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Non-motor features of Parkinson disease

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Abstract | Many of the motor symptoms of Parkinson disease (PD) can be preceded, sometimes by several years, by non-motor symptoms that include hyposmia, sleep disorders, depression and constipation. These non-motor features appear across the spectrum of patients with PD, including individuals with genetic causes of PD. The neuroanatomical and neuropharmacological bases of non-motor abnormalities in PD remain largely undefined. Here, we discuss recent advances that have helped establish the presence, severity and effect on the quality of life of non-motor symptoms in PD, and the neuroanatomical and neuropharmacological mechanisms involved. We also discuss the potential for the non-motor features to define a prodrome that may enable the early diagnosis of PD.

Parkinson disease (PD) is a progressive neurodegenerative disorder that involves multiple neurotransmitter pathways within the brain and autonomic nervous system that in turn are associated with a range of clinical features (TABLE 1). The diagnosis of PD is currently dependent on the presence of motor deficits including bradykinesia, rigidity and tremor, usually manifesting unilaterally or at least asymmetrically[1]. The motor features are predominantly a consequence of the loss of dopaminergic neurons in the substantia nigra pars compacta (SNc), and the symptomatic therapy used in PD currently focuses on dopamine replacement strategies. Advancing disease and increased doses of levodopa result in the development of motor complications that are characterised by wearing off periods and off periods, during which bradykinesia and rigidity reappear, an absence of on periods and the development of involuntary dyskinesias[2].

Although the diagnosis of PD relies on the clinical effects of dopamine deficiency, this disease is associated with other neurotransmitter deficits that are recognized to cause various motor and non-motor symptoms and signs. Some of these symptoms and signs — for example. hyposmia, rapid eye movement (REM) sleep behaviour disorder (RBD), depression and constipation — can precede the symptoms related to dopamine deficiency by several years[3]. Alternatively, these and other non-motor problems may arise later in the disease (FIG. 1). Global cognitive decline, in particular executive dysfunction and problems with working memory, has been also described in people at risk of developing PD [4].

Although subtle cognitive deficits may be present at the diagnosis of PD, these become more significant in the later years of the disease, and they are often present in people with PD aged over 70 years old regardless of the age of disease onset[5]. Indeed, with the progression of neurodegeneration and advancing disease, non-motor problems such as cognitive impairment, autonomic dysfunction and sleep disorders come to dominate the clinical picture and are the main determinants of quality of life and institutionalisation (FIG. 2)[6]. Indeed recent evidence suggests that PD may have several endophenotypes, and some of these endopheotypes are dominated by non-motor symptoms[7].

Two of the major therapeutic challenges for PD are the development of disease-modifying treatments to slow or prevent the progression of neurodegeneration, and the development of effective symptomatic interventions for non-motor features. This Review will summarise the spectrum of non-motor problems in PD, addressing the pathological, pharmacological and clinical aspects of each, the model systems developed to study them, and the prospects of using non-motor features to define a pre-diagnostic prodrome of PD. In discussing the potential modelling of non-motor features of PD, we recognise the limitations of

existing toxin and genetic animal models in recapitulating the clinical and pathological characteristics of the disease, as well as its progressive nature — a feature specifically lacking in the toxin models. It is also important to distinguish animal models based on toxins, such as rotenone or 6-hydroxydopamine (6-OHDA), which do not act through mechanisms that reflect the complex pathogenic processes underlying PD, from those based on genetic forms of PD, most frequently α-synuclein transgenic mice. The lessons from these mice are limited by the lack of comprehensive investigation of non-motor symptoms in any one study or any one non-motor symptom with different models, including different species and strains. No model type, toxin or genetic, has shown consistency in the evaluation of any specific non-motor feature. Furthermore, we also accept that the presence of motor symptoms may interfere with the ability to evaluate of non-motor abnormalities such as anxiety, depression and cognition. Despite these caveats, the animal models described can provide some insight into the pathology and pharmacology of non-motor dysfunction in PD. The pharmacological basis of the non-motor features of PD is of relevance to the development of future therapies. Currently, dopaminergic treatments are the most widely used therapies, but they have no impact on those aspects of the disease that are related to other neurotransmitter deficits. This is reflected in the limited therapies available for non-motor deficits[8].

[H1] Sensory features

Sensory symptoms, and pain in particular, are common non-motor features of PD. Indeed, virtually all patients with PD experience at least one sensory symptom as part of their prodrome, and such symptoms increase in prevalence and severity with the progression of the disease.

[H3] ***Olfactory deficits***. Hyposmia or anosmia develops in more than 90% of patients with PD, is usually bilateral and may precede the onset of the dopamine deficiency-related motor features[9]. Although hyposmia is not often reported by patients, the presence or progression of hyposmia could represent a biomarker for early pre-motor PD, particularly if it is combined with other early clinical, imaging and/or biochemical markers, such as reduced noradrenergic denervation of cardiac tissue and cognitive dysfunction[10-14]. The development of hyposmia and RBD (see below) may reflect the evolving distribution and spread of Lewy bodies in PD from the lower medulla, as described by Braak and colleagues (FIG. 3)[15]. However, the presence of olfactory dysfunction in later stages of PD may also be linked to cholinergic denervation and the onset of cognitive deficits and dementia[16,17].

Alterations in olfaction in PD seemingly owe to changes in central olfactory processing, as biopsy samples of the olfactory epithelium from individuals with the disease are normal[18]. Indeed, MRI studies revealed that, compared with healthy controls, individuals with PD showed varying degrees of decreased volume of and sulcus depth in the olfactory bulb[19]. Moreover, Lewy bodies and Lewy neurites, as detected by α-synuclein immunoreactivity, were found in the olfactory bulb, the olfactory cortex and other brain regions related to olfaction (including the amygdala) in PD and in incidental Lewy body disease (ILBD) but rarely in healthy controls[20,21,]. Individuals with PD also showed a loss of mitral cells and substance P-containing cells in the olfactory bulb, and a reduction in the level of calcium binding protein in this region, but dopaminergic- or somatostatin-containing cells are rarely affected in either the olfactory bulb or associated nuclei[22]. Patients with PD also showed an increase in periglomerular dopaminergic neurons, although this finding was not specific to PD as it also occurred in Alzheimer disease (AD) and in frontotemporal dementia. The failure of olfactory deficits to respond to dopaminergic medications probably reflects the lack of involvement of dopaminergic systems in the olfactory defects[23].

Some evidence exists for olfactory deficits in rodent models of PD but this evidence has proved controversial. Mice and rats receiving intranasal or intra-peritoneal 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) to model PD exhibited impaired olfaction and reductions in the levels of dopamine and noradrenaline in the olfactory bulb[24,25]. However, impaired olfaction following intranasal administration of MPTP may simply reflect damage to the olfactory epithelium[26]. No evidence exists to suggest that administration of MPTP causes olfactory changes in primates.

