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REVIEW ARTICLE

Autonomic dysfunction in Parkinson disease and animal models

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Abstract
Parkinson disease has traditionally been classified as a movement disorder, despite patients' accounts of diverse symptoms stemming from impairments in numerous body systems. Today, Parkinson disease is increasingly recognized by clinicians and scientists as a complex neurodegenerative disorder featuring both motor and nonmotor manifestations concomitant with pathology throughout all major branches of the nervous system. Dysfunction of the autonomic nervous system, or dysautonomia, is a common feature of Parkinson disease. It produces signs and symptoms that severely affect patients' quality of life, such as blood pressure dysregulation, hyperhidrosis, and constipation. Treatment options for dysautonomia are limited to symptom alleviation because the cause of these symptoms and Parkinson disease overall are still unknown. Animal models provide a platform to interrogate mechanisms of Parkinson disease-related autonomic nervous system dysfunction and test novel treatment strategies. Several animal models of Parkinson disease are available, each with different effects on the autonomic nervous system. This review critically analyses key dysautonomia signs and symptoms and associated pathology in Parkinson disease patients and relevant findings in animal models. We focus on the cardiovascular system, adrenal medulla, skin/thermoregulation, bladder, pupils, and gastrointestinal tract, to assess the contribution of animal models to the understanding of Parkinson disease autonomic dysfunction.

Keywords Dysautonomia · Parkinson disease · Animal models · Orthostatic hypotension · Constipation · Thermoregulation

Introduction

Dr. James Parkinson's 1817 "An Essay on the Shaking Palsy" is the first account of the devastating impact of Parkinson disease (PD) and details the breadth of symptoms these patients suffered. In addition to the tremor and rigidity characteristic of PD motor symptoms, Dr. Parkinson shares stories of "bowels, which had been all along torpid, now, in most cases, demand stimulating medicines", sleep "much disturbed", and food "with much difficulty retained in the mouth […] then as difficultly swallowed" [1]. 200 years of research following Dr. Parkinson's seminal essay have led to the characterization of a wide array of PD nonmotor signs and symptoms. A subset of these are associated with altered function of one or more components of the autonomic nervous system (ANS), termed dysautonomia. Orthostatic hypotension, hyperhidrosis, and gastrointestinal (GI) dysfunction are common manifestations of PD dysautonomia that greatly affect patient quality of life [2]. Treatment options for dysautonomia are limited to symptom alleviation because the etiology of these features and PD overall is still unknown.

Animal and clinical research efforts have largely focused on PD motor signs and symptoms, as they are the basis for PD diagnosis. The extrapyramidal motor features of PD emerge when 30–50% of dopamine producing neurons in the substantia nigra have been lost [3]. This neurodegeneration is associated with the presence of alpha-synuclein (α-syn)-immunoreactive intraneuronal inclusions termed Lewy bodies (LBs) in neuronal soma and Lewy neurites (LNs) in axons or dendrites. The trigger for LB and LN formation and the precise mechanistic link between α-syn aggregation and nigral neuronal loss have yet to be defined; notably, PD protein accumulation is associated with increased inflammation and oxidative stress [4]. In addition to the substantia

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nigra, LBs and LNs are found throughout the central and peripheral nervous systems of PD patients, including in the ANS. α-Syn accumulation and neuronal loss are proposed to also be involved in PD dysautonomia.

The ANS is well conserved across mammalian species [5], thus making animal models an excellent platform for investigating the effects of PD on the ANS. The ANS consists of the sympathetic, parasympathetic, and enteric nervous systems. Sympathetic and parasympathetic nervous systems have both pre- and post-ganglionic neurons, and pre-ganglionic neurons of both systems are cholinergic. Sympathetic preganglionic neurons reside in the thoracolumbar spinal cord and synapse with noradrenergic postganglionic neurons in the paravertebral ganglia, which then innervate appropriate organs. Parasympathetic preganglionic neurons originate in either brainstem nuclei or the sacral spinal cord and extend long axons to cholinergic postganglionic neurons in terminal ganglia near target organs. Enteric nervous system (ENS) ganglia are embedded in the wall of the GI tract in the net-like submucosal and myenteric plexuses; they also receive input from the sympathetic and parasympathetic nervous systems. ENS neurons express, and often co-express, diverse neurotransmitters including acetylcholine, dopamine, and serotonin.

Animal research has been critical to understanding the neurophysiological basis of PD motor symptoms and developing treatments including dopamine replacement therapy and deep brain stimulation. Novel modeling methods are helping to shed light on PD etiology. Can current animal models provide the same insight into PD dysautonomia causes and potential treatments? What signs and pathology would an ideal PD dysautonomia animal model display? This review critically analyses dysautonomia manifestations and hypothesized associated pathology in PD patients, relevant findings in animal models of PD, and the contribution of animal models to the understanding of PD autonomic dysfunction.

Clinical features and pathology of PD autonomic dysfunction

An important step in modeling and treating PD dysautonomia is determining which nonmotor signs and symptoms are tied to ANS dysfunction. This has proven to be difficult, due to the widespread pathology of PD and the complex interrelationship of the ANS with the somatic and central nervous systems. In this section, we review clinical evidence of PD nonmotor features association with ANS dysfunction and pathology in key organ systems: cardiovascular system, adrenal medulla, skin/thermoregulation, bladder, pupils, and gastrointestinal tract (Table 1).

Cardiovascular system

An estimated 80% of PD patients experience heart rate and blood pressure abnormalities [6]. Heart rate variability decreases in PD, and a lower maximum heart rate can be present at PD diagnosis [7]. Prolonged QT interval of the heartbeat is observed in association with accelerated worsening of the disease over 5 years [8]. Blood pressure variability is increased in PD, leading to signs and symptoms ranging from fatigue during exercise to orthostatic hypotension [9]. Orthostatic hypotension, the inability to regulate blood pressure with changes in body position, affects 40% of PD patients, causes dizziness and syncope, and increases the risk of falls and injury [9, 10]. It frequently coexists in PD with other manifestations of blood pressure dysregulation including supine hypertension, loss of nocturnal blood pressure dips (non-dipping), and low blood pressure after eating (post-prandial hypotension) [9].

Heart rate abnormalities appear to be due to dysfunctional parasympathetic responses, while the inability to regulate blood pressure is related to loss of sympathetic regulation [9]. α-Syn accumulates in the vagus nerve [11], potentially blunting cardiovascular parasympathetic tone. α-Syn pathology and neurodegeneration are also observed in the parasympathetic neurons of the dorsal motor nucleus of the vagus (DMV) [12], but the relevance of this to cardiovascular autonomic dysfunction is unclear as the main source of vagal afferents to the heart is nucleus ambiguous. Postganglionic parasympathetic loss may also be a feature of PD, as positron emission tomography (PET) with the radioligand 5-[(11)C]-methoxy-donepezil shows decreased acetylcholinesterase in the myocardium [13].

