergic neurons that are exposed to α-synuclein fibrils[45]. Heterozygous mutations in the gene encoding the lysosomal enzyme GBA, the most common genetic risk factor for Parkinson disease[46], are coupled to reduced LAS function[47]. GWAS have revealed two polymorphisms in the *GBA* locus associated with altered risk of developing Parkinson disease[24], and normal ageing is reported to result in a progressive decline in GBA activity[48]. Recent evidence from clinical cohort studies also suggests an increased risk for dementia in individuals with Parkinson disease who carry *GBA* mutations that, in the homozygotic state, are associated with the neuronopathic type of Gaucher disease[49,50]. Reduced GBA activity coincides with increased levels of α-synuclein both in cell cultures and animal models[51,52]. Mutations in the gene encoding vacuolar protein sorting-associated protein 35 (*VPS35*), which cause autosomal dominant Parkinson disease[53,54], also seem to affect α-synuclein handling. VPS35 is part of the retromer complex, which has a key role in sorting lipids and proteins that are newly synthesized or have undergone endocytosis and directs them to either the lysosome, the cell surface or the Golgi apparatus[55]. Notably, *Vps35*-deficient mice exhibit increased levels of α-synuclein in nigral dopaminergic neurons[56], whereas overexpression of *Vps35* reduces α-synuclein accumulation in transgenic mice who also overexpress α-synuclein and in cultured neurons that are exposed to α-synuclein fibrils[57]. Both VPS35 deficiency and the D620N mutation in *VPS35* that causes autosomal dominant Parkinson disease are coupled to reduced cellular levels of lysosome-associated membrane glycoprotein 2 (LAMP2)[56], suggesting once again that LAS perturbation is key to disease pathogenesis. Finally, mutations in *ATP13A2* (also known as *PARK9*), which encodes a type 5 P-type ATPase that is present in lysosomes and autophagosomes[58], are associated with a rare juvenile-onset neurological condition (Kufor–Rakeb syndrome) that includes parkinsonian features and responds to dopaminergic therapy[58]. Dysfunction of LAS and vesicular trafficking probably contribute to neurodegeneration in people with mutations in *ATP13A2* (REF. 59). Notably, GWAS have revealed that certain *ATP13A2* variants are associated with increased

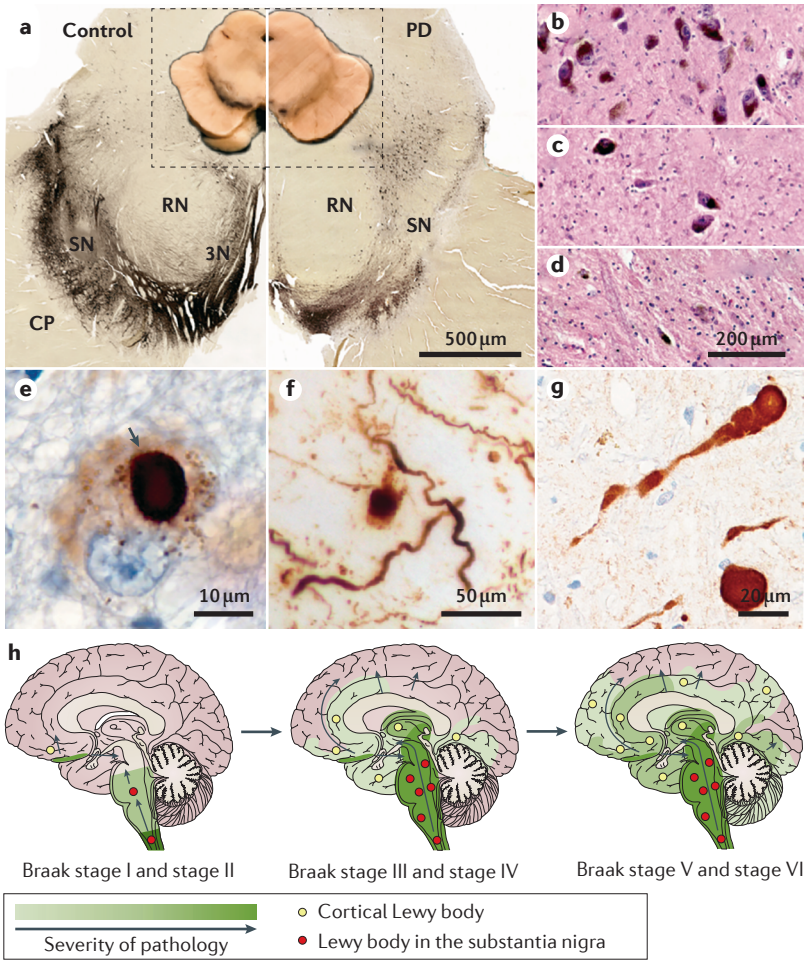

Figure 2 | **The main diagnostic neuropathologies for Parkinson disease. a** | Parkinson disease (PD) is defined by depigmentation of the substantia nigra (SN) (right panel) compared with control (left panel). Macroscopical (inset) and transverse sections of the midbrain upon immunohistochemical staining for tyrosine hydroxylase, the rate limiting enzyme for the synthesis of dopamine, are shown. Selective loss of the ventrolateral parts of the SN with sparing of the more medial and dorsal regions is evident in the histological section. **b–d** | Haematoxylin and eosin staining of the ventrolateral region of the SN showing a normal distribution of pigmented neurons in a healthy control (part **b**) and diagnostically significant moderate (part **c**) or severe (part **d**) pigmented cell loss in PD. **e–g** | Immunohistochemical staining of α-synuclein shows the round, intracytoplasmic Lewy bodies (arrow in part **e**), more diffuse, granular deposits of α-synuclein (part **e** and part **f**), deposits in neuronal cell processes (part **f**), extracellular dot-like α-synuclein structures (part **f**) and α-synuclein spheroids in axons (part **g**). **h** | The theorized progression of α-synuclein aggregation in PD without Alzheimer pathology. α-Synuclein inclusions occur in cholinergic and monoaminergic lower brainstem neurons in asymptomatic cases (Braak stage I and stage II), infiltrate similar neurons in the midbrain and basal forebrain in those with the motor symptoms of PD (Braak stage III and stage IV), and then are found later in limbic and neocortical brain regions with disease progression (Braak stage V and stage VI)[236]. 3N, 3rd nerve fibres; CP, cerebral peduncle; RN, red nucleus. Part **h** adapted with permission from REF. 236, Wiley.

Table 1 | **Classification of hereditary parkinsonism***

Locus symbol	New designation‡	Gene locus	Gene	OMIM (phenotype MIM number; gene/ locus MIM number)	Clinical clues
Autosomal dominant Parkinson disease					
PARK1 or *PARK4*	PARK-*SNCA*	4q22.1	*SNCA*	• 168601; 163890 (*PARK1*) • 605543; 163890 (*PARK4*)	Missense mutations (*PARK1*) cause classic Parkinson disease phenotype. Duplication or triplication of this gene (*PARK4*) causes early-onset Parkinson disease with prominent dementia
PARK8	PARK-*LRRK2*	12q12	*LRRK2*	607060; 609007	Classic Parkinson disease phenotype. Variations in *LRRK2* include risk-conferring variants and disease-causing mutations
PARK17	PARK-*VPS35*	16q11.2	*VPS35*	614203; 601501	Classic Parkinson disease phenotype
Early-onset Parkinson disease (autosomal recessive inheritance)					
PARK2	PARK-*Parkin*	6q26	*PARK2* encoding parkin	600116; 602544	Often presents with lower limb dystonia
PARK6	PARK-*PINK1*	1p36.12	*PINK1*	605909; 608309	Psychiatric features are common
PARK7	PARK-*DJ1*	1p36.23	*PARK7* encoding protein deglycase DJ1	606324; 602533	Early-onset Parkinson disease
PARK19B	PARK-*DNAJC6*	1p31.3	*DNAJC6*	615528; 608375	Onset of parkinsonism between the third and fifth decades of life
Complex genetic forms (autosomal recessive inheritance)§					
PARK9	PARK-*ATP13A2*	1p36.13	*ATP13A2*	606693; 610513	Early-onset parkinsonism with a complex phenotype (for example, dystonia, supranuclear gaze palsy, pyramidal signs and cognitive dysfunction); also known as Kufor–Rakeb syndrome
PARK14	PARK-*PLA2G6*	22q13.1	*PLA2G6*	256600; 603604	PLAN (or NBIA2) is characterized by a complex clinical phenotype, which does not include parkinsonism in the majority of cases
PARK15	PARK-*FBXO7*	22q12.3	*FBXO7*	260300; 605648	Early-onset parkinsonism with pyramidal signs and a variable complex phenotype (for example, supranuclear gaze palsy, early postural instability, chorea and dystonia)
PARK19A	PARK-*DNAJC6*	1p31.3	*DNAJC6*	615528; 608375	Juvenile-onset parkinsonism that is occasionally associated with mental retardation and seizures
PARK20	PARK-*SYNJ1*	21q22.11	*SYNJ1*	615530; 604297	Patients may have seizures, cognitive decline, abnormal eye movements and dystonia
PARK23	Not yet assigned	15q22.2	*VPS13C*	616840; 608879	Young-adult-onset parkinsonism associated with progressive cognitive impairment that leads to dementia and dysautonomia

The locus symbols are in accordance with the Online Mendelian Inheritance in Man (OMIM) catalogue (https://omim.org). Seven loci, which have been assigned a PARK designation, have a yet unconfirmed relationship to disease (that is, PARK3, unknown gene on 2p13; PARK5, *UCHL1* on 4p13; PARK11, *GIGYF2*5 on 2q37.1; PARK13, *HTRA2* on 2p13.1; PARK18, *ELF4G1* on 3q27.1; PARK21, *DNAJC13* on 3q22; and PARK22, *CHCHD2* on 7p11.2) and three are classified as risk loci (PARK10 on 1p32; PARK12 on Xq21–q25; and PARK16 on 1q32). Mutations in *TMEM230* on 20p12 have also very recently been described to cause monogenic Parkinson disease, but causal relationship to disease is still uncertain[134,240]. MDS, International Parkinson and Movement Disorder Society; NBIA2, neurodegeneration with brain iron accumulation 2A; PLAN, PLA2G6-associated neurodegeneration. *See REFS 133,241. ‡On the basis of the recommendations of the MDS Task Force on the nomenclature of genetic movement disorders, which will be regularly updated: MDSGene; available at http://www.mdsgene.org[133,241]. §Complex genetic forms that have parkinsonism as a key clinical feature but also present with atypical, multisystem features or other movement disorders.

penetrance of *LRRK2* mutations and increased risk of Parkinson disease in *GBA* mutation carriers, which supports the idea that the proteins encoded by these genes act in shared molecular pathways[60].