Mice overexpressing human wild-type α-synuclein, a transgenic model of PD, have olfactory deficits: they show progressive losses in the abilities to detect and discriminate odours, which is associated with α-synuclein accumulation in the olfactory bulb, although no evidence exists for dopaminergic cell loss at least in the substantia nigra[27-29]. Mice expressing α-synuclein–green fluorescent protein (GFP) also display olfactory dysfunction as well as progressive motor impairment and the accumulation of α-synuclein-GFP in the olfactory bulb [30,31]. These mice do not show increased sensitivity to olfactory neuronal loss following the administration of paraquat[32]. Furthermore, mice carrying the human α-synuclein A53T mutation show progressive α-synuclein accumulation in the olfactory bulb, marked loss of glutamatergic and calcium binding protein immunoreactivity, but no change in the number of dopaminergic cells[33]. However, in this particular study, no assessment of olfaction was made.

Why rodents express some abnormalities in olfactory function and pathology in these toxin and genetic models is not clear, but these deficits may reflect the greater CNS representation of olfaction in these animals than in primates. Interestingly, the temporal expression pattern of α-synuclein modulates olfactory neurogenesis in transgenic mice[34]. Therefore, overall, these findings are consistent with the concept that olfactory changes occur early in the course of PD and can precede the onset of motor deficits that owe to dopaminergic cell loss, and that they may be linked to α-synuclein-mediated pathology and to altered neurogenesis. Olfactory function has emerged as an important component of the PD clinical prodrome but our ability to model its pathological basis has limited our understanding of its relationship to the progression of the disease.

[H3] ***Visual disturbances.*** Visual disturbances in general are relatively common in PD with some studies reporting that up to 78% of patients are affected by such disturbances[35,36], although another study reported that visual symptoms occurred in 22% of people with PD versus 4% of age-matched controls[37]. The incidence of visual hallucinations and diplopia (double vision) in PD increases with disease progression[38]. Impaired acuity does not improve with dopaminergic therapy, and indeed visual hallucinations may worsen, particularly with dopamine agonist treatment[39]. Some of the visual disturbances in PD, particularly hallucinations, have been linked to the presence of Lewy bodies in the occipital lobe and in retinal neurons, and to the loss of dopaminergic amacrine cells and the regulatory role of D1 dopamine receptors (D1Rs) and D2Rs in the eye[40]. Altered visual fields occur in primates following administration of the dopaminergic toxin MPTP and intra-ocular injection of the catecholaminergic toxin 6-OHDA, again suggesting some direct involvement of altered dopaminergic function in the eye[41,42]. There is also some evidence to suggest that thinning of the retinal nerve fibre layer occurs in patients with PD, as identified by ocular coherence tomography, but this finding is disputed[43,44]. Mutations in glucocerebrosidase (*GBA*) are numerically the most important risk factor for PD[45] and retinal thinning has been described in carriers of these mutations with and without PD[46].This finding suggests that retinal thinning may be used as part of a PD risk calculator for *GBA* mutation carriers. In PD patients with normal vision, electrical activity of the fovea, which is responsible for central acuity, is decreased and retinal thinning is present[47], which may reflect decreased innervation around the fovea and reduced retinal dopamine concentrations in these individuals.

Hallucinations, previously thought to be typical drug-related adverse effects in advancing PD, have now been reported to occur even in untreated PD in the prodormal phase[48]. The

development of visual hallucinations is associated with cognitive impairment and dementia in PD and such hallucinations may be a good predictor of cognitive decline in later disease[49]. Visual hallucinations in PD have been linked with perceptual, executive and sleep dysfunction and probably reflects the distribution of Lewy body pathology[22,50]. Treatment with dopaminergic therapies, especially dopamine agonists, is associated with an increased risk of visual hallucinations, implying that dopaminergic signalling is involved in their generation[39].

[H3] ***Pain and somatosensory disturbances.*** Changes in sensory function and onset of pain are a common feature of PD affecting 30–85% of the patient population[51,53], and remain under-reported [51,54-60]. Pain in PD has various causes[6,54-61]. Several methods have been proposed to classify the complex pain syndrome of PD, and they mainly cover, or have been applied to two broad categories of pain, namely nociceptive and neuropathic pain[51,55] . Pain also fluctuates with the motor state of the patient, often worsening during the off state (termed 'off related pain'), whereas in some patients a central variant of pain is evident[55-57, 62,63].

A variety of causes of sensory-related symptoms in PD have been identified, which can be largely divided according to whether they have a musculo-skeletal origin (for example, causes that result in stiffness, dystonia or muscle cramps) or they have a central origin and are primarily related to the neurodegenerative process in PD[6]. Other sensory changes occur in PD, including peripheral paraesthesia, burning sensation and the so called 'burning mouth syndrome', all of which can be recognised using the Chaudhuri–Schapira classification of pain in PD[6].

The basal ganglia sustain sensory function through the modulation and integration of information from the substantia nigra, cortex, thalamus and many other nuclei. In PD, loss of dopaminergic input to the basal ganglia alters sensory perception and changes pain thresholds[64,65]. However, dopamine can also modulate pain in regions outside of the basal ganglia, including the spinal cord, thalamus, periaqueductal grey and cingulate cortex[66]. Evidence exists indicating that dopaminergic function may modulate sensory perception: for instance, pain occurs more frequently in patients during off periods and pain thresholds are raised by dopaminergic medication[67]. However, dopaminergic medication does not eliminate pain in PD and therefore additional non-dopaminergic mechanisms must underlie this symptom. The ascending and descending pathways are involved in pain: for example, the spino-thalamic tract sends collaterals to the locus coeruleus, raphe nuclei, amygdala and thalamus, and these areas receive inputs from higher centres to control the sensitivity and excitability of the somatosensory system[68-70]. The serotonergic raphe nuclei and the noradrenergic locus

coeruleus are both affected by pathological change in PD and both play a role in 'gain setting' for pain control[71].The raphe nuclei send descending fibres to the dorsal horn of the spinal cord that modulate pain processing[72] and the nociceptive neurones in lamina I of the dorsal horn show α-synuclein immunoreactive inclusions in PD[73]. Peripheral de-afferentation may also occur in PD, which may affect nociceptive input to the spinal cord[74]. Thus multiple neurotransmitter pathways subserve the symptom of pain in PD, and it is challenging therefore to provide specific pain-relieving treatments.

In the clinical arena, classification of the type of pain in PD is essential for correct diagnosis and treatment. There are both dopaminergic and non-dopaminergic pain pathways, as well as neuropathic and nociceptive pain. Clinical classification is aided by the recent validation and description of the Kings Parkinson Pain Scale (KPPS), which is based on the Chaudhuri–Schapira classification of pain and classifies pain in PD to musculoskeletal, fluctuation related, central, nocturnal orofacial and peripheral pain[75]. The KPPS has aided the reporting of the first ever randomised placebo controlled trial of an opiate (oxycodone combined with naloxone) to treat pain in PD (the PANDA study (NCT014391000))[76] and of a randomized trial with the rotigotine transdermal patch (the DOLORES study (NCT01744496)[77].

The treatment of pain in PD is first directed to the relief of symptoms related to off periods and involves administration of dopaminergic medications; such agents may be combined with analgesics or pain-modulating drugs as required[52]. Painful dystonia may be relieved with botulinum injections in selected patients who do not respond to changes in their dopaminergic therapy[78]. Current evidence, therefore, allows clinical classification of pain using the KPPS and the initiation of individualised therapies. Fluctuation-related pain could be managed by strategies that use continuous drug delivery such as the rotigotine patch or other drugs given by infusion while non-dopaminergic medication-responsive pain may require use of opiate or other analgesia, as suggested by the PANDA study[79].