Extensive clinical research illustrates that PD orthostatic hypotension is related to both the loss of postganglionic sympathetic innervation to the heart and baroreflex failure. Radioimaging evidence of decreased cardiac postganglionic sympathetic innervation is well documented in PD and is now a supportive criterion for clinical diagnosis [14]. 60% of PD patients have loss of cardiac sympathetic innervation at diagnosis [15], which is estimated to affect 100% of patients as the disease progresses [16]. PD cardiac sympathetic nerve loss is heterogeneous in the left ventricle, with the cardiac apex more affected than the base [17, 18] and sparing of the anterior and proximal regions [17, 19]; this loss progresses and becomes diffuse over time [20]. A chronological relationship between sympathetic nerve loss and α-syn has been suggested [21]. In patients with intact cardiac sympathetic innervation, α-syn is abundant in distal postganglionic axons and minimal in sympathetic ganglia. However, loss of sympathetic innervation to the heart is accompanied by decreased α-syn in

Table 1 Summary of dysautonomia signs and symptoms and proposed areas of associated pathology in Parkinson disease patients

Organ/Organ System	Major Sign(s) and Symptom(s)	ANS Neurodegeneration	ANS α-Syn Accumulation	Pathology Outside of the ANS
Cardiovascular System	Decreased Heart Rate Variability	Cardiac Parasympathetic Innervation (?)[a]	Vagus Nerve[b] Cardiac Plexus	LBs and Neuron Loss in the Locus Coeruleus
	Increased Blood Pressure Variability (OH)	Cardiac Sympathetic Innervation Thoracic Intermediolateral Spinal Column[b]	Cardiac Sympathetic Innervation Cervicothoracic Sympathetic Ganglia[b] Thoracolumbar Intermediolateral Spinal Column[b] Cardiac Plexus	LBs and Neuron Loss in the Locus Coeruleus and Rostral Ventrolateral Medulla
Adrenal Medulla	Increased Blood Pressure Variability (OH) Associated with Decreased Plasma Norepinephrine	Chromaffin Cells of the Adrenal Medulla (Reduced Catecholamine Markers)	Adrenal Medulla	NR
Skin/ Thermoregulation	Axial Hyperhidrosis	Cutaneous Sympathetic Innervation of Blood Vessels and Sweat Glands	Cutaneous Sympathetic Fibers	Hypothalamic LBs and Dopamine Loss
Bladder	Urinary Frequency and Urgency Nocturia	NR	Lumbar Spinal Cord[b] Sacral Parasympathetic Nuclei[b] Pelvic Plexus[b]	Nigrostriatal Neurodegeneration LBs in Numerous Central Nuclei (Onuf's Nucleus, Raphe Nuclei, Locus Coeruleus)
Pupils	Irregular Pupil Reactivity	Sympathetic Innervation of the Iris Dilator Muscle (?)[a] Parasympathetic Innervation of the Iris Sphincter Muscle (?)[a]	Superior Cervical Ganglion[b] Edinger-Westphal Nucleus	NR
Upper GI Tract	Dysphagia	NR	Esophageal Enteric Neurons Thoracic Intermediolateral Spinal Column[b] Cervicothoracic Sympathetic Ganglia[b] DMV and Vagus Nerve[b]	Nigrostriatal Neurodegeneration LBs in the Submandibular Gland and Glossopharyngeal Nerve
	Delayed Gastric Emptying	NR	Gastric Enteric Neurons Thoracic Intermediolateral Spinal Column and Sympathetic Ganglia[b] DMV and Vagus Nerve[b]	Nigrostriatal Neurodegeneration
Lower GI Tract	Constipation	Colonic Parasympathetic Innervation (?)[a] Colonic Dopamine Content (?)[a]	Colonic Enteric Neurons Thoracolumbar Intermediolateral Spinal Column and Sympathetic Ganglia[b] DMV and Vagus Nerve[b]	Nigrostriatal Neurodegeneration

ANS autonomic nervous system, *α-Syn* alpha-synuclein, *LB* lewy bodies, *OH* orthostatic hypotension, *GI* gastrointestinal, *DMV* dorsal motor nucleus of the vagus, *NR* not reported in current literature

[a](?) refers to limited data or mixed evidence

[b]anatomical areas of the ANS in which pathology could affect numerous organs/organ systems; areas are listed when literature strongly suggests a relationship between pathology and signs/symptoms

cardiac nerve fibers and increased α-syn in paravertebral ganglia. LBs are also found in the cardiac plexus itself [22]. Baroreflex failure is thought to be elicited by currently unknown central lesions. For example, α-syn pathology and neuron loss have been found in the thoracolumbar intermediolateral spinal column, the nucleus from which preganglionic sympathetic neurons originate [11, 23], in addition to cell loss observed in the locus coeruleus [24] and in rostral ventrolateral medulla in some patients [25].

Adrenal medulla

Most PD patients with orthostatic hypotension present reduced supine plasma norepinephrine [26]. Sympathetic postganglionic neurons and the adrenal medulla are both important sources of circulating norepinephrine. Histological evaluation of the adrenal medulla in PD patients has confirmed that this organ is affected by the disease. Typical findings are reduced catecholamine content [27], LBs [28], and inclusions known as 'hyaline globules' or 'adrenal bodies' [29].

Interestingly, 10% of PD patients with early PD in one study had orthostatic hypotension with high supine norepinephrine [30], suggesting that PD orthostatic hypotension can present with sparing of the peripheral sympathetic system and greater deterioration of central components.

Skin/thermoregulation

Effective thermoregulation depends on a delicate balance between cooling (e.g.: vasodilation) and warming (e.g.: thermogenesis) responses [31]. Sudomotor, thermoregulatory, and vasomotor dysfunction occur in two-thirds of PD patients [32]. Features include heat intolerance, cold intolerance, and profuse periodic sweating [32]. Excessive sweating of the face, neck, and upper body, known as axial hyperhidrosis, is common in PD [33] and can occur episodically without a stimulus, especially at night [34]. Axial hyperhidrosis is hypothesized to be a compensatory phenomenon for lower sympathetic activity in extremities [35].

Clinical tests confirm decreased sympathetic nerve function in the skin of hands, feet [35], and legs [36] of PD patients. This dysfunction has been linked to histological findings of loss of cutaneous nerves innervating blood vessels, sweat glands, and erector pili muscles [37]. α-Syn pathology is observed in autonomic cutaneous fibers [38, 39], although both autonomic [38] and sensory [38, 40] fibers are lost in PD. It should be noted that not all studies replicated the findings of α-syn accumulation in cutaneous fibers in PD, likely due to methodological differences [41]. Additionally, the hypothalamus is a critical coordinator of thermoregulation [31]. Decreased hypothalamic dopamine [42] and LBs found in every nucleus of the hypothalamus [28, 43] may also elicit these symptoms.