Prion-like propagation of α-synuclein. An additional mechanism for the development of α-synuclein aggregates has recently been proposed. The prion-like hypothesis for α-synuclein posits that once α-synuclein aggregates have formed in a neuron, they can be transported intra-axonally to other brain regions, be released into the extracellular space, be taken up by neighbouring neurons and seed aggregation of endogenous α-synuclein once inside their new cellular host[61,62]. Cell culture studies have demonstrated that LAS impairment leads to increased secretion of α-synuclein into the extracellular space through exosomes and that endocytosis is a key mechanism of uptake of extracellular α-synuclein[63,64]. Thus, initial α-synuclein misfolding in a small number of cells could progressively lead to the spread of α-synuclein aggregates to multiple brain regions over years or decades following the initial insult. This is consistent with the idea that α-synuclein pathology gradually engages more brain regions as the disease progresses, as suggested by Braak *et al.*[23] (FIG. 2h). In addition, this model supports the idea that the first sites of α-synuclein aggregation might be in the gut enteric nerves and the olfactory bulb where they underlie the signs and symptoms associated with prodromal Parkinson disease (for example, anosmia and constipation)[65,66], before they spread, eventually leading to motor dysfunction once the substantia nigra becomes involved[67].

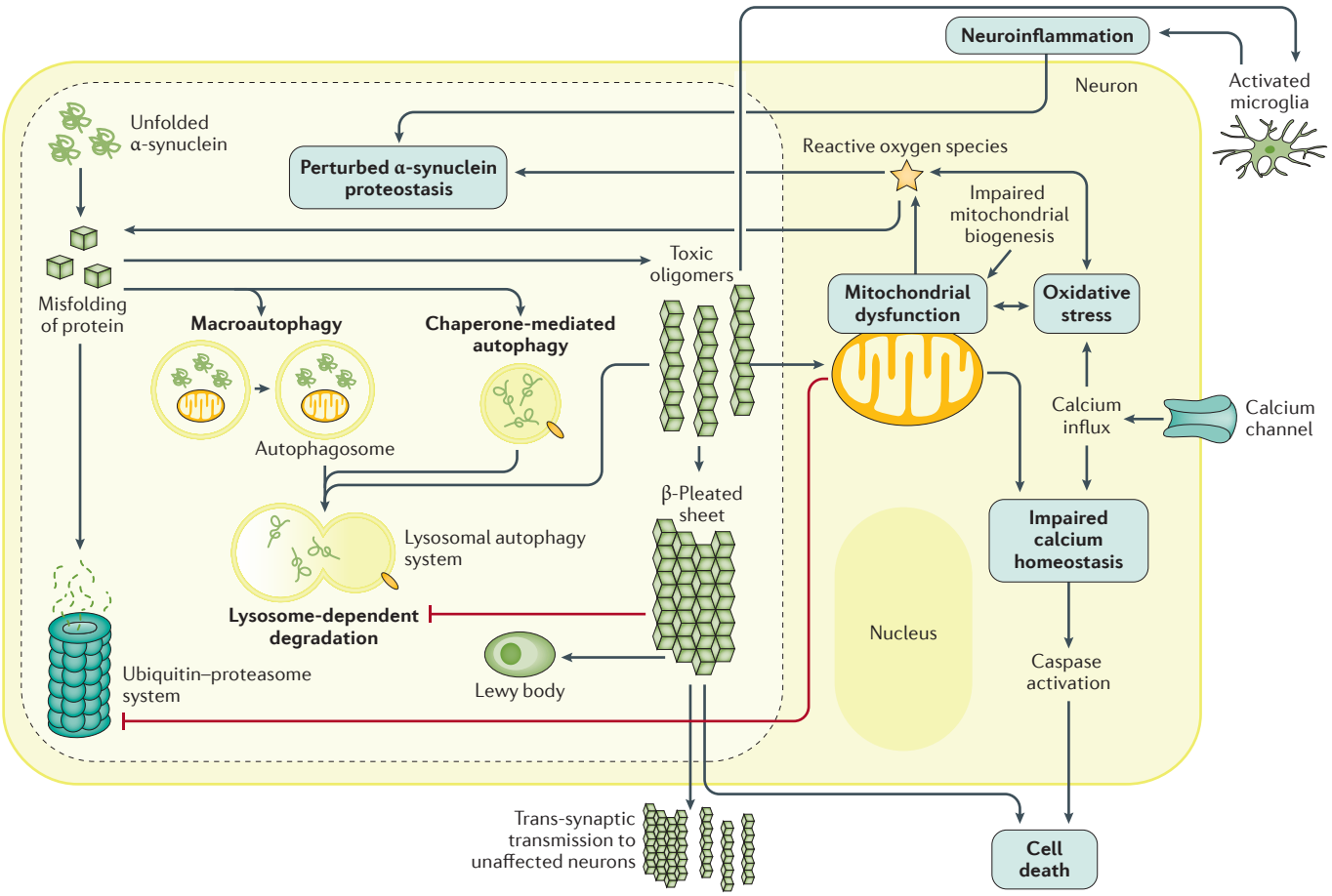

Figure 3 | **Molecular mechanisms involved in Parkinson disease.** Schematic diagram depicting interactions between major molecular pathways that are implicated in the pathogenesis of Parkinson disease.

Mitochondrial dysfunction

Several lines of evidence have implicated mitochondrial dysfunction as a key element in the pathogenesis of Parkinson disease (reviewed in detail in REFS 68,69; FIG. 3). An emerging picture is one of a vicious cycle in which α-synuclein aggregation and mitochondrial dysfunction exacerbate each other, which could explain why these cellular changes are observed together in degenerating neurons in Parkinson disease.

Activity of mitochondrial complex I, a compound of the electron transport chain, is reduced in several tissues isolated from patients with Parkinson disease[68,69]. Peroxisome proliferator-activated receptor-γ (PPARγ) co-activator 1α (PGC1α), a mitochondrial master transcriptional regulator, target genes are generally underexpressed in Parkinson disease[70]. It has been proposed that low levels of α-synuclein are normally present in mitochondria, but that accumulation of the protein inside mitochondria leads to mitochondrial complex I deficits and oxidative stress[71]. Activation of PGC1α results in reduced α-synuclein oligomerization and less toxicity *in vitro*, whereas induced PGC1α deficiency by genetic knockdown increases vulnerability to α-synuclein oligomers[72]. Conversely, exposure to α-synuclein oligomers reduces the levels of cellular PGC1α[72]. In animal models, injection of several toxins that impair mitochondrial function replicates features of Parkinson disease neuropathology[68,69]. When mitochondrial transcription factor A, which is essential for mitochondrial DNA expression, is selectively depleted in dopaminergic neurons of mice — so-called MitoPark mice — mitochondria in dopaminergic neurons in the substantia nigra develop a defective electron transport chain, leading to neuronal degeneration in adulthood[73]. Adult mice that lack one allele of *En1* — encoding for engrailed 1, which enhances nuclear translation of the mitochondrial complex proteins NADH-ubiquinone oxidoreductase 75 kDa subunit (NDUFS1) and NDUFS3 — replicate several important features of Parkinson disease neuropathology, such as perturbations of autophagy, neuroinflammation and progressive nigral dopaminergic neuron death following retrograde axonal degeneration[74]. Importantly, axonal degeneration, potentially owing to the energy deficiency, might be an upstream and early neurodegenerative event in Parkinson disease. Human brain imaging studies have demonstrated changes in the striatum in people with Parkinson disease even several years before they are diagnosed[75,76], and recent post-mortem studies suggest that nigrostriatal axon terminals are dysfunctional or have degenerated several years before the neuronal cell bodies in the substantia nigra die[77].

An alternative explanation for the axonal degeneration is that α-synuclein aggregates eventually become obstacles to normal axonal transport[78].

Recent advances in the understanding of molecular pathways governed by proteins encoded by genes associated with Parkinson disease have provided additional support to the notion that mitochondrial failure is a key event in disease process. For example, *LRRK2* mutations are not only associated with changes in autophagy but also with mitochondrial impairments[69]. Moreover, proteins encoded by *PARK2* and *PINK1*, which are autosomal recessive Parkinson disease genes, cooperate in the clearance of damaged mitochondria through mitophagy[79]. Impaired degradation of MIRO (a protein in the outer mitochondrial membrane that connects the organelle to microtubule motors) seems to have a role in defective clearance of damaged mitochondria. In neurons derived from induced pluripotent stem cells from patients with inherited or sporadic Parkinson disease, degradation of MIRO is reduced, and as a consequence, mitophagy is inefficient, which ultimately could lead to energy failure[80].

Oxidative stress

Evidence that oxidative stress, as a consequence of mitochondrial dysfunction, is increased in the brain tissue of patients with Parkinson disease is compelling[81] (FIG. 3), but it is debatable whether it occurs early or late during the demise of neurons. Mutations in *DJ1* (also known as *PARK7*), encoding a putative antioxidant, which cause early-onset autosomal recessive Parkinson disease[82], are associated with increased cellular oxidative stress[83,84]. Knocking out *Dj1* in mice results in increased protein oxidation in stressed nigral dopaminergic neurons.

Nigral dopaminergic neurons have been suggested to be particularly vulnerable to metabolic and oxidative stress for several reasons. First, they possess particularly long (up to 4.5 metres), unmyelinated axons, with large numbers of synapses (estimated at 1–2.4 million per nigral dopaminergic neuron), which require great energy to be sustained[85,86]. Second, they (unlike the dopaminergic neurons in the neighbouring ventral tegmental area, which are relatively resilient in Parkinson disease) exhibit autonomous pacemaking activity involving cytosolic calcium oscillations and calcium extrusion at the expense of energy[87,88]. Third, increased levels of cytosolic dopamine and its metabolites can cause toxic oxidative stress[89,90]. Last, mitochondrial dysfunction and increased oxidative stress can lead to the depletion of lysosomes[91] and functional impairment of LAS, further demonstrating that several putative pathogenetic pathways in Parkinson disease are intimately linked.