[H1] Neuropsychiatric features

Neuropsychiatric features such as anxiety and depression occur in PD from the prodromal pre-motor phase to the late stages of the disease and they fluctuate with the motor state; anxiety in particular is dominant during off periods. Overlap between anxiety and depression is also common, the anxious depressed phenotype and recognition is important for effective management.

[H3] ***Anxiety***. Anxiety affects up to 60% of patients with PD and encompasses generalized anxiety (apprehension, fear and worry), panic attacks and social phobias, and it is commonly but not always accompanied by depression[80,81]. Anxiety is seen more commonly in females, patients with disease onset at a young age and patients with advanced disease[82]. Levels of anxiety increase with motor fluctuations, which are associated with periods of low dopamine levels, and with the onset of off periods or freezing[83]. Dopaminergic therapy and deep brain stimulation improve symptoms of depression, which may be secondary to improved motor function and could also indicate a dopaminergic component to anxiety[81,84]. Anxiety, often in association with depression, can occur prior to the onset of motor signs of PD, suggesting this symptom may be related to pathology outside the nigrostriatum[85].

Positron emission tomography (PET) imaging using the catecholaminergic binding ligand ^{11}C-RTI-32 has revealed that in PD patients with depression and anxiety, but not PD patients without depression, there was a decrease in the binding of this ligand, and that the level of binding was inversely correlated with the severity of anxiety but not depression[86]. This suggests that anxiety has a separate neurochemical basis to depression in PD patients with both. Clinical studies have also suggested the existence of several phenotypic variants of anxiety and depression in individuals with PD, ranging from those who exhibit both anxiety and depression to those with anxiety- or depression-alone subtypes[82].

Bilateral 6-OHDA lesioning of the nigro-striatal pathway in rats leads to increased anxiety-like behaviour in the elevated plus maze and is associated with reductions in dopamine, noradrenaline and 5-HT levels[87]

in this task[88]. In genetic models of PD, parkin-null mice and vesicular monoamine transporter 2 (VMAT2)-deficient mice at 6 months show signs of anxiety-like behaviour in the elevated plus maze[89,90]. Overexpression of wild-type α-synuclein in mice decreases anxiety-like behaviour in the elevated plus maze and the light–dark box paradigm, but this change in behaviour may reflect hyperactivity, as increased anxiety-like behaviour is observed in fear-conditioning tests in these mice[28]. In rats, subcutaneous infusion of paraquat and orbilateral delivery of α-synuclein into substantia nigra using a viral vector induced anxiety-like behaviour[91]. However, despite the behavioural changes observed in these models, little evidence exists to explain the pathological or biochemical basis for the expression of anxiety in people with PD.

[H3] ***Depression***. Depression is common in patients with PD and considered clinically significant in 35% of the patient population[92]. In comparison with depression observed in people

without PD, PD-related depression is generally milder, although it more frequently involves apathy and anhedonia.

Depression in PD may predate the onset of motor symptoms[93]. It has been correlated with disease duration, the severity of motor symptoms, the occurrence of motor complications or fluctuations and the dosage of dopaminergic medication[94]. Moreover, cognitive decline and dementia, psychotic episodes, anxiety, sleep disturbance and autonomic symptoms have all been linked to an increased risk of depression in PD[95]. Thus, depression in PD is a complex phenomenon that may be a consequence of PD pathology, a reaction to the PD-associated disability, a separate phenomenon, or a combination of all three[96]. This possible complexity in the causation of PD probably accounts for the improvement of depression in only a proportion of PD patients with dopaminergic therapy.

As in endogenous depression, depression in PD is related to changes in dopaminergic, noradrenergic and serotonergic systems[86]. In addition, the loss of cortical cholinergic neurons may contribute to depression in PD. However, as the loss of this neuronal population also underlies the onset of dementia, it may be difficult to discriminate the clinical effects of such neurodegeneration in the early phase of dementia[97].

Dopamine transporter availability in the striatum and limbic brain regions (the anterior cingulate cortex, amygdala and ventral striatum) is reduced in PD patients with depression compared with individuals with PD but not depression[86,98]. Furthermore, MRI has revealed that people with PD-related depression also show a loss of white matter loss in cortico-limbic regions, which is a major site for the dopaminergic regulation of mood, motivation and reward[99].

Serotonergic function is linked to depression in the general population but there is mixed evidence for its involvement in depression in PD[86]. Degeneration of neurons in the raphe nuclei occurs in PD with a corresponding decrease in forebrain 5-HT innervation, as shown in imaging studies and post-mortem investigations. However, although there may be changes in 5-HT availability in the raphe nuclei and hypo-echogenicity on trans-cranial sonography, other functional imaging studies using PET failed to show any differences between the serotonergic systems in cases of PD with and without depression[100]. Cell loss in the dorsal raphe nuclei did not differ between PD patients with and without depression[99]. In addition, mixed evidence exists regarding whether selective 5-HT reuptake inhibitors are effective treatments for depression in PD[101].

By contrast, there is stronger evidence for a change in noradrenergic function in depression in PD. Imaging studies have showed that PD patients with depression exhibit reductions in dopaminergic and noradrenergic innervation in the locus ceruleus, thalamus and

limbic brain regions and increases in neuronal loss and gliosis in the locus ceruleus[82, 102, 103]. Interestingly, anti-depressant drugs that affect noradrenaline reuptake, namely tricyclic antidepressants like nortriptyline, may be more effective than other drugs in the treatment of PD-related depression[104].

Increased depression-like behaviour has been observed using the forced swim and sucrose preference tests in 6-OHDA-lesioned and MPTP-treated rodents, and rotenone infusion into substantia nigra in rats was associated with altered dopaminergic and serotoninergic transmission[89,105]. VMAT2-deficient mice that showed a progressive depressive-like syndrome in the forced swim test also exhibited alterations in forebrain dopamine, noradrenaline and 5-HT levels[91].

[H3] ***Apathy and fatigue****.* Apathy occurs in 60% of individuals with PD and it is increasingly recognised as a distinct non-motor component of the disease[106]. Apathy may co-exist with depression and dementia in PD but can also occur independently of both, and has been reported in cases of early-stage PD[107,108]. A report showed that among individuals with PD, those with apathy had reductions in grey matter density in the cingulate gyrus and inferior frontal gyrus[109], although another investigation did not find any fronto-temporal atrophy in PD patients with apathy[110]. Alternatively, apathy in PD may involve ventral striatal and limbic brain areas, as a group of PD patients developed apathy after deep brain stimulation in the subthalamic nucleus. Apathy in PD patients has also been associated with atrophy of the left nucleus accumbens[111]. Finally, subtypes of apathy have been described and defined according to whether they are. underpinned by a dopaminergic or a cholinergic dysfunction[112].