Bladder

Lower urinary tract signs and symptoms such as nocturia and increased frequency and urgency to urinate occur in 27–85% of patients [44]. Moreover, the detrusor muscle, which contracts during urination, is overactive in 58% of untreated PD patients [45].

The pathophysiology of PD bladder dysfunction is likely multifocal [46, 47]. The bladder itself appears unaffected [44]. However, the basal ganglia are known to regulate micturition [48], and clinical imaging demonstrates a correlation between severity of striatal dopamine transporter loss and bladder symptoms [49], suggesting a connection to nigral neurodegeneration. In the ANS, LBs are found in micturition-associated autonomic preganglionic neurons in the lumbar and sacral spinal cord and in the pelvic plexus [11, 28]. PD pathology also affects additional anatomical structures involved in bladder function including Onuf's nucleus, the raphe nuclei, and the locus coeruleus [50, 51].

Pupils

PD impact on patients' vision encompasses visual hallucinations, abnormal eye movements, decreased blinking, and deficits in visual acuity, motion perception, contrast sensitivity, and pupil reactivity [52]. Dopamine loss in the CNS and the retina are likely responsible for most of the issues listed above, with exception of pupillary abnormalities, which are thought to be related to autonomic dysfunction [52]. PD patients exhibit decreased pupil constriction speed and decreased light-induced pupil constriction amplitude [53, 54]. Clinical tests show supersensitivity to the 0.05% pilocarpine hydrochloride eye drop test and abnormal responses to 0.02% dipivefrine hydrochloride eye drops, suggesting compromised parasympathetic and sympathetic innervation of the iris sphincter and dilator muscles, respectively [55].

Parasympathetic pupillary constriction dysregulation may be related to 54% neuron reduction and 2–3% neurons containing LBs in the Edinger–Westphal nucleus [56], the parasympathetic preganglionic nucleus that innervates the iris sphincter muscle and the ciliary muscle. LBs have also been identified in the origin of sympathetic postganglionic innervation to the eye, the superior cervical ganglion [57].

Gastrointestinal tract

Upper gastrointestinal tract

The upper GI tract includes structures from the mouth to the stomach. In PD, drooling occurs in 10–81% of patients and is hypothesized to be due to insufficient salivary clearance in association with difficulty swallowing [58], as salivary production is actually decreased in PD [59]. The stomach is also affected in PD; delayed gastric emptying occurs in 70–100% of patients causing nausea, vomiting, early satiety, and bloating [60].

It is unclear what role ANS dysfunction plays in PD upper GI abnormalities. Decreased saliva production could be related to LBs in the superior cervical ganglion, vagus nerve, and submandibular glands [57] or to central dopamine deficiency [61]. Swallowing is a complex but stereotyped activity regulated by a central pattern generator in the medulla oblongata [58]. Oropharyngeal dysphagia in PD is thought to be associated with central dopamine insufficiency-related bradykinesia and poor muscle control of the tongue [58, 62]. Aggregates of α-syn in the glossopharyngeal and vagus nerves innervating the pharynx may also impact swallowing [63]. α-Syn aggregation in the DMV could disturb both esophageal and gastric motility [64]. The ENS itself is affected in PD, in both the myenteric and submucosal plexuses [11], with a rostrocaudal gradient of serine 129 phosphorylated α-syn (p-α-syn), a marker of α-syn pathology associated with mitochondrial impairment [65]. Subthalamic nucleus deep brain stimulation improves gastric emptying in PD, substantiating a connection between PD upper GI clinical features and nigrostriatal loss [66].

Lower gastrointestinal tract

The lower GI tract includes structures from the small intestine to the anal canal. 50–80% of patients experience constipation and it can onset many years before PD motor symptoms [67]. Clinical evaluation reveals both increased transit time in the small and large intestine [68] and dyssynergic defecation, in which a paradoxical increase in puborectalis muscle activity occurs during attempted defecation [69].

Histopathologically, a significant decrease in dopamine immunoreactivity has been reported in the colon of PD patients with extremely severe constipation [70]. However, more recent publications find no changes in ENS neurochemical phenotypes or evidence of ENS neurodegeneration in PD [71, 72]. Interestingly, mRNA expression is reported to be increased for dopamine receptor D1, vasoactive intestinal peptide, and serotonin receptor 3A and decreased for serotonin receptor 4 and muscarinic receptor 3 in submucosal rectal biopsies from PD patients; alterations in protein levels were not investigated [73]. As mentioned above, α-syn pathology is found extensively throughout the myenteric and submucosal plexuses of the ENS in PD, including in the small and large intestine [11]. LBs can also be present in the thoracolumbar intermediolateral spinal column, paravertebral sympathetic ganglia, DMV, and sacral parasympathetic nuclei [28], which may dysregulate autonomic coordination of colonic activity. Decreased acetylcholinesterase (a marker of cholinergic neurons) in the small intestine as detected by PET further implicates parasympathetic abnormalities [13]. Neuronal density in the substantia nigra [74] and reduced dopamine transporter availability in the caudate nucleus [75] have been reported to correlate with bowel movement frequency in PD patients, and administration of the dopaminergic type-2 agonist apomorphine improves symptoms of dyssynergic defecation [76], implicating central dopamine deficiency in PD constipation. Recent clinical evidence indicates that intestinal microbiome and permeability alterations may contribute to PD GI dysmotility [77]. In addition, presence of aggregated α-syn has been reported in the vermiform appendix, and appendectomies are associated with decreased risk and delayed onset of PD, suggesting that the appendix may be involved in PD initiation [78].

Animal models of PD dysautonomia

Understanding the characteristics and limitations of different animal models is critical to appropriately matching the model to the scientific question. As PD neuropathology has been identified beyond the nigrostriatal system, classic animal models are being re-evaluated and novel models are being developed with the goal of capturing the complexity of PD.

Classic PD animal models use catecholaminergic neurotoxins such as 6-hydroxydopamine (6-OHDA) or 1-methyl-4-phenyl-1,2,3,6-tetrahydro-pyridine (MPTP) to target the dopamine producing neurons of the substantia nigra and recreate the cardinal motor features of the disease [79, 80]. 6-OHDA can be injected unilaterally or bilaterally into the substantia nigra or medial forebrain bundle to cause rapid (days) nigrostriatal loss or into the striatum to cause a slower (weeks) partial loss [81]. 6-OHDA does not cross the blood brain barrier, but systemic injection can be used to model PD peripheral nervous system sympathetic loss [81, 82]. MPTP is typically administered systemically, although delivery to the brain via carotid artery infusion is a common technique performed in nonhuman primates [83]. MPTP is blood brain barrier permeable, therefore systemic administration results in catecholaminergic loss in the central and peripheral nervous systems, with the severity and stability of the lesion dependent on dosing regimen. Unilateral intracarotid delivery of MPTP induces nigral

Table 2 Summary of key organ/organ systems with Parkinson disease (PD) dysautonomia-like signs and symptoms and pathology in animal models