Neuroinflammation

A large number of post-mortem, brain imaging and fluid biomarker studies shows that neuroinflammation is a salient feature of Parkinson disease[92] (FIG. 3). Although maybe not the initial trigger, neuroinflammation is probably an essential contributor to pathogenesis[93,94]. Catecholaminergic neurons in the brain tissue of patients with Parkinson disease and cultured dopaminergic neurons (when exposed to activated microglia or L-DOPA) have been reported to be particularly inclined to express MHC class I proteins, which exposes them to cytotoxic T cell-mediated death if they present antigens[95].

GWAS indicate that genes associated with the risk of developing Parkinson disease often encode proteins that are expressed in immune cells and that are involved in immune regulation, such as LRRK2 (which is involved in autophagy by immune cells)[24,96,97]. Close links between certain genes, protein aggregates and neuroinflammation exist. Evidence from patients and experimental models suggests that α-synuclein aggregation induces both innate and adaptive immunity in Parkinson disease[93,94] and neuroinflammation can also promote α-synuclein misfolding[98], suggesting that the two processes participate in a self-aggravating cycle. During prodromal Parkinson disease, tissue inflammation in the olfactory system or gut has been suggested to trigger a sufficient level of α-synuclein misfolding that some α-synuclein aggregates eventually escape the normal degradation mechanisms[99]. Indeed, recent evidence from experiments in *Snca*-overexpressing mice suggests a role of gut microbiota in promoting microglial activation and α-synuclein pathology, as well as motor deficits[100].

However, it would be misleading to suggest that activated immune cells only contribute to the initiation or deterioration of Parkinson disease pathology in the brain. Microglia can phagocytose and degrade extracellular α-synuclein aggregates, and immunotherapies that target α-synuclein, which are currently being developed for clinical trials, rely on the clearance of antibody-bound α-synuclein by activated immune cells[101].

Motor circuit pathophysiology

The basal ganglia are part of several parallel, but anatomically segregated thalamo–cortico–basal ganglia circuits, which have important functions in the control of actions and goal-directed behaviour. These circuits are anatomically characterized by a strong convergence of cortical input onto relatively few subcortical output neurons and back to the cortex, suggesting a 'filter-like' function. Four circuits with a functionally similar, yet topographically distinct, organization have been identified to subserve limbic, prefrontal-associative, oculomotor and motor functions by linking the corresponding frontal cortical areas and subregions of the thalamus and basal ganglia[102,103].

Parkinsonism results from a decreased dopaminergic transmission in the motor region of the striatum with opposing effects on the direct and indirect pathways, which results in increased γ-aminobutyric acid (GABA)-ergic inhibition of thalamocortical projections (FIG. 4). This firing rate model provided a rationale for the renaissance of stereotactic surgery for Parkinson disease in the early 1990s, as akinesia was no longer considered a loss-of-function symptom, but rather the physiological consequence of increased inhibitory output activity of the basal ganglia. Indeed, lesioning of the globus pallidus internus or the subthalamic nucleus proved to be effective in alleviating bradykinesia in animals and

humans[104,105]. Meanwhile, the model has been amended by additional connections, such as the 'hyperdirect pathway', a monosynaptic link between motor cortical areas and the subthalamic nucleus, which changed the perception of the subthalamic nucleus from a passive relay nucleus to a second input structure of the basal ganglia[106]. The hyperdirect pathway might have a role in preventing premature responses by reinforcing indirect pathway activity and thereby the 'breaking' function of the basal ganglia, thus allowing more time for the selection of the most appropriate response at the cortical level[107]. Moreover, recent animal studies have suggested that antidromic activation of the hyperdirect pathway might drive the strong anti-akinetic effect of subthalamic nucleus DBS, which further underlines the functional significance of this second basal ganglia input[108,109].

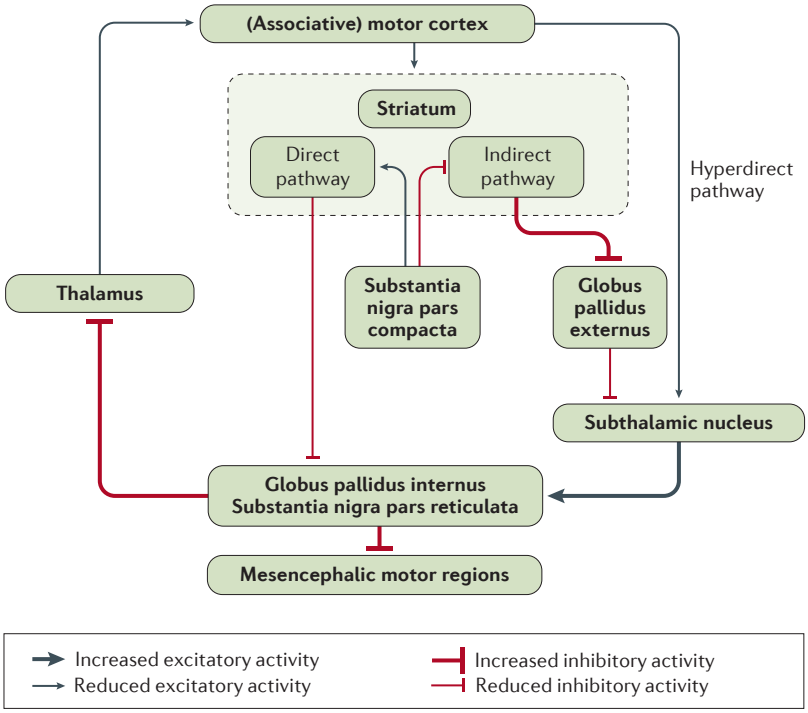

Figure 4 | **Motor cortex circuitry activity changes in Parkinson disease.** The motor circuit consists of corticostriatal projections from the primary motor cortex, supplementary motor area, cingulate motor cortex and premotor cortex, terminating on dendrites of striatal medium spiny neurons. The hyperdirect pathway has direct glutamatergic connectivity from the motor cortex to the subthalamic nucleus. The globus pallidus internus and the substantia nigra pars reticulata are the two main output nuclei of the basal ganglia and project to the brainstem and ventrolateral thalamus. The striatal projections to these output nuclei are divided into 'direct' and 'indirect' pathways. The direct pathway is a monosynaptic connection between medium spiny neurons that express dopamine D1 receptors and GABAergic neurons in the globus pallidus internus and the substantia nigra pars reticulata. The 'indirect' pathway originates from medium spiny neurons that express D2 receptors, which project to the globus pallidus externus, and reaches the globus pallidus internus via the subthalamic nucleus as a glutamatergic relay. Through these two pathways, the striatal dopaminergic tone regulates the GABAergic output activity of the basal ganglia. As indicated, parkinsonism is associated with changes in these relays. Indeed, nigrostriatal dopamine deficiency has opposing effects on the direct and indirect pathways. Although D1-mediated direct pathway activity becomes reduced, D2-mediated indirect pathway activity increases, resulting in the net effect of a strong increase in the firing rate of GABAergic basal ganglia output neurons, which over-inhibit downstream thalamocortical and brainstem areas.

However, changes in firing rate are not capable of fully explaining the pathophysiology of hyperkinetic or hypokinetic movement disorders. Growing evidence suggests that movement disorders are characterized by more-complex changes in information processing, such as abnormal neural synchronization and cortico–subcortical coupling in specific frequency bands as indexed by electroencephalogram power density and spectral coherence. The parkinsonian off-state is characterized by enhanced beta-band activity (~20 Hz) in local field potential recordings from the basal ganglia, which is suppressed by dopaminergic medication or DBS in parallel with the clinical improvement of bradykinesia and rigidity[110,111]. By contrast, hyperkinesia — such as L-DOPA-induced dyskinesia in Parkinson disease — has been associated with increased theta-band activity in the same structures (4–12 Hz)[112]. High-frequency DBS suppresses either activity and might thus act like a 'filter' for abnormally synchronized basal ganglia activity, irrespective of the underlying disorder.

In addition, changes in cerebellar activity and the interaction between the basal ganglia and the cerebellum might be important for the pathophysiology of tremor in Parkinson disease[113], and disorders of balance and gait probably involve abnormal basal ganglia output via projections into the midbrain locomotor region (pedunculopontine and cuneiform nuclei)[114]. A better understanding of this expanded motor network may help to define alternative targets for DBS in Parkinson disease that target specific symptom profiles.

Diagnosis, screening and prevention

Clinical diagnosis and natural history

Parkinson disease is clinically defined by the presence of bradykinesia and at least one additional cardinal motor feature (rigidity or rest tremor), as well as additional supporting and exclusionary criteria[115–118] (BOX 1). Onset of motor symptoms is usually unilateral and asymmetry persists throughout the disease. The average age of onset is in the late fifties, with a broad range from <40 to >80 years of age. Young-onset Parkinson disease is commonly defined by an age of onset <45 years and >10% of those individuals have a genetic basis, and the proportion of genetically defined cases rises to >40% of those with disease onset before 30 years of age[119,120].

In addition to the cardinal motor features, a majority of patients with Parkinson disease also have non-motor symptoms[121] (FIG. 5). Non-motor symptoms involve a multitude of functions, including disorders of sleep–wake cycle regulation, cognitive impairment (including frontal executive dysfunction, memory retrieval deficits, dementia and hallucinosis), disorders of mood and affect, autonomic dysfunction (mainly orthostatic hypotension, urogenital dysfunction, constipation and hyperhidrosis), as well as sensory symptoms (most prominently hyposmia) and pain[121]. Some of these can antedate the onset of classic motor symptoms by years or even decades. Non-motor symptoms become increasingly prevalent over the course of the illness and are a major determinant of QOL, progression of overall disability and of nursing home placement. In one

Box 1 | **MDS diagnostic criteria for Parkinson disease**

Step 1: diagnosis of parkinsonism (core feature)

- Presence of bradykinesia as a slowness of movement and a decrement in amplitude or speed (or progressive hesitations or halts) as movements are continued
- In combination with at least one of: rigidity and/or rest tremor

Step 2: determining Parkinson disease as the cause of parkinsonism with two levels of diagnostic certainty

Diagnosis of clinically established Parkinson disease requires all three of the below parameters:

- Absence of absolute exclusion criteria. These criteria include clinical or imaging evidence for alternate diagnoses of parkinsonism, such as atypical parkinsonism, drug-induced parkinsonism or essential tremor.
- Two or more supportive criteria. These include L-DOPA responsiveness, the presence of classic rest tremor, the presence of L-DOPA-induced dyskinesias, the presence of either olfactory loss or cardiac sympathetic denervation on metaiodobenzylguanidine (MIBG) scintigraphy.
- No red flags. This refers to features that are unusual but not absolutely exclusionary for Parkinson disease, for example, the rapid progression of gait impairment that requires wheelchair use or the development of severe autonomic failure within 5 years after onset.