MPTP-treated non-human primates also display apathetic behaviour. In such primates, apathetic behaviour correlated more strongly with loss of dopaminergic cells in the ventral tegmental area, which projects to the nucleus accumbens, and with expression levels of the dopamine transporter in the nucleus accumbens, than with the degree of motor impairment. In PD patients, apathy may improve with dopaminergic medication but there has been little controlled evaluation of drug treatment[105,106], although apathy occurring after DBS responded to treatment with a dopamine agonist (ropinirole)[113]

Few clinical trials have focused on PD populations with apathy (as defined by the use of validated scales). One, 12-week placebo-controlled, double-blinded randomised study of piribedil, a dopamine agoinst, found that treatment with this agent at a dosage of up to 300mg/day led to a 34.6% reduction in apathy scores at 12 weeks (by contrast placebo reduced such scores by 3.2%)[114]. In addition, the role of the cholinergic system in apathy was translated

to a 6-month multicenter, parallel, double blind, placebo-controlled randomised controlled trial of rivastigmine (administered via a transdermal patch at 9.5 mg/day; CT00767091), which reported that this treatment led to a marked improvement in apathy[115].

Fatigue in PD is characterised by a lack of energy, exhaustion and tiredness, is distinct from apathy, and affects approximately 50% of the patient population[52]. Fatigue can be a consequence of motor dysfunction in PD or be directly related to the neuropathology, as it can be observed in treated patients with good motor function. The presence and severity of fatigue is not associated with the duration of PD or the severity of motor symptoms and it can appear before motor signs are recognised. In some patients, but not all, fatigue may be associated with the presence of depression, nocturnal sleep disturbance and autonomic symptoms. There is no association between the presence of fatigue and the type, duration or dosage of anti-parkinsonian medication used for treatment, although it improves with a reduction in off periods[116]. Basal ganglia dysfunction has been implicated in fatigue because of their connections to the limbic system[117]. However, no differences in dopamine transporter expression in the striatum have been found between PD patients with and without fatigue[118]. By contrast, patients with PD and fatigue showed reduced 5-HT transporter levels in the caudate nucleus, putamen, ventral striatum, thalamus, cingulate and amygdala compared with PD patients without fatigue[119].

[H3] ***Cognitive deficits and dementia.*** Cognitive decline and dementia are usually considered to be a component of late-stage PD or as a consequence of senescence; up to 83% of patients with PD may be affected by some level of cognitive dysfunction[120]. Individuals with a predominantly bradykinetic-rigid form of PD are more at risk of subsequently developing dementia than people who have the tremor-dominant form of the disease[121]. Late-onset dementia is characterised by visual spatial constructional deficits and recognition, semantic and episodic memory loss. These deficits do not have a basal ganglia origin but are associated with Lewy bodies in posterior cortical regions, notably the parietal and temporal lobes. The density of cortical Lewy bodies and Lewy neurites seems to correlate with the severity of dementia[122]. Distinguishing individuals with PD with dementia from those patients with dementia with Lewy bodies (DLB) or AD is sometimes difficult because both clinical and pathological changes can overlap. Indeed, tau-, amyloid- and α-synuclein-positive inclusions are present in all three conditions[123].

Dementia in PD is accompanied by a substantial reduction in cortical cholinergic markers, explaining the limited clinical response to cholinesterase inhibitors that can be seen in

some patients[124]. By contrast, dopaminergic drugs have little effect and can worsen psychosis and hallucinations associated with the dementia. However, the continual degeneration of brainstem nuclei as PD progresses may also be a contributory factor to cognitive decline in older patients. A greater loss of the dopamine transporter and dopaminergic terminals in the striatum and inferior frontal gyrus has been observed in PD with dementia than in PD without dementia[125,126]. There is also some evidence for a more severe loss of noradrenergic input from the locus coeruleus to cortical regions in cases of PD with dementia than in cases of PD but no dementia[127].

Mild, usually clinically asymptomatic cognitive impairment is also a common but under-recognised component of early PD, and the main feature of this early cognitive syndrome is impairment in executive function[128]. Early cognitive impairment is considered to be a fronto-striatal disorder that is dopamine dependent and, for which, some components (for example, executive function) may be improved by dopaminergic drugs[129]. Other features such as recognition memory and cognitive flexibility do not respond to such drugs, suggesting the involvement of different neurotransmitters[128]. Early cognitive impairment may also be influenced by polymorphisms affecting dopaminergic function. Polymorphisms determining high enzyme activity in the gene encoding catechol-O-methyl transferase (COMT) are associated with less impairment and therefore suggest that early cognitive dysfunction is attributable to a state of relative hyperdopaminergic activity in the dorsolateral prefrontal cortex compared with that in the striatum.[130] Importantly, cortical dopamine levels rise in early PD to compensate for the loss of dopamine that occurs in the striatum[131], and this compensation may adversely affect cognition, as there is an inverted U-shaped relationship between the dopamine concentration and cognition[132]. However, no change occurs in the density of D1Rs, which represent the dominant subtype of dopamine receptor that is present in cortical areas[133]. Too little or too much dopamine may therefore be detrimental and this may explain why cognition fluctuates with disease progression and with dopaminergic medication[134].

Cognitive deficits in PD have been extensively studied in rodents using lesions of the nigro-striatal pathway induced by 6-OHDA or MPTP[28,135]. A variety of tests on such rodents have shown that they exhibit impairments in cognition, but these deficits reflect the consequences of acute or severe lesions, rather than the progressive pathology of PD, and so will not necessarily reflect the cognitive decline and dementia that are observed in humans with this disease. These observations of cognitive dysfunction are also limited by many tests being dependent on motor function and the consequent effect of an induced parkisonian state on test performance. Changes in cognition have also been reported in ageing mice that overexpressed

wild-type or mutant α-synuclein[136]. In a conditional model, mice expressing high levels of human wild-type α-synuclein in midbrain and forebrain regions showed cognitive impairment and developed mild nigral and hippocampal neuropathology[137]. However, in a different study, mice expressing human wild-type α-synuclein and showing extensive cognitive deficits had no pathology in the hippocampus but exhibited cholinergic deficits in the cortex[138]. The cholinergic deficit may reflect early changes in brain regions outside the basal ganglia as this deficit preceded striatal dopamine loss. Early cognitive decline is also seen in MPTP-treated non-human primates, in which chronic low dose treatment leads to alterations in executive function and attention[139]. These abnormalities are the same as those seen in patients in the early stages of PD, so this model appears promising for the testing of new drug entities for cognitive dysfunction — for example, D1R agonists and α-7 subunit-containing nicotinic acetylcholine receptor agonists[140,141], or other drugs that may target a specific pharmacological defect. However, MPTP is not associated with α-synuclein pathology and so could not be used to test drugs designed to target α-synuclein pathology and its role in cognitive decline.

[H3] ***Psychosis***. Psychosis in PD typically occurs later in the course of the illness and common symptoms include visual hallucinations and delusions, which are present in up to 40% of cases of PD[100,142-144]. Dopaminergic therapy with levodopa and dopamine agonists can induce psychosis and such therapy was originally thought to explain its occurrence in PD.