Animal Model of PD[b]		PD Dysautonomia-like Signs and Symptoms	PD Dysautonomia-like Pathology[c]
Neurotoxin	6-OHDA (CNS)	Cardiovascular System Bladder Upper GI Tract Lower GI Tract	NR
	6-OHDA (systemic)	Adrenal Medulla	Cardiovascular (Loss of Sympathetic Innervation) Adrenal Medulla (Loss of Catecholamine Producing Enzymes) Skin/Thermoregulation (Loss of Sympathetic Innervation) Pupil (Loss of Sympathetic Innervation)
	MPTP (systemic)	Bladder Pupil (?)[a]	Cardiovascular (*Transient* Loss of Sympathetic Innervation) Pupil (Loss of Sympathetic Innervation)
	Rotenone	Cardiovascular System Adrenal Medulla Upper GI Tract (?)[a] Lower GI Tract	Cardiovascular (Rostral Ventrolateral Medulla Neurodegeneration) Upper GI Tract (α-Syn Accumulation and Phosphorylation in the ENS, Intermediolateral Spinal Cord, and DMV) Lower GI Tract (α-Syn Accumulation and Phosphorylation in the ENS, Intermediolateral Spinal Cord, and DMV)
	Paraquat	Upper GI Tract	Upper GI Tract (Neurodegeneration and Increase in α-Syn in the DMV)
α-Syn	Transgenic[d]	Cardiovascular System Bladder Upper GI Tract Lower GI Tract	Cardiovascular (α-Syn Aggregation in Nerves in the Heart) Adrenal (α-Syn Oligomerization) Upper Gastrointestinal Tract (α-Syn Aggregation in the Gastric ENS and Accumulation in the DMV) Lower Gastrointestinal Tract (α-Syn Aggregation in the Colonic ENS and Accumulation in the DMV)
	Fibrils (ENS)	Lower GI Tract (*Transient*)	Upper/Lower Gastrointestinal Tract (Increase in Phosphorylated α-Syn in the ENS and *Transient* Increase in the DMV)

CNS central nervous system, *6-OHDA* 6-hydroxydopamine, *MPTP* 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, *GI* gastrointestinal, *α-Syn* alpha-synuclein, *ENS* enteric nervous system, *DMV* dorsal motor nucleus of the vagus, *NR* not reported in current literature

[a](?) refers to limited data or mixed evidence

[b]The information about each animal model combines reports from multiple species and agent delivery methods (e.g. mice administered intraperitoneal 6-OHDA and rhesus administered intravenous 6-OHDA in "6-OHDA (systemic)"; see text for more information)

[c]Table does not describe the effect of the model on the nigrostriatal system, which may be involved in multiple dysautonomia signs and symptoms (see text for more information)

[d]Includes multiple transgenic murine models (Thy1-α-syn mice, Prnp-α-syn mice, Thy1-α-syn-A53T, Prnp-α-syn-A53T, PAC generated α-syn-A53T mice)

dopaminergic loss restricted to the ipsilateral administration side [81, 83]. The pesticide rotenone and herbicide paraquat have also been used to model PD, impacting both the central and peripheral nervous systems, yet their application has been limited as their effects have large inter-animal variability, affecting reproducibility [81, 84, 85]. These neurotoxins alter mitochondrial function in dopaminergic neurons and increase oxidative stress and

inflammation [80, 86]. Their effects on α-syn are variable. Reports indicate that MPTP exposure leads to either upregulation of α-syn protein levels immediately following acute exposure or α-syn accumulation and aggregation following chronic exposure [87–89]; however, LBs or LB-like inclusions have not been observed. Rotenone appears to reliable produce accumulation of phosphorylated α-syn in affected rodents, which closely resembles PD pathology [84, 90].

In 1997, the first genetic mutation associated with familial PD was identified in the α-syn gene. The mutation produces a threonine to alanine replacement in the 53rd residue of the protein (A53T) [91]. This watershed discovery led to the identification of α-syn as the major component of LBs and LNs [92] and the finding that the A53T mutation accelerates protein aggregation relative to wild type α-syn [93]. PD-associated mutations have been also identified in genes encoding LRRK2, DJ-1, Parkin, and other proteins, which are reviewed in detail elsewhere [94]. Carriers of these mutations present a PD syndrome largely similar to sporadic PD, including the typical nigral dopaminergic loss and the presence of LBs and LNs (with the exception being carriers of Parkin mutations, who typically lack LBs) [94]. Animal models have since been created to test the effects of knocking out, mutating, and increasing the expression of these wild type and mutated proteins. Additionally, reports of LBs in transplanted fetal tissue grafted a decade earlier into the striatum of PD patients [95, 96] have spurred questions about the ability of misfolded α-syn to spread trans-synaptically in a prion-like fashion [97, 98]. Animal models to test the role of α-syn in PD and the trans-synaptic spreading hypothesis include α-syn transgenic mice, models of α-syn overexpression induced by viral vector administration, and injection of different forms of α-syn, such as monomers, oligomers, fibrils, or PD patient-derived LB extracts.

In this section, we review current literature on animal models of PD-associated ANS dysfunction and pathology. Similar to the previous patient section, we focus in key organ systems: cardiovascular system, adrenal medulla, skin/thermoregulation, bladder, pupils, and gastrointestinal tract (Table 2).

Cardiovascular system

The finding that PD cardiovascular autonomic dysfunction is associated with loss of postganglionic sympathetic innervation in the heart has prompted the study of systemic administration of catecholaminergic toxins to model this pathology. Systemic MPTP mimics these findings, but the effect is temporary at the administered doses in mice and rhesus macaques [99, 100]. Systemic 6-OHDA creates a stable lesion model and has been evaluated in rats, dogs, and rhesus macaques [82, 101–104]. In rhesus, cardiac nerve loss induced by intravenous 6-OHDA mirrors the left ventricle pattern observed in PD, with the greatest loss at the apex and in the inferior region [82, 103, 104]. More traditional models of PD point to a complex role of central dopamine deficiency in cardiovascular autonomic dysfunction. For example, bilateral 6-OHDA injection into the substantia nigra of rats has been reported to either decrease or increase blood pressure, heart rate variability, and baroreflex sensitivity [105, 106], while unilateral nigral injection blunts baroreflex sensitivity and increases blood pressure variability [107]. Bilateral striatal 6-OHDA injection to rats decreases night/day cycle heart rate change [108, 109] and attenuates phenylephrine-induced bradycardia [110], suggesting decreased heart rate variability. Additionally, bilateral injection of 6-OHDA into the rat ventral tegmental area eliminates loss of blood pressure decrease during the light cycle in rats [111], mimicking PD non-dipping pattern. Rotenone administration to rats produces loss of neurons in the rostral ventrolateral medulla, decreases cardiac sympathetic activity [112], increases blood pressure variability, and reduces baroreflex sensitivity [107].