Diagnosis of clinically probable Parkinson disease requires:

- Absence of absolute exclusion criteria (mentioned above)
- Presence of red flags (mentioned above) that are counterbalanced by supportive criteria

For a full listing of absolute exclusion criteria, red flags and supportive criteria see REF. 118.

MDS, International Parkinson and Movement Disorder Society.

long-term study, dementia was present in 83%, hallucinosis in 74%, symptomatic orthostatic hypotension in 48%, constipation in 40% and urinary incontinence in 71% of those patients with Parkinson disease surviving for >20 years. Progressive disability ultimately included treatment-resistant motor symptoms, such as freezing of gait (81%), postural instability and falling (87%, with fractures in 35%) and choking (48%)[122]. Although these milestones of progression are key events in the long-term evolution of Parkinson disease, clinical trials and observational studies so far have focused on the progression of motor impairment as captured by the Unified Parkinson's Disease Rating Scale (UPDRS), which is the most commonly used scale to monitor motor disability associated with Parkinson disease in research settings[123,124].

In cases presenting with fully developed classic motor features of Parkinson disease, the clinical diagnosis might seem a straightforward exercise. However, early in the disease, error rates for a clinical diagnosis can be as high as 24% even in specialized centres. The most common misclassifications in clinicopathological series are multiple system atrophy, progressive supranuclear palsy and, less frequently, corticobasal degeneration, and in clinically based studies, common errors relate to essential tremor, drug-induced parkinsonism and vascular parkinsonism[116]. Accuracy of a clinical diagnosis of Parkinson disease can be improved by the stringent use of standard clinical criteria, such as the UK Parkinson's Disease Society Brain Bank (UKPDSBB) criteria, but even then diagnostic accuracy at first visit is only slightly above 80%, as shown by a recent meta-analysis of 11 studies assessing a UKPDSBB-based clinical diagnosis against post-mortem pathological examination as the gold standard[125]. Such findings highlight the need for diagnostic tests and biomarkers to enhance diagnostic confidence in early disease, or to eventually diagnose Parkinson disease in its prodromal stages.

Diagnostic tests

Imaging. Visualization of striatal dopamine depletion in patients with Parkinson disease using ^{18}F-labelled L-DOPA (FIG. 6) and PET was a breakthrough in molecular neuroimaging in the early 1980s[126]. Since then, the field of neuroimaging has seen dramatic advances that are becoming increasingly relevant to Parkinson disease[127]. For example, ^{123}I-ioflupane single-photon emission CT (SPECT) (also known as DaTscan (GE Healthcare)) is approved for clinical routine use and can be used to differentiate between Parkinson disease and clinical mimics that are not associated with presynaptic nigrostriatal terminal dysfunction[127,128]. Structural MRI helps to identify symptomatic parkinsonism and various MRI techniques can reveal specific changes in the basal ganglia and infratentorial structures in atypical parkinsonism[129]. Advanced MRI techniques and post-processing procedures, including diffusion weighted imaging, volumetric imaging, automated subcortical volume segmentation and multimodal imaging, are being explored to enhance diagnostic accuracy for Parkinson disease versus other types of degenerative parkinsonism[129–131]. Myocardial sympathetic denervation, assessed with PET or SPECT using noradrenergic tracers, is common in Parkinson disease, but is not seen in patients with atypical parkinsonism or other Parkinson disease mimics[132]. An overview of imaging findings in Parkinson disease is provided in FIG. 6 and Supplementary information S1 (table).

Genetics. The list of mutations causing monogenic types of Parkinson disease continues to grow, as does the number of genes associated with complex phenotypes that include parkinsonism and have been assigned PARK loci (TABLE 1). Several other genes (including *GBA*, *GCH1*, *ADH1C*, *TBP*, *ATXN2*, *MAPT* and *GLUD2*) have been identified that contribute to an increased risk for the sporadic form of the disease, of which the most prevalent and important are heterozygous mutations in *GBA*. Large meta-analyses of data sets from GWAS have identified and confirmed many more common low-risk susceptibility variants in other loci in Parkinson disease, which account for additional heritability, each potentially acting in a small but additive manner[24,133,134].

Genetic forms only account for a small percentage of Parkinson disease cases in clinical practice, and, as of yet, genetic testing is not part of the routine diagnostic process, except in patients in whom there is a specific suspicion for a possible genetic cause (for example, suggestive family history, early onset (which is typical for several recessive genes) or specific clinical features, such as dystonia as a presenting symptom).

Overall, the implications of genetic testing in clinical routine are limited by reduced penetrance and variable expressivity, and there is currently no impact of genetic findings on practical treatment decisions. This might well change in the future as data from prospective studies on the prognostic implication of genetic mutations emerge and specific therapeutic targets in carriers of mutations associated with Parkinson disease are being pursued. Examples for this are the recently reported increased risk for dementia in patients who have Parkinson disease and carry neuronopathic *GBA* mutations[49,50] or development programmes for inhibitors of LRRK2 (REF. 135).

Cerebrospinal fluid and blood tests. Although several studies have assessed differential levels of various proteins, most prominently the levels of different α-synuclein species, in the cerebrospinal fluid (CSF) of patients with Parkinson disease versus controls (see Supplementary information S2 (table)), the sensitivities and specificities have been suboptimal and there is currently no clinically useful CSF-based diagnostic test for Parkinson disease[136]. This is also true for blood biomarkers, although associations of different serum or plasma parameters with disease progression have been described, including correlations of lower plasma levels of apolipoprotein A1 with greater severity of motor symptoms[137].

Screening and prevention

Neuronal dysfunction in Parkinson disease is believed to start long before the defining motor features have become apparent[138] (FIG. 5). In an attempt to define at-risk individuals or prodromal disease stages, current research efforts have focused on risk factors and biomarkers that have been associated with later diagnosis of Parkinson disease in epidemiological studies[136,139]. Subtle motor abnormalities (mild parkinsonian signs), such as reduced arm swing, changes in walking pattern, stiffness, tremor or changes in fine motor skills, might be found in as many as 40% of the elderly population, in whom they have been associated with an increased risk for incident Parkinson disease or with other Parkinson disease risk markers[66]. In addition, several studies have demonstrated that subtle motor abnormalities can be detected in individuals a considerable time before the eventual diagnosis, and more-sensitive digital tools to identify these early motor features are being tested[140].

Non-motor symptoms seem to long antedate the onset of classic motor symptoms in individuals with Parkinson disease[66,139,141] (FIG. 5). Idiopathic rapid eye movement (REM)-sleep behaviour disorder (RBD), in particular, carries a high risk for the development of Parkinson disease or other α-synucleinopathies[139]. Recent prospective studies in large RBD cohorts have found conversion rates to Parkinson disease, dementia associated with Parkinson disease or multiple system

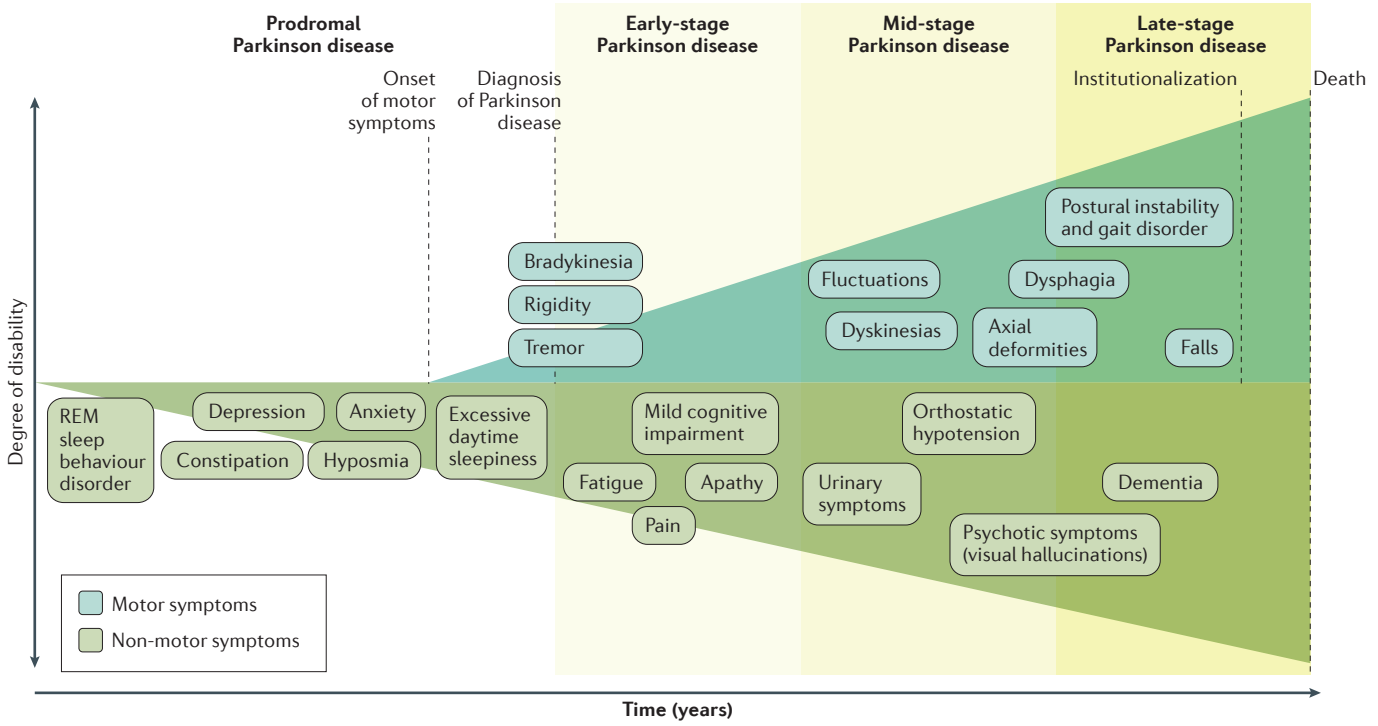

Figure 5 | **Clinical symptoms associated with Parkinson disease progression.** Diagnosis of Parkinson disease occurs with the onset of motor symptoms (early-stage Parkinson disease) typically in the late fifties, but can be preceded by a prodromal phase of years or even decades, which is characterized by specific non-motor symptoms (prodromal Parkinson disease). Non-motor symptoms become increasingly prevalent and obvious over the course of the illness, but can be present to a variable degree throughout all stages of Parkinson disease. Progressive disability from Parkinson disease is driven by the combination of these non-motor problems with increasing severity of cardinal motor features, the development of L-DOPA-induced motor complications (mid-stage Parkinson disease) and the evolution of poorly L-DOPA-responsive motor disabilities, such as postural instability, gait problems (including freezing) and dysphagia (late-stage Parkinson disease). REM, rapid eye movement.