Abnormal visual processing, sleep dysfunction and pathological and neurochemical changes have all been linked to psychosis in PD[144]. Although MRI studies have shown little structural change in cortical regions in PD patients with psychosis compared with PD patients without psychosis, they have shown alterations in the processing of visual stimuli[145]. Decreases in retinal dopamine concentrations (see above) may also contribute to changes in visual perception and processing in PD[146]. During sleep, vivid dreams, nightmares and night terrors occur more frequently in those patients with psychoses and these phenomena may have similar underlying mechanisms to daytime hallucinations[147, 148].

Classical anti-psychotics such as dopamine antagonists and atypical 5-HT-based antipsychotics are used to control symptoms of psychosis, suggesting that dopamine and 5-HT may have a role in psychosis in PD. Among individuals with PD, forebrain 5-HT levels are lower in those with psychosis than in those without psychosis[149]. Acetylcholine may also contribute to psychosis, as cortical dennervation in later stages of PD is related to susceptibility to psychosis in PD as well as in AD[150]. Anticholinergic drug use can also cause the emergence of psychosis in PD possibly by further impairing already diminished cortical cholinergic transmission[151].

Hallucinations in PD are associated with the presence of Lewy bodies in the amygdala and the frontal, temporal, parietal and visual cortices, suggesting that pathological changes in PD may directly contribute to hallucinations[152].

Few studies of experimental models of PD have investigated psychosis. In one study, a rating scale for psychosis-like behaviour in response to dopaminergic drugs was reported in MPTP-treated nonhuman primates[153-155]. Whether the behavioural changes observed reflected psychotic processes is a matter of conjecture but the behaviours rated do respond to typical and atypical antipsychotic drug treatment.

[H1] Sleep disorders

Disturbances in sleep and wakefulness affect most of the PD patient population and their prevalence increases with the duration of disease[156]. Such disturbances take a variety of forms. Daytime somnolence and 'sleep attacks' can be differentiated from nocturnal sleep disturbances. Night time sleep disorders include insomnia, which can be disease or drug-related and involve sleep fragmentation and frequent, prolonged awakening, RBD, periodic limb movements, restless leg syndrome and akathisia[157]. The return of motor symptoms when drug effects wear off during the night, dyskinesia and/or dystonia related to drug action, nightmares, hallucinations and nocturia can all exacerbate sleep disturbances[158].

Dopamine, noradrenaline and 5-HT are involved in the control of sleep and all of these transmitter systems are affected in PD[159]. Dopaminergic cells in the periaqueductal grey are activated during wakefulness in the rat and lesions of this region increase sleep periods[160]. Excessive day time sleepiness and sleep attacks may be worsened by some dopamine receptor agonist drugs, and sleep disorders, such as narcolepsy, may be treated using dopaminergic medications, suggesting a link to altered dopaminergic neuronal function[161].

Dopaminergic neurons in the ventral tegmental area–substantia nigra receive inputs from hypothalamic hypocretin (orexin) neurons and form loops controlling arousal and wakefulness ascending through the thalamus and cortex and descending via the pedunculopontine nucleus and the reticular formation.[162] Hypocretin is almost undetectable in both PD and non-PD patients with narcolepsy and decreases in the number of hypocretin neurons and in hypocretin levels in the cerebrospinal fluid and frontal cortex have been reported in PD[163,164]. Similarly, restless leg syndrome, periodic limb movements and akathisia appear to have a dopaminergic component given that levodopa and dopamine receptor agonists can improve these symptoms[81,165]. However, what is not clear is whether the dopaminergic components are central, peripheral or both.

Insomnia in patients with PD also may be related to disease pathology, but also to too little or too much dopaminergic therapy. MPTP-treated mice and monkeys have changes in sleep patterns and in REM sleep that can be manipulated by dopaminergic drugs, notably D1R agonists[166-169]. By contrast, RBD appears to have a different origin as it can occur early in the course of the disease process, long before the onset of obvious motor signs[170].

Braak and colleagues have observed the distribution of Lewy bodies in non-PD post-mortem brains and suggested that early pathology begins in the lower brain stem and ascends to involve the mid-brain and then the cortex[15]. The olfactory nucleus may also be involved at the time of medullary Lewy body pathology, although neurodegeneration begins in the substantia nigra. Wild-type α-synuclein overexpression leading to brain stem and cortical accumulation is associated with sleep disturbances in mice[171]. The concept of early brain stem involvement has been used to explain the early non-motor features of hyposmia and sleep disturbance in patients with PD[172,173].

[H1] Autonomic dysfunction

Autonomic dysfunction in PD is common and may precede motor features, but it becomes more prevalent as the disease progresses. Autonomic problems encompass bladder, bowel and sexual dysfunction, as well as cardiovascular complications such as postural hypotension.

[H3] ***Bladder dysfunction.*** Urinary dysfunction in PD includes nocturia, and increased frequency and urgency of micturition, which are associated with detrusor hyper-reflexia. Micturition regulation is dependent on the autonomic arc of the sacral spinal cord segments, but it is tonically facilitated by the pontine micturition centre; the storage function is facilitated by the hypothalamus, cerebellum, frontal cortex and basal ganglia[174-176]. Bladder hyper-reflexia in PD is thought to be related to loss of the basal ganglia's inhibitory role. Reduced dopaminergic function and globus pallidus activity can be seen in imaging studies in people with PD and bladder dysfunction compared with PD patients with normal bladder function[177,178]. More specifically, the D1R-mediated output from the basal ganglia has an inhibitory effect on micturition but the D2R mediated output is facilitatory[179]. Striatal dopamine transporter loss correlates with the severity of bladder symptoms, and caudate neurodegeneration with transporter loss may be a greater predictor for bladder symptoms than putaminal loss[68]. Bladder symptoms may improve in a minority of PD patients with dopaminergic therapy[180]. The dopaminergic effects are complex with postulated roles for D1Rs and D2Rs, dopamine auto-receptors and post-synaptic sites and central and peripheral dopamine receptor stimulation[181].

The complex pharmacological innervation presumably reflects the complexity of control of bladder function at multiple levels within the central and autonomic nervous systems.

The bladder itself is innervated by muscarinic and nicotinic cholinergic inputs and adrenergic and noradrenergic inputs[182]. No specific morphological, pathological or biochemical alterations have been found to occur in the bladder in PD patients[183]. Most evidence for dopaminergic involvement in bladder function has arisen from experimental studies in animals. Unilateral lesions of the nigro-striatal pathway using 6-OHDA in the rat cause bladder hyper-reflexia as does the administration of MPTP in non-human primate species[184-187]. Electrical stimulation of the substantia nigra and the direct injection of dopamine into the striatum can reverse these changes. Interestingly, D1R agonists improve bladder function whereas D2R agonists either have no effect or make it worse[188]. More recently, stem cell placement in the median forebrain bundle of 6-OHDA-lesioned rats was shown to ameliorate bladder dysfunction[189]. Together, this evidence suggests a centrally mediated mechanism underlying hyper-reflexia in PD. There has been little activity in developing novel treatments specifically aimed at bladder dysfunction in PD, although A2A receptor adenosine antagonists have been suggested as potentially effective in PD, based on action at a supraspinal site in 6-OHDA-lesioned rats[176].