Rodent genetic models of PD have also been evaluated for cardiovascular pathology and functional deficits. Mice overexpressing human α-syn under the Thy1 promoter (Thy1-α-syn) show proteinase K resistant α-syn aggregates in the heart [113], a sign of α-syn pathology, and abnormal sympathetic and parasympathetic responses to sodium nitroprusside and atropine, respectively [114]. Thy1-α-syn-A53T mice, which express the human A53T mutant α-syn, experience dampened heart rate response to atropine and increased baseline heart rate [115]. In contrast, heart rate variability is not altered in A53T mice generated using P1-derived artificial chromosome (PAC) transgenesis [116], potentially related to lower transgene protein expression [114]. Knockout of other PD associated genes, DJ-1, PINK1, and Parkin, affects cardiomyocyte mitochondrial function and/or oxidative stress sensitivity in mice, but cardiovascular autonomic dysfunction has not been reported in these models [117–119]. LRRK2 knockout in rats is not associated with histopathological changes in the heart [120].

Adrenal medulla

Similar to its transitory impact on the heart sympathetic system, MPTP effects in the adrenal gland and on circulating catecholamines appear to be variable and temporary in rats [121]. Systemic administration of 6-OHDA to rhesus macaques significantly decreases plasma norepinephrine and 3,4-dihydroxyphenylacetic acid (DOPAC), a metabolite of dopamine, and the expression of the catecholamine-producing enzyme tyrosine hydroxylase in the adrenal medulla; these changes persist up to 3 months post-neurotoxin administration [82]. Rotenone treatment to rats seems to increase

adrenal tyrosine hydroxylase levels [122], although a separate study reports a rotenone-induced decrease in plasma norepinephrine and epinephrine [112].

Transgenic mice expressing human A53T α-syn under the prion protein promoter (Prnp-α-syn-A53T) exhibit increased α-syn oligomerization (indicative of pathological accumulation) in the adrenal gland and hyperactivity of tyrosine hydroxylase [123].

Skin/thermoregulation

6-OHDA and MPTP, but not paraquat, affect thermoregulation, producing acute hypothermia in mice requiring supplemental heating post-intoxication, which resolves over time [124, 125]. Axial hyperhidrosis cannot be evaluated in mice and rats, as eccrine sweat glands are limited to the foot pads of rodents and function in frictional gripping [126]. To the authors' knowledge, there are no reports of axial hyperhidrosis in nonhuman primate PD models. Intraperitoneal injections of 6-OHDA to mice and rats reproduces the loss of sympathetic innervation of sweat glands and blood vessels documented in PD [127, 128].

In genetic PD models, Thy1-α-syn mice show expression of human α-syn in the skin [113], although this report did not evaluate for α-syn aggregation or p-α-syn. Thy1-α-syn-A53T mice did not show altered thermoregulation [115].

Bladder

In agreement with clinical research, multiple animal models of nigrostriatal degeneration support the involvement of central dopamine loss in PD-associated bladder dysfunction. Unilateral 6-OHDA injection into the middle forebrain bundle [129] or substantia nigra [130, 131] of rats produces bladder overactivity, which is attenuated by stem cell transplantation [132]. MPTP injected intraperitoneally in marmosets [133] or intravenously in cynomolgus macaques [134] similarly provokes bladder hyperreflexia. Electrical field stimulation of isolated strips of urinary detrusor muscle generates increased contractile response in rats treated with unilateral injection of 6-OHDA into the medial forebrain bundle [135] and marmosets that received subcutaneous MPTP [136], suggesting an impact on local neuronal circuits in the bladder.

Thy1-α-syn mice exhibit increased bladder size at postmortem; bladder function has not been assessed [113]. Prnp-α-syn mice show urinary bladder hyperreflexia with increased voiding frequency, decreased voided volumes, and the presence of non-voiding contractions at 4 months of age which persisted to 16 months [137]. In these animals, mRNA levels of in vasoactive intestinal peptide, substance *P*, and neuronal nitric oxide synthase mRNA are altered throughout the spinal cord, autonomic paravertebral ganglia, detrusor muscle, and bladder, but changes in protein levels have not been confirmed and the electrical properties of the pelvic ganglia are unaffected.

Pupils

Reports of toxin models of PD support clinical findings that dopamine loss in the CNS [138, 139] or in the retina [140, 141] contribute to visuospatial abnormalities and visual detection deficits in PD. Animal research connecting pupillary abnormalities to specific pathological findings in PD models is more limited.

Systemic administration of 6-OHDA intraperitoneally to rats [142] and subcutaneous delivery of MPTP mice [143] destroys sympathetic fibers or decreases norepinephrine in the iris, respectively, although no functional deficits of the eye have been reported. In one study, intravenous MPTP in cynomolgus macaques diminished pupillary light-responsiveness in one animal out of five [144]. These animals also exhibit electroretinogram irregularities, which the authors suggest could be due to damage to sympathetic innervation regulating retinal blood flow. 6-OHDA applied topically to the eye in rabbits produces attenuated pupil response to cholinergic agonists and supersensitivity to adrenergic agonists [145], and intravitreal 6-OHDA-treated cynomolgus macaques show electroretinogram and pattern visual evoked potential abnormalities [146], highlighting the importance of sympathetic innervation in iris function.

In murine genetic models of PD, overexpressing human α-syn under either the Thy1 or PDGFβ promoter produces accumulations of α-syn in the inner nuclear layer and ganglion cell layer of the retina and in the optic nerve [147]. Similarly, mice expressing α-syn fused to GFP under the PDGFβ promoter accumulate α-syn in retinal ganglion cells and the edges of arterial blood vessels [148].

Gastrointestinal tract

Upper gastrointestinal tract

PD animal models that exhibit swallowing difficulties include both toxin-induced nigrostriatal degeneration [149] and genetic models of the disease [150, 151]. However, this work implicates central rather than ANS pathology in PD dysphagia. It should be noted that the DMV, the source of vagal innervation of the esophagus, is often affected in toxin models of PD [152, 153], potentially leaving a role for ANS dysfunction.