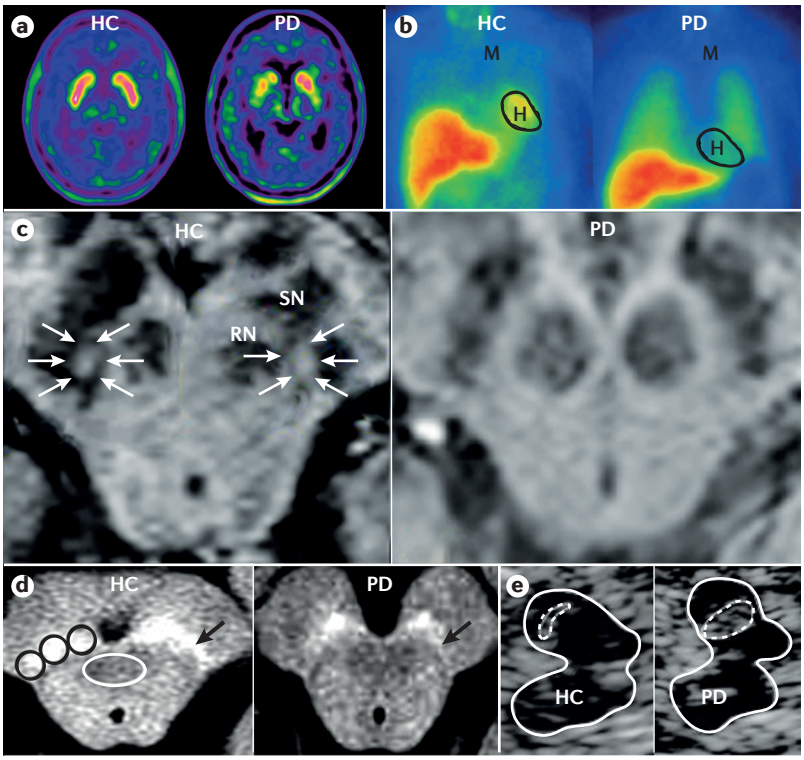

Figure 6 | **Imaging methods used to study Parkinson disease. a** | ^{18}F-DOPA-PET images show normal bilateral tracer uptake in the putamen and caudate nuclei (a typical comma-shaped structure) in a healthy control (HC; left panel), whereas uptake is asymmetric with more marked reduction in the right compared with the left putamen in a patient with early-stage predominantly left-sided Parkinson disease (PD; right panel). **b** | Metaiodobenzylguanidine single-photon emission CT (MIBG SPECT) shows cardiac sympathetic denervation with a profound reduction in MIBG uptake in the heart (H) of a patient with early PD (right panel) compared with a HC (left panel). **c** | MRI of the substantia nigra (SN). Left panel shows a susceptibility weighted imaging (SWI) scan of a HC demonstrating an ovoid area of hyperintensity (arrows) within the dorsolateral SN, which is absent in patients with PD (right panel). **d** | Neuromelanin-sensitive MRI of the SN (black circles in the left panel) shows reduced signal intensity in the lateral part (arrow) in a patient with early PD (right panel) compared with the HC (left panel). No changes are observed in the periaqueductal grey matter (white circle in the left panel). **e** | Transcranial ultrasonography (axial plane) shows an enlarged area of echogenicity in the region of the SN in a patient with PD (right panel) compared with a HC (left panel). The solid lines mark the midbrain area, the dotted lines mark the echogenic area at the anatomical site of the SN on the side of insonation. M, mediastinum; RN, red nucleus. Part **c** is adapted with permission from REF. 237, Wiley. Part **d** is adapted with permission from REF. 238, Elsevier. Part **e** is adapted with permission from REF. 239, Wiley.

atrophy between 15% and 40% over 2–5 years and up to 90% with longer follow-up beyond 10 years[142], but the need for polysomnographic confirmation limits the use of RBD for screening at the population level.

Conversely, hyposmia is an established, albeit less specific risk factor for Parkinson disease, which is easy to screen at relatively low cost and has a relatively high prevalence in the general population[66]. A two-step approach using smell testing as a primary screen and dopamine transporter scan imaging as a secondary screen in hyposmic individuals is being used as a screening approach in the population-based PARS study, in which hyposmia when combined with older age and constipation was associated with deficits in dopamine transporter binding in >40% of such individuals[143]. In a small cohort of individuals with idiopathic RBD, the presence of hyposmia yielded a predictive value for conversion to Parkinson disease or dementia associated with Parkinson disease of >60% over 5 years[144], which has obvious implications for the calculation of sample sizes for future 'neuropreventive' trials targeting prodromal Parkinson disease.

The International Parkinson and Movement Disorder Society (MDS) has published research diagnostic criteria for prodromal Parkinson disease, which are based on epidemiological data about the effects of a large number of risk and prodromal markers[65]. Their predictive validity and, therefore, usefulness for selecting populations for 'disease prevention' trials still await prospective testing, but a population-based study has provided first evidence to this effect[145].

Management

Dopaminergic pharmacological targets

Loss of dopaminergic neurons in the substantia nigra pars compacta leading to striatal dopamine depletion is the core mechanism underlying the cardinal motor features of Parkinson disease. Substituting striatal dopamine loss via the systemic administration of the dopamine precursor amino acid L-DOPA represented a revolutionary breakthrough in the treatment of Parkinson disease >50 years ago. Since then, important advances in the understanding of the pharmacological players that regulate nigrostriatal dopaminergic transmission have revealed multiple additional targets for dopaminergic therapies. These can be broadly classified into interventions with primarily presynaptic or postsynaptic activity (FIG. 7).

L-DOPA. L-DOPA has remained the gold standard for Parkinson disease and parkinsonism, and over time, practically all patients with Parkinson disease will require treatment with this agent[146,147]. However, its use is complicated by the evolution of motor complications, including motor response oscillations and drug-induced dyskinesias (BOX 2). The mechanisms underlying these phenomena, in particular, those responsible for the development of dyskinesias with chronic L-DOPA replacement, are still incompletely understood. Both presynaptic and postsynaptic mechanisms are involved, which eventually lead to non-physiological pulsatile striatal dopamine receptor stimulation and give rise to various maladaptive neuronal responses[148,149]. The key cause is discontinuous drug delivery due to the short half-life of L-DOPA and the variability in its gastrointestinal absorption and blood–brain barrier transport[150]. Novel sustained-release formulations of L-DOPA as well as continuous delivery (either intestinally via percutaneous endoscopic gastro-jejunostomy tubes or subcutaneously via mini-pumps) have been or are being developed to address this problem[150]. Clinical observations of reductions of pre-existing dyskinesias with intestinal gel infusions of L-DOPA indeed support the value of the concept of continuous dopaminergic receptor stimulation as a means to prevent the evolution of drug-induced dyskinesias[150,151].

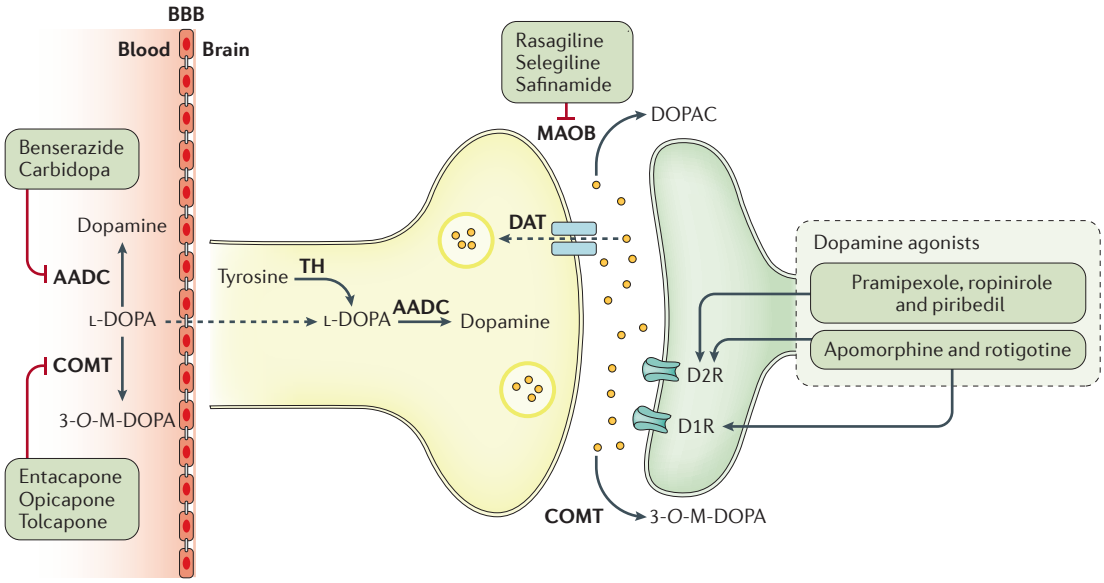

Figure 7 | **Dopaminergic drug targets in Parkinson disease.** Presynaptic targets include L-DOPA substitution combined with peripherally active inhibitors of aromatic amino acid decarboxylase (AADC) or catechol-*O*-methyltransferase (COMT). Monoamine oxidase type B (MAOB) inhibitors enhance the synaptic availability of dopamine (both endogenous and exogenous), whereas dopamine agonists act postsynaptically. Dashed arrow from blood to brain designates blood–brain barrier (BBB) transport of L-DOPA. Dashed arrow through the dopamine transporter (DAT) denotes reuptake of dopamine from the synaptic cleft. 3-*O*-M-DOPA, 3-*O*-methyl-DOPA; D1R, dopamine D1 receptor; DOPAC, 3,4-dioxy-phenylacetic acid; TH, tyrosine hydroxylase.