[H3] ***Gastrointestinal dysfunction****.* Dysfunction occurs along the entire length of the gastro-intestinal tract in PD, and includes excessive salivation, dysphagia, impaired gastric emptying, constipation and impaired defecation[190]. Small intestinal bacterial overgrowth may complicate 25–67% of cases with PD[191]. The cause of the gastrointestinal dysfunction is not well understood and may involve extrinsic and intrinsic pathological and biochemical changes. Multiple neurotransmitters and neuromodulators (for example, acetylcholine, 5-HT, dopamine, noradrenaline, vasoactive intestinal peptide (VIP) and nitric oxide) control bowel function and it is unlikely that there is a single pharmacological basis that is responsible for all the gastro-intestinal symptomatology that is observed in PD. The dorsal motor nucleus of the vagus (DMNV) is important in autonomic control of the bowel, and pathological change in this area occurs early in the development of PD. This may explain why gastrointestinal disturbances such as constipation may also occur earlier than alterations in motor function[192].

Changes in the enteric nervous system (ENS) have also been reported in PD; for example, in one study, immunohistochemistry revealed a reduction in dopamine levels in the ENS, although there was no loss of tyrosine hydroxylase immunoreactivity, implying that no neurodegeneration had occured[193]. A further study failed to show any neuronal loss in the

myenteric plexus along the length of the gastro-intestinal tract in control subjects, individuals with PD and cases of ILBD[194]. Also, no difference was observed between these groups in the relative abundance of tyrosine hydroxylase-, VIP- and nitric oxide-containing neurons. What is clear, however, is the presence of Lewy bodies (and/or α-synuclein inclusions and Lewy neurites) in PD at almost every level of the gastro-intestinal tract[195]. There is virtually no co-localisation of α-synuclein with tyrosine hydroxylase, VIP or nitric oxide, suggesting that it is located in other neuronal types — perhaps cholinergic neurons.

The presence of α-synuclein aggregations along the gastro-intestinal tract has been proposed as a diagnostic tool allowing early detection of the disease process prior to the onset of motor symptoms. Biopsy samples have been taken at multiple levels from the salivary glands to the rectum to determine the validity of this approach[196-201]. α-synuclein aggregates in colonic tissue so far appear to be the more predictive of pre-clinical PD. However, α-synuclein is abundantly expressed in all nerve plexuses of the ENS in normal individuals, and levels increase with age, so its pathological relevance needs to be carefully assessed before use as a predictive biomarker of PD[202].

Abnormalities of gastro-intestinal motility may be improved with both apomorphine and levodopa infusions[81,,203]. The gastro-intestinal effects of apomorphine are not prevented by the peripheral dopamine antagonist domperidone, suggesting that they have a central origin. There may also be a serotoninergic component to impaired motility and this is supported by enhanced gastrointestinal function following treatment with cisapride and related 5-HT4 receptor agonists[176].

Rodents treated with dopaminergic toxins or overexpressing wild-type or A53T mutant α-synuclein can show slowed intestinal motility and constipation[204-207]. In mice overexpressing human wild-type α-synuclein, functional assessments demonstrated a reduction in faecal water content and faecal pellet output, and increased whole gut transit time, which is indicative of constipation[208]. Delayed gastric emptying was observed in 6-OHDA-lesioned rats and this may reflect the delayed emptying that is observed in PD that can affect levodopa absorption[209]. In unilateral 6-OHDA-lesioned rats, there was a marked loss of nitric oxide synthase-positive neurons and an increased number of VIP-positive cells in the myenteric plexus[204]. Moreover, in the colon of these animals, there was no change in choline acetyl transferase immunoreactivity but there was selective loss in D2R density. In the colon of MPTP-treated non-human primates, by contrast, there was increased number of nitric synthase immunoreactive neurons, a decrease in tyrosine hydroxylase immunoreactivity and no change in cholinergic- or VIP-immunoreactive populations[210]. The differences in the rat and primate findings may lie in the

focal degeneration of nigro-striatal neurons that is produced by intra-nigral 6-OHDA administration as opposed to the systemic administration of MPTP that could potentially also destroy peripheral dopaminergic cells. However, these results seem to contrast with the effects in man and neither toxin would destroy neurons in the DMNV.

[H3] ***Cardiovsacular features***. The heart is innervated by sympathetic (noradrenergic and adrenergic) and parasympathetic (cholinergic) autonomic fibres that control heart rate and contractility. Cardiac autonomic dysfunction may occur in up to 80% of patients with PD[211]. This dysfunction encompasses orthostatic hypotension and labile hypertension. Orthostatic hypotension is a marker of sympathetic dysfunction and is common in PD with a reported frequency of 30–58%[212]. Twenty-four hour blood pressure monitoring showed that alterations in blood pressure profile and supine hypertension often occur in PD, usually in patients who develop orthostatic hypotension[213]. Nocturnal (supine) hypertension in PD has been shown to be associated with target organ damage as well as an increased risk for stroke and cardiovascular events[214].

Motor response fluctuations in PD may also affect cardiovascular function, and off periods have been shown to be associated with hypertension, a higher resting heart rate and a greater orthostatic fall of blood pressure[215]. A study of non-motor features in untreated PD and healthy controls reported that the former had a markedly raised heart rate, suggesting this may serve as a marker of early PD[216]. Postprandial hypotension has also been documented in PD, which appears to worsen the motor state in PD after a carbohydrate load and may explain the absence of on periods that are often seen after a meal[217]. A retrospective analysis of cardiovascular stress testing in asymptomatic individuals showed that during peak exercise, the maximum heart rate and the percentage of theoretical maximum heart rate were markedly lower in people that developed PD than in control subjects[218].

Despite the clinical evidence for altered cardiovascular function in PD, there has been relatively little investigation of this change in function in experimental models of the disorder. An impaired baroreflex response occurs in mice overexpressing human wild-type α-synuclein[219]. Moreover, mice expressing A53T mutant α-synuclein show aberrant autonomic control of the heart, which is characterised by elevated resting heart rate and an impaired cardiovascular stress response, associated with reduced parasympathetic activity[220]. Systemic MPTP treatment of mice can lead to decreased cardiac uptake of ^{125}I-metaiodobenzylguanidine (MIBG), a physiological analogue of noradrenaline, decreased activity of cardiac noradrenaline transporter and reduced circulating and tissue levels of noradrenaline[221-223]. There may be recovery over

time following toxin treatment and myocardial nerve fibres are preserved despite changes in cardiac contractility [224,225]. By contrast, a single study of MPTP administration to non-human primates showed, if anything, an acute increase in 6-^{15}F-fluorodopamine (^{15}F-DA) on PET but no long term changes in ^{15}F-DA imaging[226]. The differences in effects on cardiac innervation may be a reflection of the much higher doses of MPTP used to treat mice versus primates and also to its relative selectivity for dopaminergic neurons, although acute MPTP treatment can exert a reversible 'reserpine'-like effect that depletes all monoamines[227].