The presence of delayed gastric emptying in rats injected with 6-OHDA into the substantia nigra either bilaterally [152, 154] or unilaterally [155, 156], indicates that central dopamine deficiency may contribute to this

manifestation. Furthermore, while substantia nigra stimulation with N-methyl-D-aspartate normally increases gastric tone and motility, this effect is lost in rats previously treated with unilateral nigral 6-OHDA [157]; cholera toxin B tracing in this study validates the existence of a monosynaptic nigro-vagal pathway that modulates gastric tone. Several studies demonstrate that toxin-induced nigrostriatal loss alters gastric ENS neurochemical phenotype, such as increased tyrosine hydroxylase [155, 158] and dopamine D2 receptor expression [154], in addition to reducing choline acetyl transferase expression in the DMV [152]. Systemic administration of MPTP to mice via intraperitoneal injection [159] does not induce delayed gastric emptying. Rotenone models have also been evaluated for upper GI changes; a delay in gastric emptying has been reported [160] but not replicated [161]. Pathologically, rotenone increases α-syn accumulation in the ENS and the intermediolateral cell column of the spinal cord [162], which contains preganglionic sympathetic neurons. Paraquat dosing to rats leads to reduced gastric tone and motility, which is associated with increased α-syn and decreased choline acetyl transferase and tyrosine hydroxylase immunoreactivity in the DMV [157]. Interestingly, in a subsequent study by the same group, gastric gavage administration of subthreshold doses of paraquat and lectin to rats for 7 days led to misfolded α-syn in the DMV and substantia nigra. Although loss of tyrosine hydroxylase-positive neurons in the substantia nigra was observed, loss of cholinergic neurons in the DMV was not identified. These findings were associated with impaired nigro-vagally evoked gastric motility prior to the onset of motor dysfunction; vagotomy was sufficient to prevent motor dysfunction and the spread of α-syn misfolding beyond the ENS [163].

Prnp-α-syn-A53T mice exhibit delayed gastric emptying with age [164] concomitant with human A53T expression in the vagus nerve, but not in ENS neurons or sympathetic ganglia. In contrast, A53T mice generated using PAC transgenesis do show proteinase K resistant aggregations of α-syn in the gastric ENS [116]. Thy1-α-syn mice do not show a delay in gastric emptying [165, 166].

Injection of different forms of α-syn (monomer, oligomer, fibril, etc.) into the GI tract yields mixed results regarding the ability of α-syn to spread trans-synaptically and has not yet reproduced PD GI dysfunction. Two studies illustrate movement of α-syn injected into the stomach to the DMV in rats [167] and mice [168]. In one study [168], the number of aggregates in the DMV decreased over time, DMV α-syn aggregation was abolished by cervical vagotomy, and there was no finding of aggregated α-syn in the thoracic spinal cord or any caudorostral spread beyond the DMV.

Lower gastrointestinal tract

PD-like constipation can be seen in rodent models of PD with nigrostriatal loss, such as those induced by unilateral [155, 169–172] or bilateral [173] injection of 6-OHDA into the substantia nigra or the medial forebrain bundle, as well as rotenone-treated mice [174, 175]. Systemic administration of MPTP to mice shows mixed results [159, 176].

Reminiscent of findings in the upper GI tract of PD models, central dopamine deficiency impacts the neuronal composition of the colonic ENS. Rats injected unilaterally with 6-OHDA in the substantia nigra or medial forebrain bundle that develop constipation-like signs can exhibit increased colonic tyrosine hydroxylase [155], increased dopamine levels [170], decreased neuronal nitric oxide synthase [155, 171, 172] among other alterations. This is dissimilar to findings in PD patients, whose constipation is not associated with neuron loss or change in proportions of types of neurons in the ENS [71, 72], as discussed earlier. The explanation for this discrepancy between the effect of PD-associated and toxin-induced nigral degeneration on ENS neurons is currently unclear. Systemic delivery of catecholaminergic toxins such as intravenous 6-OHDA to rhesus macaques [177] or intraperitoneal MPTP to mice [159, 178, 179] decreases tyrosine hydroxylase-immunoreactivity in the ENS; in rhesus this decrease is associated with increased soft feces, while MPTP delivery to mice either increases [159] or decreases [178, 179] colonic motility. Rotenone-induced colonic dysfunction in mice is sometimes [175], but not always [161] associated with changes in the ENS. Additionally, rotenone-treated mice frequently recapitulate the accumulation [174, 180] and S129 phosphorylation [180] of α-syn in the colonic ENS observed in PD. The murine rotenone model of PD with constipation-like signs also shows increased α-syn in the intermediolateral column of the spinal cord, DMV [153], and nigrostriatal system [174, 180] in addition to alterations in the fecal microbiome [180]. Interestingly, hemi-vagotomy has been reported to reduce α-syn accumulation in the ipsilateral DMV and neurodegeneration in the ipsilateral substantia nigra following rotenone treatment [153].

Murine models of α-syn overexpression such as Thy1-α-syn [113, 165, 181], A53T mice generated using PAC transgenesis [116], and Prnp-α-syn-A53T [164, 182], present constipation-like features. They also present α-syn accumulation in the ENS [113, 116, 165, 182] and sometimes [164], but not always [113, 116], in the DMV. Because these animals typically lack nigral cells loss [79], these findings suggest that α-syn accumulation in the ANS is a contributor to PD-like constipation.

Similar to studies discussed above related to upper GI function, different forms of α-syn have been injected in the descending colon of rats and the colon and stomach of

crab-eating macaques [183] to test theories of trans-synaptic α-syn spreading from the peripheral to the central nervous system. 1 month after injection, the rats that received α-syn pre-formed fibrils in the colonic ENS had decreased fecal water content and α-syn accumulation in the DMV, yet both effects disappeared by 12 months [183]. Aggregated α-syn was found in the ENS of both species throughout the duration of the study (12 months). The monkeys showed neither functional deficits nor α-syn pathology outside of the ENS, suggesting differences between species or modeling strategies.

Discussion

Successful management of autonomic dysfunction remains an unmet need in PD patient care. In addition to the signs and symptoms addressed in this review, dysautonomia can spill over into other facets of PD. Orthostatic hypotension compounds the effects of PD motor dysfunction on body movement and is associated with cerebral microbleeds which contribute to dementia [184]. Nocturia worsens daytime sleepiness [185]. Sexual dysfunction correlates with PD autonomic dysfunction [186], although whether this is a result of damage to the ANS or of autonomic dysfunction making sexual activity more difficult is not known. Unfortunately, the failure rate for drugs designed to prevent or slow cell loss in neurodegenerative diseases is extremely high in clinical trials [187, 188], and treating PD dysautonomia is made more difficult by the limited understanding of pathophysiology.