Catechol-O-methyltransferase inhibitors. Current L-DOPA preparations include inhibitors of aromatic amino acid decarboxyalse (AADC) — for example, carbidopa or benserazide — to prevent peripheral metabolism of dopamine and enhance bioavailability (FIG. 7). As a consequence, the peripheral metabolism of L-DOPA is shifted towards the activity of a secondary metabolic pathway that involves ortho-methylation of L-DOPA via catechol-*O*-methyltransferase (COMT). Inhibition of this enzyme in the periphery will further enhance bioavailability and the half-life of L-DOPA, which is of particular benefit in patients who have developed motor fluctuations of the wearing-off type[152]. Extending the duration of effect of individual L-DOPA doses via COMT inhibitors has become a first-line treatment in these individuals, and currently, three preparations are available for clinical use[153,154].

Monoamine oxidase type B inhibitors. Oxidation via monoamine oxidase type B (MAOB) in glial cells is a major clearance mechanism for synaptically released dopamine, next to presynaptic reuptake via the dopamine transporter[155] (FIG. 7). Inhibition of MAOB prolongs and increases synaptic dopamine concentrations, and symptomatic efficacy of MAOB inhibition using the selective inhibitor selegiline as an adjunct to L-DOPA was shown already in the 1970s[156]. More recent studies have established the antiparkinsonian efficacy of monotherapy with selegiline and the newer MAOB inhibitor rasagiline, which has also been found to be efficacious when added to L-DOPA in patients with motor fluctuations[153]. Although both selegiline and rasagiline are irreversible ('suicide') inhibitors of MAOB, the most recent marketed agent, safinamide, acts as a reversible MAOB inhibitor[157].

Dopamine agonists. The actions of dopamine on striatal medium spiny neurons are mediated via two classes of dopamine receptors (FIGS 4,7). Dopaminomimetics with direct activity to dopamine receptors (dopamine receptor agonist) mainly target the D2 receptor family and were first introduced into Parkinson disease therapy in the 1970s with the ergot alkaloid bromocriptine and have since become an important medical therapy for motor symptoms[153,158]. Initial members of this family of drugs were ergoline derivatives, which also activate 5-hydroxytryptamine (5-HT) receptors, including the 5-HT_{2B} subtype, and these became associated with pleuropulmonary and cardiac valvular fibrosis, which introduced important safety concerns. Currently used agents (listed in FIG. 7) are all non-ergoline drugs and are devoid of this activity. An important advantage of dopamine agonists is their longer half-life than L-DOPA, which makes them attractive candidates as adjunct therapies in patients with motor fluctuations[153,159]. In addition, rotigotine is available as a transdermal patch formulation that affords continuous drug delivery. Overall, dopamine agonists are believed to induce less pulsatile striatal dopamine receptor stimulation than L-DOPA and this is taken as an explanation for the markedly reduced risk to induce motor complications when dopamine agonists are used as initial monotherapy in Parkinson disease[158,159]. Drawbacks include their reduced overall effect size as compared with L-DOPA and their potential to induce drowsiness and impulse dyscontrol — the latter being possibly associated with their preferential activity at D3 receptors that are located in the ventral striatum, which causes excessive stimulation of the brain reward systems[160]. Apomorphine stands out among the other dopamine agonists in terms

of combined activity at both D1 and D2 receptors and equipotency to L-DOPA[161]. Continuous subcutaneous apomorphine infusions not only smoothen out motor response fluctuations but have also been associated with reductions of pre-existing L-DOPA-induced dyskinesias[162]. Currently, new apomorphine formulations, for sublingual use, are in clinical development[163].

Non-dopaminergic pharmacological targets

Despite the remarkable effect of dopaminergic therapy on the symptoms of Parkinson disease, there is a clear need for therapies that target other pharmacological systems. The symptom categories that need to be addressed by such treatments include the complications of L-DOPA therapy, such as motor fluctuations and L-DOPA-induced dyskinesia as well as L-DOPA-resistant ('non-dopaminergic') motor features including treatment-resistant tremor, freezing of gait, postural instability and falls, swallowing and speech disturbances. Currently, the only available and effective pharmacological treatment for L-DOPA-induced dyskinesia is amantadine, which is thought to work as an *N*-methyl-D-aspartate receptor antagonist[153,158,159]. TABLE 2 provides a summary of non-dopaminergic pharmacological treatments that are used or are under development to address various motor problems in Parkinson disease.

In some patients, selected non-motor complaints (such as pain, anxiety, panic, depression and restlessness) can fluctuate in response to dopaminergic therapy and these 'non-motor fluctuations' can be equally or more disabling than the motor symptoms[121,164]. Many non-motor symptoms do not respond to dopamine replacement therapy and some are indeed aggravated or precipitated by this treatment[121]. Anatomical targets for these problems include afferent, efferent and intrinsic basal ganglia connections, various brainstem-originating projections as well as intrinsic cortical connections and, finally, numerous targets outside the central nervous system (for example, in the autonomic nervous system)[165]. Non-dopaminergic neurotransmitter and neuromodulatory systems in these various regions that have been implicated in the symptoms of Parkinson disease include glutamatergic, adenosinergic, noradrenergic, serotonergic, GABAergic, opioidergic, cholinergic and histaminergic pathways[166].

Cognitive dysfunction, depression and autonomic failure are among the most prevalent and troublesome non-motor issues in Parkinson disease. Cholinesterase inhibitors can have striking beneficial effects on the cognitive disturbances of patients with Parkinson disease who also have dementia, an effect that is possibly related to the considerable loss of cholinergic projections from the nucleus basalis of Meynert[167,168]. The most effective therapy for psychotic symptoms in Parkinson disease is clozapine[167,168]. All other available atypical neuroleptics, apart from quetiapine, worsen parkinsonism, probably by blocking striatal dopamine D2 receptors. The exact mechanism of action of clozapine in psychosis associated with Parkinson disease is uncertain; a serotonergic effect is strongly supported by the recent positive results using the 5-HT_{2A} inverse agonist pimavanserin[169]. It is not known whether depression in Parkinson disease has the same anatomical and pathogenetic bases as depression in the general population[170]. In fact, consistent with depression in other circumstances, it is likely that depression in Parkinson disease is not a uniform, homogeneous disorder. Although patients may respond to all types of antidepressant medications, there is limited evidence that tricyclic antidepressants may be more effective than selective serotonin reuptake inhibitors, suggesting a greater role for noradrenergic systems; although this remains to be firmly established[167]. Finally, autonomic dysfunction is extremely common, particularly in late-stage Parkinson disease, and pharmacological therapies are largely directed at autonomic nervous system targets. They include the mineralocorticoid fludrocortisone and adrenergic agents (such as midodrine and etilefrine), the noradrenaline precursor (that is, droxidopa) to treat orthostatic hypotension, antimuscarinics (such as oxybutynin, tolterodine or trospium chloride) for urinary urgency or incontinence, and pro-kinetic drugs (such as macrogol or lubiprostone) to improve constipation[158,167,171].

DBS

The breakthrough for DBS as a treatment for Parkinson disease came in 1993 when new concepts of the basal ganglia circuitry led to the identification of the subthalamic nucleus (FIG. 4) as a novel target for DBS[172]. DBS is based on the finding that high-frequency (100–200 Hz) electrical stimulation of specific brain targets can mimic the effect of a lesion without the need for destroying brain tissue and involves the implantation of an electrode in brain tissue. Since then, numerous

Box 2 | **L-DOPA-induced motor complications**

Chronic exposure to L-DOPA is associated with the development of motor complications in ~30% of patients with Parkinson disease after 2–3 years of exposure and >50% after >5 years. Major risk factors are high L-DOPA dose, longer disease duration and younger age. Motor response fluctuations are often referred to as on–off oscillations in analogy to a switch-like action, in which individual doses of L-DOPA produce symptom control ('on' state), which is replaced by the 'off' state when the drug effects have worn off and symptoms recur. They reflect the short half-life of L-DOPA, but variations in gastrointestinal absorption and blood–brain barrier transport as well as striatal pharmacodynamic changes also have a role, thus producing different patterns of variation in motor response.

L-DOPA-induced dyskinesias are adventitious involuntary movements that may be choreic, dystonic or mixed in appearance and occur in different temporal association to the L-DOPA response cycle: dyskinesias associated with the on state are most often choreic in nature and affect the limb, trunk, face and neck, whereas movements associated with the off state are dystonic with painful cramps that chiefly affect the foot and lower limb. Some patients experience dyskinesias (choreic or mixed) at times of transitioning into an on phase or off phase (biphasic dyskinesias). Mechanisms underlying L-DOPA-induced dyskinesias include presynaptic and postsynaptic mechanisms: the loss of dopaminergic nigrostriatal terminals leads to reduced presynaptic dopamine storage capacity and dysregulated dopamine release, whereas discontinuous delivery of L-DOPA results in pulsatile activation of postsynaptic dopamine receptors. Striatal output activity becomes altered owing to supersensitivity of dopamine receptors and structural and molecular changes that lead to altered signal processing in striatal neurons. Serotonergic maladaptive plasticity associated with sprouting of striatal serotonergic terminals, which might result in ectopic dopamine release, and excessive glutamatergic activity in corticostriatal and subthalamopallidal projections both contribute to altered activity patterns in basal ganglia–thalamocortical networks.