The effects of MPTP on non-human primates is in marked contrast to the effects of peripheral 6-OHDA treatment of primates, which led to a marked reduction in ^{15}F-DA uptake, as would be expected from its known toxicity to noradrenergic innervation in peripheral tissues[226]. Indeed, in a subsequent study, intravenous administration of 6-OHDA to monkeys caused an almost total loss of ^{11}C-meta-hydroxyephedrine uptake, as judged by PET, followed by a partial progressive recovery but with decreased levels of circulating catecholamines[228]. This finding raises the issue of whether central dopamine loss has a role in peripheral cardiovascular change, which has been partially addressed in rats. Injection of 6-OHDA in to the medial forebrain bundle decreased the nocturnal heart rate in rats, whereas injection in to the ventral tegmental area altered circadian blood pressure regulation[28,229]. In a recent study, bilateral injection of 6-OHDA into rat substantia nigra lowered the mean arterial pressure, decreased heart rate and reduced sympathetic activity[230]. Overexpression of wild-type α-synuclein in mice caused increased heart rate variability whereas expression of A53T mutant α-synuclein did not induce cardiac autonomic abnormalities despite inducing profound ENS changes[28].

[H1] Perspectives

Until relatively recently, PD has primarily been considered a motor disorder, with its dominant clinical features the result of dopaminergic neuron degeneration. Although dopamine cell loss clearly has a major role in PD symptomatology and has been the basis for the development of dopamine-replacement symptomatic therapies, this focus on motor deficits has relegated non-motor problems to a secondary role. As a result, valuable insights on disease pathogenesis, clinical evolution and progression, and novel therapies have been missed or delayed. The emergence of non-motor abnormalities before motor deficits in PD has led to their use to help define an at-risk cohort of individuals (BOX 1). Probably the most useful of the prodromal non-motor features that may help define a premotor phase are the loss of olfaction, the development

of RBD, depression and constipation. However, before these features can be used to identify individuals at risk of PD, additional, more-specific clinical, genetic and/or biochemical markers will need to be identified.

The pattern and sequence of the emergence of non-motor symptoms support the concept of a prion-like conformational templating spread of α-synuclein deposition from the gut through the autonomic plexi to the brain stem and beyond to the cortex.[231,232]nter-neuronal spread of α-synuclein has been confirmed in cell and animal models[233-237]. The observation that the injection of either the proteasomal inhibitor PSI (proteasomal inhibitor-1; N-[(phenylmethoxy)carbonyl]-L-isoleucyl-L-α-glutamyl-tert-butyl ester-N-[(1S)-1-formyl-3-methylbutyl]-L-alaninamide) into the gastric wall, or intragastric administration of the mitochondrial inhibitor rotenone may initiate α-synuclein release in the gut and its transmission to the dorsal motor nucleus of the medulla and substantia nigra of the mid-brain support two important concepts emerging in PD pathogenesis[238,239]. The first is that an intestinal trigger (for example, a toxin) may initiate α-synuclein release (and possibly oligomer formation) from autonomic nerves in the gut. The second is the potential for spread of α-synuclein pathology through connected neuronal pathways to the brain. The pattern of spread from the gut to brain may underlie the pre-motor features of autonomic gastro-intestinal dysfunction in PD; for example, constipation, cardiac denervation as shown by MIBG and the development of RBD. It has been suggested that the neurodegenerative process spreads from the olfactory bulb, the autonomic gut plexi, the intermediolateral nucleus of the spinal cord and the dorsal motor nucleus of the vagus in a caudorostral direction to the brain and also from the brainstem into the spinal cord (FIG. 4) [73,240]. However, this pattern of spread may not apply to all PD patients and 7–8% of patients have been reported with no α-synuclein pathology in the dorsal motor nucleus[241,242].

Thus, the focus on non-motor dysfunction in PD has informed and supported novel concepts of aetiology and pathogenesis. The early disturbance of olfaction, sleep and/or autonomic function implies neuronal dysfunction and is consistent with the sequence and pattern of the hypothesised spread of Lewy body α-synuclein pathology. These early features have been proposed as indicators of prodromal, pre-motor PD.

[H1] Conclusion

The increasing focus of research on non-motor aspects of PD has provided valuable insights into the diversity of the clinical, pathological and neurochemical features of this disorder. The

symptoms and signs of non-motor symptoms and signs of PD are now the subject of validated clinical assessments that can detect their presence and follow their progression over time. The recognition that non-motor features may develop before motor signs is leading to their evaluation as possible biomarkers, although their detectionis likely to be most effective in conjunction with imaging and biochemical parameters. Importantly, attention is now being focussed on the treatment of non-motor features to improve patients' quality of life. As non-motor problems are a significant, if not even the predominant determinant of PD quality of life, it is essential that any intervention in PD pathogenesis to slow the disease targets not only dopaminergic signalling but also non-dopaminergic pathways.

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Competing interests statement

The authors declare no competing interests.

Box 1 **| Non-motor features as biomarkers for Parkinson disease**

Two areas of Parkinson disease (PD) research in non-motor features are of particular relevance to progress in this area: the development of biomarkers to identify pre-symptomatic PD[243,244] and modifying pathogenetic pathways that cause degeneration of dopaminergic and non-dopaminergic neurotransmitter systems[245].

The diagnosis of PD remains dependent on the identification of motor signs that include bradykinesia and rigidity, with a unilateral resting tremor, and a subsequent good response to levodopa. However, it has been recognised that these diagnostic features may be preceded by non-motor symptoms and signs[246], which include hyposmia, RBD, constipation and depression. Each of these symptoms may be present several years before the emergence of motor deficits. None of these symptoms are specific for PD, but the presence of combinations of these symptoms, and correlation with pre-clinical loss of dopamine observed by imaging, can improve sensitivity and specificity of the prediction for conversion from pre-symptomatic to symptomatic PD[222,247.]

A putative biomarker that changes in parallel to the progression of pathology and clinical features would be of particular value for testing treatments designed to slow the course of PD. The identification of genetic causes of PD, and the recognition that they also cause non-motor features[248], have helped identify predisposed individuals to participate in longitudinal studies to track the development of prodromal, pre-clinical symptoms and signs. However, only the cohorts of individuals with PD-associated mutations in leucine-rich repeat serine/threonine-protein kinase 2 (*LRRK2*) or glucocerebrosidase (*GBA1*) are of sufficient size to perform such studies. It also may be possible to undertake 'reverse genetics' by metabolomic screening of defined population groups (for example, patients with *PINK1* or *PARK2* mutation-related PD) to identify a specific biochemical profile within this group, and then seek this same profile to define those among an idiopathic group that might have an underlying mitochondrial defect. This approach is being used in the *GBA1* mutation population where non-motor features of prodromal PD have been found in asymptomatic mutation carriers[249]. Follow up of this cohort has shown progression of the non-motor as well as motor consequences of neurodegeneration evolving towards clinical PD[250]. It is hypothesised that those that convert to clinical PD will have exhibited a specific clinical and metabolic prodrome that may be used to identify those at risk of PD in the *GBA1*-mutation carrier population. These individuals may then be the most

appropriate population for stratification for disease-modifying treatments that may include small molecule chaperones[251,252].