As stated in the introduction, in this article we aimed to answer two questions: First, can current animal models provide insight into PD dysautonomia causes and potential treatments? Second, what signs and pathology should an ideal PD dysautonomia animal model display? Our review of the literature supports the value of animal models in discerning the neuroanatomy, pathology, and mechanisms precipitating each manifestation of PD dysautonomia. Toxin models give clues to the impact of loss of specific neuronal populations in the development of clinical signs and symptoms, while models of genetic mutations and/or protein aggregation inform on pathways of cell dysfunction. For example, models of central dopamine loss have provided evidence supporting a role for nigrostriatal neurodegeneration in a number of nonmotor symptoms, including oropharyngeal dysphagia [58, 62] and bladder dysfunction [48, 49]. Clinical investigation enhancing the understanding of PD itself aids researchers in the identification of which signs and pathology an ideal model of PD dysautonomia should display (see Tables 1 and 2). A model does not need to exhibit all of the features to add to our understanding of PD autonomic dysfunction. An example is the research surrounding the cause of constipation in PD. It has previously been hypothesized that a loss of dopamine in the colonic ENS leads to PD-associated constipation [70]. However, a combination of research in patients illustrating a lack of neurodegeneration in the colonic ENS [71, 72] and studies in animal models demonstrating that a loss of ENS dopamine is not sufficient to produce constipation [159, 177] suggest an alternate cause. More recent work using transgenic α-syn overexpressing mice [113, 116, 164, 165] and injection of α-syn into the ENS [183], together with evidence of LBs in human PD ENS [11], suggest that α-syn pathology in enteric neurons, and possibly elsewhere in the ANS, contributes to dysregulated GI motility. These models can serve as platforms to test therapies aiming to affect α-syn accumulation and to investigate the relationship between ENS α-syn pathology and the development of the hallmark PD CNS pathology and cardinal motor symptoms. Animal models also allow for interrogation of neurodegenerative mechanisms as they are occurring, ideally, at multiple time points to monitor progression of the disease. For example, our recent work in rhesus macaques used in vivo PET imaging to map cardiac inflammation and oxidative stress before, 1, and 12 weeks after 6-OHDA-induced postganglionic sympathetic nerve loss [104], providing clues to mechanisms of neurodegeneration, possible biomarkers, and potential drug targets. This novel mechanistic research approach is difficult to apply in PD patients for several reasons, including the extensive neuronal damage and dysfunction already present by the time of diagnosis.

Honestly acknowledging the limitations of each animal model is critical to fruitful, translational experimental design. Toxin models can have confounding off-target effects, such as vascular damage, myocardial degeneration, and interstitial hemorrhages of the kidneys and lungs as observed in rotenone-treated rats [189]. Murine models utilizing α-syn transgenesis can result in aberrant expression of α-syn in nonneuronal cell types; although Thy1 is not expressed on human mature T cells, it is extremely abundant on murine T cells [190]. Age of the animal should also be considered. PD is typically observed in patients over 60 years of age, and many PD symptoms worsen with age [191]. In that regard, oligomerized α-syn has been shown to increase in the aging cynomolgus ENS [192] and α-syn to accumulate in the substantia nigra of aging rhesus [193]. Although the ANS is conserved across many species, differences in neuroanatomy should also be considered when selecting a research model. Notably, invertebrate species such as the model organism *Drosophila melanogaster* do not have a clear parallel to the human ANS [194]. Zebrafish autonomic innervation shows noticeable differences in the location of sympathetic ganglia [5] and in the lack of organized ganglia in the ENS [195]. Comparing rodents to humans, sympathetic preganglionic neurons are present in

the T1–L3 vertebrae of humans and rats, but they are limited to T1–L2 in mice; parasympathetic preganglionic cell bodies are in S2–S4 in humans but L6–S1 in rats and mice [196]. Additionally, rodent preganglionic sympathetic neurons typically lack myelin, in contrast to large mammals [197]. The exact number and location of sympathetic ganglia differ between species, but they also show variability between individuals within the same species [197], including in humans [198]. Finally, researchers should verify that methods of assessing autonomic function are species-appropriate, e.g.: application of species-specific corrections for cardiovascular parameters, including QT interval during ECG evaluations [199].

Progress understanding the pathological basis of signs and symptoms in clinically relevant animal models of ANS dysfunction moves investigators one step closer to finding solutions. Part of this scientific evolution is the recognition that, like human PD, no single model can encompass all the possible different risk factors of the disease (e.g.: LRRK2 G2019S mutation, SNCA A53T mutation, environmental toxin exposure, age). Furthermore, the diversity of PD clinical presentation cautions against oversimplification and overinterpretation, as no single model can recapitulate all of PD motor and nonmotor features, including the range of autonomic dysfunction. An ongoing effort to address these issues is the development of a new generation of PD models. A subset of them are based on the multiple-hit hypothesis that different pathways synergistically contribute to PD neurodegeneration. These mixed models combine catecholaminergic neurotoxins, transgenesis, and/or α-syn injection [200] to assess links between PD associated genes and toxin administration, such as DJ1-/- mice which are more vulnerable to MPTP [201]. Additionally, transgenic and genome-edited nonhuman primate PD models are currently being developed [202]. Genetically modified monkeys will allow investigators to study the impact of genetics in species more physiologically and anatomically similar to humans, helping to define the progression of PD, including when ANS dysfunction first appears, and the best timing for introducing disease-modifying therapies. Overall, future work in animal models has great potential to bring important insights into PD dysautonomia etiology and, ultimately, better treatments.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

References

1. Parkinson J (2002) An essay on the shaking palsy 1817. J Neuropsychiatry Clin Neurosci 14(2):223–236. https://doi.org/10.1176/jnp.14.2.223 **(discussion 222)**
2. Tomic S, Rajkovaca I, Pekic V, Salha T, Misevic S (2017) Impact of autonomic dysfunctions on the quality of life in Parkinson's disease patients. Acta Neurol Belg 117(1):207–211. https://doi.org/10.1007/s13760-016-0739-6
3. Fazio P, Svenningsson P, Cselenyi Z, Halldin C, Farde L, Varrone A (2018) Nigrostriatal dopamine transporter availability in early Parkinson's disease. Mov Disord. https://doi.org/10.1002/mds.27316
4. Hirsch EC, Jenner P, Przedborski S (2013) Pathogenesis of Parkinson's disease. Mov Disord 28(1):24–30. https://doi.org/10.1002/mds.25032
5. Nilsson S (2011) Comparative anatomy of the autonomic nervous system. Autono Neurosci 165(1):3–9. https://doi.org/10.1016/j.autneu.2010.03.018
6. Goldstein DS, Holmes C, Li ST, Bruce S, Metman LV, Cannon RO (2000) Cardiac sympathetic denervation in Parkinson disease. Ann Intern Med 133(5):338–347
7. Palma JA, Carmona-Abellan MM, Barriobero N, Trevino-Peinado C, Garcia-Lopez M, Fernandez-Jarne E, Luquin MR (2013) Is cardiac function impaired in premotor Parkinson's disease? A retrospective cohort study. Mov Disord 28(5):591–596. https://doi.org/10.1002/mds.25431
8. Gibbons CH, Simon DK, Huang M, Tilley B, Aminoff MJ, Bainbridge JL, Brodsky M, Freeman R, Goudreau J, Hamill RW, Luo ST, Singer C, Videnovic A, Bodis-Wollner I, Wong PS (2017) Autonomic and electrocardiographic findings in Parkinson's disease. Auton Neurosci 205:93–98. https://doi.org/10.1016/j.autneu.2017.04.002
9. Jain S, Goldstein DS (2012) Cardiovascular dysautonomia in Parkinson disease: from pathophysiology to pathogenesis. Neurobiol Dis 46(3):572–580. https://doi.org/10.1016/j.nbd.2011.10.025
10. Matinolli M, Korpelainen JT, Korpelainen R, Sotaniemi KA, Myllyla VV (2009) Orthostatic hypotension, balance and falls in Parkinson's disease. Mov Disord 24(5):745–751. https://doi.org/10.1002/mds.22457
11. Beach TG, Adler CH, Sue LI, Vedders L, Lue L, White Iii CL, Akiyama H, Caviness JN, Shill HA, Sabbagh MN, Walker DG, Consortium APsD (2010) Multi-organ distribution of phosphorylated alpha-synuclein histopathology in subjects with lewy body disorders. Acta Neuropathol 119(6):689–702. https://doi.org/10.1007/s00401-010-0664-3
12. Greene JG (2014) Causes and consequences of degeneration of the dorsal motor nucleus of the vagus nerve in Parkinson's disease. Antioxid Redox Signal 21(4):649–667. https://doi.org/10.1089/ars.2014.5859
13. Gjerloff T, Fedorova T, Knudsen K, Munk OL, Nahimi A, Jacobsen S, Danielsen EH, Terkelsen AJ, Hansen J, Pavese N, Brooks DJ, Borghammer P (2015) Imaging acetylcholinesterase density in peripheral organs in Parkinson's disease with 11C-donepezil PET. Brain 138(Pt 3):653–663. https://doi.org/10.1093/brain/awu369
14. Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, Obeso J, Marek K, Litvan I, Lang AE, Halliday G, Goetz CG, Gasser T, Dubois B, Chan P, Bloem BR, Adler CH, Deuschl G (2015) MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord 30(12):1591–1601. https://doi.org/10.1002/mds.26424
15. Kashihara K, Imamura T, Shinya T (2010) Cardiac 123I-MIBG uptake is reduced more markedly in patients with REM sleep behavior disorder than in those with early stage Parkinson's