clinical trials have confirmed the initial observation on the dramatic antiparkinsonian efficacy of DBS of the subthalamic nucleus, which is now an established evidence-based therapy for motor fluctuations and dyskinesia in patients with advanced Parkinson disease[153]. The stimulation-induced improvement is linked to the previous treatment response to L-DOPA, that is, patients with motor symptoms who do not respond to dopaminergic treatment are unlikely to respond to DBS. The only exception to this rule is drug-resistant tremor in patients with an otherwise good response to L-DOPA, in whom DBS can successfully control tremor. In general, ideal candidates have idiopathic Parkinson disease with an excellent L-DOPA response but motor complications due to long-term medical treatment[173]. Dementia, acute psychosis and major depression are exclusion criteria[173]. Patients with young-onset Parkinson disease fulfil the inclusion criteria for DBS best and are over-represented among the operated group. Although older age is not an absolute exclusion criterion for surgery, surgical adverse events are more often encountered in this group, L-DOPA-resistant symptoms are more frequent, motor rehabilitation is slower and frailty might limit the degree of functional restitution. Bilateral DBS of the subthalamic nucleus reduces (that is, improves) the UPDRS II (activities of daily living) and UPDRS III (motor) scores on average by 50–60% compared with the preoperative medical off-state. Total daily dopaminergic

Table 2 | **Non-dopaminergic pharmacological treatments in the motor symptoms of Parkinson disease***

Mechanism of action	Examples	Comments
Motor fluctuations and parkinsonism		
Adenosine A_{2A} receptor antagonists	Istradefylline, preladenant and tozadenant	• Istradefylline is approved in Japan and is under further evaluation in other countries • The development of preladenant has ceased • Tozadenant is currently in phase III
Mixed activity that includes inhibition of sodium/calcium channels and monoamine oxidase type B (MAOB) activity	Safinamide and zonisamide	• Safinamide is approved in Europe and is under review at the US FDA • Zonisamide is approved for use in Japan
Tremor		
Anticholinergics	Many available	Often poorly tolerated; newer more-selective muscarinic antagonists are under development
Mixed antagonist: 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, muscarinic M1, muscarinic M4, histamine H1, α1-adrenergic, α2-adrenergic, dopamine D2 and dopamine D4 receptors	Clozapine	Not approved for this indication; requires haematological monitoring
L-DOPA-induced dyskinesia		
N-methyl-D-aspartate receptor antagonists	Amantadine and dextromethorphan	• Amantadine is in routine clinical use; extended-release formulation of amantadine has successfully completed phase III • Dextromethorphan/quinidine combination (AVP-923) is under study (quinidine is a CYP2D6 inhibitor)
Mixed antagonist: 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, muscarinic M1, muscarinic M4, histamine H1, α1-adrenergic, α2-adrenergic, dopamine D2 and dopamine D4 receptors	Clozapine	Single positive double-blind, placebo-controlled trial, not approved in this indication and requires haematological monitoring
Metabotropic glutamate receptor 5	Mavoglurant (AFQ056) and dipraglurant (ADX48621)	• Development of mavoglurant stopped after a failed phase IIb trial • Dipraglurant is in phase II
α1-Adrenergic and 5-HT_{1A} receptor agonist	Buspirone	Clinically available as an antidepressant; phase III trial in patients with Parkinson disease who have L-DOPA-induced dyskinesia is ongoing
Leviteracetam	Binds to synaptic vesicle glycoprotein 2A and reduces neurotransmitter release	Mixed results in double-blind, placebo-controlled trials
Combined 5-HT_{1A} and 5-HT_{1B} receptor agonist	Eltoprazine	Phase II is ongoing
Selective α7-nicotinic acetylcholine receptor partial agonist	AQW051	Phase II is completed, but results are unavailable
Gait disorders, falls and freezing of gait		
Procholinergic therapy (cholinesterase inhibitors)	Donepezil and rivastigmine; other cholinergic agents (for example, varenicline, a nicotinic agonist) are under study	Variable, mild effects
Noradrenaline reuptake inhibitor	Methylphenidate	Variable effects on freezing of gait using high doses (for example, 80 mg per day)

5-HT, 5-hydroxytryptophan. *See REF. 166.

drug dosage is reduced following surgery by an average of 60%. As a consequence, dyskinesias decrease by 60–70% and hypokinetic fluctuations are markedly reduced with a decrease of daily off-time by approximately 70%[174]. Several randomized controlled trials have proven that DBS provides a better QOL than best medical management in patients with clinically relevant motor fluctuations and dyskinesia[174].

The globus pallidus internus is an alternative surgical target for the treatment of motor complications but does usually not allow reduction of medication[175]. Randomized trials comparing the two targets have produced conflicting results of either similar motor benefits[176] or inferior long-term efficacy on motor function and motor fluctuations with surgery in the globus pallidus internus versus the subthalamic nucleus[177].

DBS is a complex therapy that requires a high level of interdisciplinary expertise in the correct surgical placement of the electrode, postoperative programming and the adjustment of neurostimulation and drug therapy[173]. The most relevant adverse events are intracranial bleedings and device complications (such as infections and lead misplacements, among others), which account for a permanent morbidity of >1–3%. The mortality of DBS is <0.5%[178]. Thus, the benefit–risk profile of DBS is usually considered to be favourable, in particular, with respect to the large gains in QOL compared with best medical management observed in clinical trials. Psychiatric sequelae of DBS (for example, apathy, depression, impulsiveness or mania) are not uncommon and result from a complex interplay between disease-related psychiatric symptoms, dopaminergic imbalance due to the profound medication changes and stimulation-induced effects on limbic basal ganglia circuits[179]. Better devices allowing a finer control over the spatial distribution of current around the electrode, closed-loop neurostimulation systems autoadjusting parameters based on physiomarkers and computer-assisted expert systems for surgical planning and postoperative programming are now becoming available and might help to make the procedure less dependent on expert knowledge and provide more consistent outcomes across centres[180].

Exercise-based treatment

Most patients with Parkinson disease have to cope with residual motor disabilities that affect gait and mobility, postural control and balance, as well as speech and swallowing function, which are often poorly responsive to drugs and mostly unresponsive to DBS. In addition to historic use, a steadily increasing number of trials document the effects of various exercise-based strategies on classic motor outcomes (such as the UPDRS), specific parameters (such as gait speed, balance control, freezing, muscle strength and speech) or global measures (for example, QOL)[153,181,182]. These developments are paralleled by new research evidence for neuroplastic and the potential neuroprotective effects of activity-enhancing approaches in experimental models[183] and epidemiological evidence for Parkinson disease risk modulation by physical activity[184,185].

Quality of life

Although motor symptoms have been in the foreground of clinical approaches to Parkinson disease, the introduction of patient-reported health-related QOL measures led to the recognition that the multitude of motor and non-motor features of Parkinson disease has a wider effect on the overall health of patients than just motor impairment[121]. It is clear that QOL deteriorates with advancing disease and worsening motor disability[186], but in optimally treated patients with Parkinson disease, non-motor features, in particular, autonomic, cognitive and psychiatric aspects, are of greater importance to the QOL of patients[187]. Many non-motor symptoms are under-reported and under-recognized, and only in the past years have treatment trials for specific non-motor symptoms been conducted[167,188]. The most consistently reported non-motor feature of Parkinson disease associated with poorer QOL is depressive mood, including subsyndromal depression[170]. Most studies have excluded patients with dementia from QOL studies, but evidence is emerging that the cognitive impairment is also a considerable contributor to the QOL of patients even at early stages[189]. The range of other non-motor symptoms seen in Parkinson disease, including constipation, urinary urgency, insomnia, fatigue, pain, other neuropsychiatric presentations and sexual dysfunction, contributes to lower QOL scores, particularly in advanced disease, and are potentially treatable[190].

Clinical trials on the effect of treatments on both motor and non-motor symptoms in Parkinson disease now frequently include QOL measures. QOL measures have been used to combine assessment of efficacy and tolerability of treatments and compare the overall effect of treatments on the overall QOL of patients, rather than on specific disease aspects alone. Examples of treatments that have demonstrated improvement of QOL in patients with Parkinson disease include antiparkinsonian medications, DBS surgery[146], exercise[182], multidisciplinary intervention[191] and treatments of non-motor symptoms and comorbid conditions[188].

Well-being of the carer of a patient with Parkinson disease is also affected by the challenges of supporting a person with both physical impairments and mental health issues. The most important contributing factors to carer burden include dementia, falls and non-motor symptoms[192], and the QOL of the patient and mood are closely related to carer burden[193]. Currently, no interventions are validated to improve carer burden, although several trials are under way.

Outlook

Challenges

A major challenge in research on Parkinson disease is that environmental (for example, pollutants) and lifestyle (for example, diet, exercise and smoking) factors probably contribute to lifetime risk, in part by affecting the epigenome in the nervous system. These factors are difficult to accurately measure in large cohorts over the decades that they have a role. Second, Parkinson disease is probably a multifactorial disease. Thus, both upstream pathogenetic molecular mechanisms and some of their

downstream effects probably differ between patients, even if the final outcomes (α-synuclein aggregation and nigral neurodegeneration) are shared. Third, Parkinson disease symptomatology, clinical course and neuropathology vary between patients, which supports the idea that several forms of molecular pathogenesis coexist within the diagnostic realms of the disease. Fourth, disease development might conceivably require the simultaneous activation of more than one pathogenetic pathway, and that certain cellular defence mechanisms fail concomitantly. Last, superimposed on the complex interplay between multiple triggers and failing defences is the process of normal cellular ageing. The greatest risk factor for Parkinson disease is increasing age, and, possibly, the same molecular perturbations that are handled gracefully by a young neuron have catastrophic consequences in an aged counterpart. All this makes the development and testing of putative disease-modifying interventions in clinical trials extremely complex, and the risks to fail the test of controlled trials are high.

Predictive factors

Despite these challenges, there is now also, for the first time, a realistic possibility to define populations at risk or individuals in the earliest stages of Parkinson disease. On the basis of several prospective, population-based studies, various factors that are associated with an increased risk to develop Parkinson disease have been identified. These include behavioural aspects (such as non-smoking or non-use of caffeine), physiological changes (such as hyposmia, constipation or subtle motor abnormalities) and — most strongly of all — the presence of RBD. Genetic, proteomic, metabolomic and tissue biomarkers are also being increasingly characterized, and neuroimaging might have an important future role in providing information on the risk of developing Parkinson disease. Current prospective cohort studies are trying to assess the sensitivities, specificities and predictive value of various risk markers. Such data will be crucial to define cohorts for future disease modification studies in at-risk populations. The recently proposed MDS research criteria for prodromal Parkinson disease have already been tested retrospectively in one population-based study and hold promise as a first operational step towards future preventive studies[145].