Figure 1 | **Time courses of the onset of the motor and non-motor features of Parkinson disease**. **a** | A schematic representation of the potential timeline by which the non-motor features of Parkinson disease (PD) may manifest. Non-motor symptoms may develop insidiously in the prodromal phase several years before onset of motor features. The duration of this prodromal phase is variable, as is the sequence of the appearance of the non-motor symptoms. Clinical features of motor dysfunction are required for the diagnosis of PD, and early disease may be associated with the emergence of additional non-motor symptoms. Non-motor problems continue to develop throughout the course of the disease with cognitive and autonomic features becoming common in the later stages. The sequence, timing and the development of the non-motor symptoms in PD can vary between patients. **b** |A graphic depiction of the rates of development and progression of the motor and non-motor features of PD, and the decline in dopaminergic neuronal function. The rate of decline in dopaminergic function (caused by the dysfunction and death of dopaminergic neurons) in PD may be variable (as represented by the blue shaded region) and depend on genetic and/or non-genetic influences on aetiology. It is estimated that motor features appear when approximately 50–60% of dopaminergic neurons have been lost (represented by the dark blue shaded area[253]. Diagnosis may be preceded by subtle emerging motor features not noticed by the patient. If left untreated, motor dysfunction progresses relatively rapidly after diagnosis. Symptomatic treatment with dopamine replacement drugs improves motor function and the progression rate declines as a ceiling effect of disability is reached. Non-motor features may begin with an earlier pre-motor prodrome, progress more slowly but accumulate greater disability. The majority of non-motor features are not related to dopaminergic cell loss and so are unaffected by dopamine replacement therapy.

Figure 2 | **Potential non-motor features in Parkinson disease**. The non-motor features of Parkinson disease reflect deficits in various functions of the CNS and autonomic nervous system. Multi-system involvement develops to varying levels of severity and in a variable sequence in different patients. Although some non-motor impairments precede motor abnormalities (for example, cardiac, bowel and olfactory deficits), most develop over time with progression of the underlying disease. Cognitive dysfunction usually appears late in the course of PD, although visual hallucinations may appear earlier and are a risk factor for subsequent dementia.

Figure 3 | **Lewy bodies in Parkinson disease. a |** Lewy bodies are intraneuronal intracytoplamic inclusions that are rich in α-synuclein. In the left-hand panel, a Lewy body is revealed by haematoxylin and eosin staining, whereas in the right-hand panel, this type of inclusion is revealed by α-synuclein immunohistochemistry. Inclusions are also seen in axons and are referred to as Lewy neurites (not shown). The scale bar represents 10 μm. **b** | The Braak hypothesis states that Lewy bodies first appear in the CNS in the lower medulla and olfactory nerves, and spread from the medulla up the brain stem to the mid-brain where neurodegeneration first occurs in the dopaminergic neurons of the substantia nigra pars compacta (shaded areas affected first). Subsequently, there is involvement of frontal and then occipital cortices[254]. Panel **a** is courtesy of J. Holton. [We will add the permission information for panel b here.]

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Figure 4 | **Schema representing the hypothesis of pathology spread via the intestine in Parkinson disease.** The vagus nerve provides parasympathetic innervation to the intestine from the oesophagus to the colon via the oesophageal (1), coeliac (2) and hypogastric (3) plexi, which connect to the vagal nucleus in the medulla. It is hypothesised that factors that initiate α-synuclein pathology enter the gut via the nose or mouth, and that a prion-like spread of α-synuclein misfolding may generate a cascade of pathology from the gut plexi to medulla and beyond, as proposed by Braak and colleagues[73]. [Again, we will add the necessary permission line here.]

Table 1 | Overview of the brain regions and neurotransmitters implicated in the nonmotor symptoms of Parkinson disease.

Nonmotor symptom	**Implicated brain region**	**Implicated neurotransmitter(s)**
Hyposmia	Olfactory bulb and amygdala	Substance P
Impaired colour vision	Retina	Dopamine
Hallucinations	Occipital cortex	Dopamine
Pain	Basal ganglia, locus ceruleus, taphe nucleus, amygdala and thalamus	Dopamine, serotonin and noradrenaline
Anxiety	Basal ganglia	Dopamine and noradrenaline
Depression	Limbic and cortical areas	Dopamine and noradrenaline
Early cognitive dysfunction	Frontal cortex	Dopamine
Dementia	Temporal, parietal and occipital lobes	Acetylcholine
Sleep disturbance	Hypothalamus and reticular formation	Hypocretin (orexin) and dopamine
Bladder hyper-reflexia	Basal ganglia	Dopamine

Correlations are simplified **[Au: I still feel this wording is not very clear. If this line is to be retained, I suggest using: 'The associations in the table are simplified…']** and readers are referred to the text for detail.

GLOSSARY

Bradykinesia

Abnormal slowness of movement.

Rigidity

Stiffness and increased tone of muscles.

Levodopa

Orally active dopamine precursor.

Wearing off periods

Re-emergence of dopamine deficiency-related symptoms (for example, stiffness, slowness or tremor).

Off periods

Similar to ‘wearing off’ but more severe in terms of symptom severity

On periods

Periods of effective dopamine replacement with restored motor function

Hyposmia

Reduction in the ability to detect odours.

Rotenone

A mitochondrial complex I inhibitor and common pesticide.

α-Synuclein

Protein that aggregates and forms the major constituent of Lewy bodies in neurons. Mutations in the gene encoding α-synuclein and overexpression of this protein are causes of familial PD.

Anosmia

Loss of the sense of smell.

Lewy bodies

Abnormal aggregates of proteinaceous material within neuronal cell bodies the major constituent of which is α-synuclein.

Lewy neurites

Abnormal aggregates of proteinaceous material within axons the major constituent of which is α-synuclein.

Incidental Lewy body disease

The presence on pathological examination of Lewy body deposition, but without symptoms of PD during life.

1-methyl-4-phenyl 1,2,3,6 tetrahydropyridine (MPTP).

A mitochondrial complex I inhibitor that can cause dopaminergic neuron death and induce parkinsonism in humans.

Paraesthesia

Positive sensory phenomena (for example, pins and needles).

Parkin

Parkin protein, involved in mitophagy

Endogenous depression

Depressive symptoms that are not associated with triggers such as bereavement.

Sleep attacks

Sudden onset of sleep.

Akathisia

Motor restlessness.

Nocturia

The need to pass urine during the night

Micturition

The process of passing urine.

Detrusor

A muscle that controls bladder function.

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KEY POINTS

Non-motor symptoms are common in Parkinson disease (PD) and can appear before motor features and progress in both severity and diversity as the disease evolves.

Both dopaminergic and non-dopaminergic pathology underlie the non-motor features and this pathology involves the central and autonomic nervous systems.

There is no accurate toxin-induced or genetic animal model of PD pathology and models for the study of non-motor features are limited.

A combination of non-motor features with additional biochemical and/or imaging studies may provide a means to identify prodromal, pre-motor PD.

There is accumulating evidence that α-synuclein pathology may spread along neuronal pathways and that this may originate in the gastrointestinal tract autonomic plexi.

Therapies designed to slow the course of PD will need to address pathology in non-dopaminergic neurons so as to influence non-motor as well as motor features of the disease.