Biomarkers

Specific and sensitive biomarkers that can be used to assess disease risk or progression or can enhance early diagnosis are a major need both in research and clinical care of patients with Parkinson disease. For example, increased levels of serum or plasma uric acid have been found to be associated with a decreased risk of developing Parkinson disease; a meta-analysis calculated a pooled rate ratio of 0.80 for Parkinson disease in people with a one standard deviation increase in the levels of uric acid[194]. Another recent study used data from six independent cohorts of patients with Parkinson disease and healthy controls to develop a classification model from 30 genetic risk factors, family history, olfactory function, sex and age, and found excellent separation between the two diagnostic groups[195].

Alterations of gut microbiota have only recently moved into the focus of Parkinson disease research, with several studies showing differences in the composition of the gut microbiota in patients with Parkinson disease compared with controls[196] (see Supplementary information S2 (table)). The application of 'omics' techniques — such as proteomics, metabolomics and transcriptomics — are powerful tools that are capable of mass analyses to identify small changes in protein, metabolite or RNA profiles in fluids or even tissue from healthy and diseased individuals, and they have been started to be used in Parkinson disease[197]. The recent initiation of large multi-site consortia for biomarker development in Parkinson disease holds promise for the discovery of new powerful biomarkers[136].

In addition, recent studies have tried to detect α-synuclein-related pathology in the autonomic nervous system using skin punch biopsies, biopsies of the salivary glands as well as gastrointestinal biopsies with the ultimate goal to define diagnostic markers for the earliest stages of Parkinson disease[66]. Two studies found increased aggregation of α-synuclein and fibre loss in autonomic sudomotor and pilomotor fibres in skin punch biopsies, and these characteristics separated patients with Parkinson disease from controls with a high diagnostic accuracy[198,199]. Intriguingly, studies have also found immunostaining for phosphorylated α-synuclein in colonic and submandibular gland biopsies in individuals with idiopathic RBD, suggesting that this marker might be used to detect prodromal Parkinson disease (see below)[200,201].

Experimental therapies

Two highly experimental techniques that are focused on achieving structural or neurochemical brain repair in Parkinson disease have generated great interest during recent decades: gene therapy and cell transplantation. Although progress towards successful clinical translation has not been rapid in either case, both remain conceptually important approaches that, if successful, can have great clinical impact. In addition, recent advances in our understanding of the molecular pathogenesis of Parkinson disease have revealed novel therapeutic targets for disease-modifying pharmacological therapies.

Gene therapy. The two main strategies for gene therapy in Parkinson disease are viral vector-mediated expression of growth factors or neurotransmitter-synthesizing enzymes. A vast body of experimental evidence suggests that members of the glial cell line-derived neurotrophic factor (GDNF) family protect nigral dopaminergic neurons from death and promote regeneration of their axons following damage[202]. A small open-label trial with GDNF injections into the putamen in patients with Parkinson disease generated optimism by suggesting that GDNF might reduce symptoms[203], but a larger placebo-controlled trial with injections of smaller doses of GDNF failed to show clinical benefit[204]. This disappointing outcome of the controlled GDNF trial did not deter the company Ceregene from testing gene therapy that induced expression of neurturin, a less potent

member of the GDNF family of growth factors that had demonstrated efficacy in animal models[205]. In a series of trials targeting the putamen or both the putamen and the substantia nigra, it was found that adeno-associated virus (AAV)-mediated expression of neurturin was safe, but again neither approach stood the test of randomized clinical trials[206,207]. Post-mortem findings suggested that neurturin was only expressed in relatively few cells surrounding the injection tracts, limiting its neurorestorative potential, and it has been suggested to target earlier stages of Parkinson disease, when more of the nigrostriatal axons still remain functional[206,207]. An ongoing safety trial (predicted to be completed in 2018) is testing the effects of AAV-mediated expression of GDNF in Parkinson disease, and with improved vector technology and better understanding of the effects of growth factors, it is likely that there will be additional attempts at inducing neurorestoration in the future.

Clinical trials are also underway using viral vector-mediated expression of key enzymes in the dopamine synthesis pathway. Thus, in different studies, lentiviral and AAV vectors that express tyrosine hydroxylase with cofactors and AADC have been injected into the striatum, with initial safety reports already published[208,209]. The strategy is to genetically modify cells in the striatum so that they can produce and release dopamine locally, either from tyrosine or from peripherally administered L-DOPA or dopamine. Animal studies have demonstrated that this approach is feasible and that it might not just provide relief of dopamine-dependent motor symptoms, but by providing constant dopamine receptor stimulation, it could also reduce the risk of motor fluctuations developing later on[210,211]. Another approach has targeted the subthalamic nucleus with AAV2 vector-mediated delivery of glutamate decarboxylase to induce GABAergic inhibition of subthalamic nucleus firing, with promising results from a sham-surgery-controlled phase II trial[212].

Fetal cell transplantation. In the 1990s, cell transplantation was considered a promising approach to brain repair in Parkinson disease. Open-label trials suggested that immature dopaminergic neurons obtained from aborted embryos or fetuses not only could restore striatal dopamine transmission and connectivity (as evidenced by *in vivo* PET and morphological findings upon autopsy) but also could reduce the motor symptoms[213,214]. However, the publication of two US NIH-sponsored, double-blind, placebo-controlled trials in 2001 and 2003 brought the clinical programmes to a standstill[215,216]. Not only was there no evidence of clinical benefit in these trials but it was also reported that some patients developed uncontrollable graft-induced dyskinesias[215,216], which was also confirmed in a retrospective analysis of patients in the open-label trials[217]. Although the clinical trials were halted, laboratory research into the mechanisms underlying these adverse effects started at the same time as the modern era of research into regenerative stem cell therapies was born. On the basis of animal experiments and clinical observations, today, it is believed that graft-induced dyskinesias are unlikely to develop if the number of serotonergic neurons included in the dissected graft tissue is minimized[218] and if the selected patients do not already exhibit L-DOPA-induced dyskinesias before surgery[219]. In 2008, concerns were raised about the future of the cell transplantation approach when it was reported that Lewy pathology appears inside grafted neurons over 10 years after surgery. Today, the consensus is that there are progressive signs of degeneration (loss of dopamine transporters and tyrosine hydroxylase, as well as the appearance of Lewy pathology) in grafted neurons[220], but that it takes well over a decade before these pathological changes might impair the function of the transplants. In the open-label setting, quantitative evidence of beneficial graft effects was shown in at least two patients up to 15–18 years after surgery[221]. In 2015, an open-label study with fetal dopaminergic neuron implants was initiated by the European Union-funded team TRANSEURO; this group plans to have operated on 20 patients, all at a relatively early stage of disease, before the end of 2017 (REFS 222,223). This trial will help to clarify whether graft-induced dyskinesias can be avoided and will also help to lay the foundations for future trials that use stem cell-derived neurons as the source of transplantable dopaminergic neurons.

Stem cells as donor tissue. Over the past 10–15 years, experimental stem cell therapy in animal models of Parkinson disease has developed dramatically[222]. Today, it is possible to generate dopaminergic neurons with midbrain characteristics from two forms of human pluripotent stem cells: human embryonic stem cells and human induced pluripotent stem cells[222]. Recent studies have shown that they survive grafting into animals, grow axons that innervate the brain and support functional recovery from lesion-induced deficits[222]. Current research is focused on resolving issues related to scaling up production of cells, guaranteeing safety and meeting the increasing regulatory demands that are placed on biological products[222]. Although several commercial entities already advertise different types of stem cell therapies for Parkinson disease, the underlying scientific rationale for using the proposed cell type is frequently not strong[224]. The development of stem cell-based trials should follow the guidelines set forth by the International Society for Stem Cell Research[225]. One can expect that cell transplantation clinical trials in Parkinson disease that use stem cell-derived products, which are well-validated scientifically, will commence 2–3 years from now. Progress in this area is stimulated by the existence of an international consortium of scientists called G-Force-PD, which is devoted to clinical translation of stem cell therapy in Parkinson disease and holds regular meetings in which technical advances and protocols are shared[222].

Novel targets for disease modification. The growing evidence for oligomerization and fibrillar aggregation of pathological α-synuclein species and their possible cell-to-cell transmission as a key event in the molecular pathogenesis of Parkinson disease has moved

multimerization and extracellular and intracellular handling of this protein into focus as targets for novel therapies. Two immunological approaches are currently in active clinical development. First, active immunization with a novel vaccine containing short peptides that are homologous to α-synuclein conjugated to a carrier (AFFITOPE, AFFiRiS) induced the formation of antibodies specifically directed against the carboxy terminus of human α-synuclein, cleared α-synuclein aggregates and reduced neuropathology in a transgenic mouse model of Parkinson disease[226]. A phase I/II safety trial in 28 individuals with Parkinson disease also provided evidence for induction antibody formation against α-synuclein without safety concerns, as well as immunological efficacy of booster vaccinations up to 3 years after initial immunization[227]. A placebo-controlled phase II trial of AFF03, a second AFFITOPE technology vaccine against α-synuclein, is currently ongoing.

A second approach is passive immunization via monoclonal antibodies against α-synuclein and, to date, three candidate compounds have reached early phases of clinical development[228]. Following the recent publication of a first-in-human placebo-controlled phase I study of one of these compounds (PRX002)[229], this field will almost certainly also gain momentum over the next 5 years in Parkinson disease.

Other α-synuclein targeting approaches focus on extracellular α-synuclein-binding sites, inhibitors of α-synuclein aggregation or enhancers of α-synuclein clearance via the LAS[135,230], but have not yet progressed into clinical development. However, other experimental approaches pursue different targets, including the agonist of the glucagon-like peptide 1 receptor (exenatide)[231], the urate precursor (inosine)[232], the GBA chaperone (ambroxol)[233] or the calcium channel antagonist (isradipine)[234], and some of these are currently being tested in clinical trials in Parkinson disease.

Clinical trials

To date, all clinical disease modification trials in Parkinson disease have been performed in individuals with early disease as defined by the presence of classic motor features, and they have all failed to show unequivocal positive effects. Studying interventions in the prodromal or preclinical phase of disease should offer greater promise of success, assuming less-advanced pathology and greater potential to intervene at crucial points of molecular pathogenesis. These could have a greater likelihood of success if patients who are recruited into clinical trials can be shown to share some form of biomarker that relates to the therapeutically targeted pathogenetic mechanism.

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