disease. Parkinsonism Relat Disord 16(4):252–255. https://doi.org/10.1016/j.parkreldis.2009.12.010
16. Nagayama H, Hamamoto M, Ueda M, Nagashima J, Katayama Y (2005) Reliability of MIBG myocardial scintigraphy in the diagnosis of Parkinson's disease. J Neurol Neurosurg Psychiatry 76(2):249–251. https://doi.org/10.1136/jnnp.2004.037028
17. Li ST, Dendi R, Holmes C, Goldstein DS (2002) Progressive loss of cardiac sympathetic innervation in Parkinson's disease. Ann Neurol 52(2):220–223. https://doi.org/10.1002/ana.10236
18. Courbon F, Brefel-Courbon C, Thalamas C, Alibelli MJ, Berry I, Montastruc JL, Rascol O, Senard JM (2003) Cardiac MIBG scintigraphy is a sensitive tool for detecting cardiac sympathetic denervation in Parkinson's disease. Mov Disord 18(8):890–897. https://doi.org/10.1002/mds.10461
19. Wong KK, Raffel DM, Koeppe RA, Frey KA, Bohnen NI, Gilman S (2012) Pattern of cardiac sympathetic denervation in idiopathic Parkinson disease studied with 11C hydroxyephedrine PET. Radiology 265(1):240–247. https://doi.org/10.1148/radiol.12112723
20. Wong KK, Raffel DM, Bohnen NI, Altinok G, Gilman S, Frey KA (2017) 2-Year natural decline of cardiac sympathetic innervation in idiopathic parkinson disease studied with 11C-hydroxyephedrine PET. J Nuclear Med 58(2):326–331. https://doi.org/10.2967/jnumed.116.176891
21. Orimo S, Uchihara T, Nakamura A, Mori F, Kakita A, Wakabayashi K, Takahashi H (2008) Axonal alpha-synuclein aggregates herald centripetal degeneration of cardiac sympathetic nerve in Parkinson's disease. Brain 131(Pt 3):642–650. https://doi.org/10.1093/brain/awm302
22. Iwanaga K, Wakabayashi K, Yoshimoto M, Tomita I, Satoh H, Takashima H, Satoh A, Seto M, Tsujihata M, Takahashi H (1999) Lewy body-type degeneration in cardiac plexus in Parkinson's and incidental lewy body diseases. Neurology 52(6):1269–1271
23. Wakabayashi K, Takahashi H (1997) The intermediolateral nucleus and Clarke's column in Parkinson's disease. Acta Neuropathol 94(3):287–289
24. Gesi M, Soldani P, Giorgi FS, Santinami A, Bonaccorsi I, Fornai F (2000) The role of the locus coeruleus in the development of Parkinson's disease. Neurosci Biobehav Rev 24(6):655–668
25. Gai WP, Geffen LB, Denoroy L, Blessing WW (1993) Loss of C1 and C3 epinephrine-synthesizing neurons in the medulla oblongata in Parkinson's disease. Ann Neurol 33(4):357–367. https://doi.org/10.1002/ana.410330405
26. Goldstein DS, Holmes CS, Dendi R, Bruce SR, Li ST (2002) Orthostatic hypotension from sympathetic denervation in Parkinson's disease. Neurology 58(8):1247–1255
27. Stoddard SL, Merkel GJ, Cook JA, Zinsmeister AR, Carmichael SW (1994) Adrenal medulla and Parkinson's disease. Microsc Res Tech 29(2):151–154. https://doi.org/10.1002/jemt.1070290212
28. Wakabayashi K, Takahashi H (1997) Neuropathology of autonomic nervous system in Parkinson's disease. Eur Neurol 38(Suppl 2):2–7
29. Sugie M, Goto J, Kawamura M, Ota H (2005) Increased norepinephrine-associated adrenomedullary inclusions in Parkinson's disease. Pathol Int 55(3):130–136. https://doi.org/10.1111/j.1440-1827.2005.01800.x
30. Umehara T, Oka H, Nakahara A, Matsuno H, Toyoda C (2018) High norepinephrinergic orthostatic hypotension in early Parkinson's disease. Parkinsonism Relat Disord. https://doi.org/10.1016/j.parkreldis.2018.05.025
31. Boulant JA (1994) Neurophysiology of thermoregulation: role of hypothalamic neuronal networks. In: Milton AS (ed) Temperature regulation: recent physiological and pharmacological advances. Birkhäuser Basel, Base, pp 93–101. https://doi.org/10.1007/978-3-0348-8491-4_16
32. Swinn L, Schrag A, Viswanathan R, Bloem BR, Lees A, Quinn N (2003) Sweating dysfunction in Parkinson's disease. Mov Disord 18(12):1459–1463. https://doi.org/10.1002/mds.10586
33. Beitz JM (2013) Skin and wound issues in patients with Parkinson's disease: an overview of common disorders. Ostomy Wound Manag 59(6):26–36
34. Jost WH (2017) Autonomic dysfunction in Parkinson's disease: cardiovascular symptoms, thermoregulation, and urogenital symptoms. Int Rev Neurobiol 134:771–785. https://doi.org/10.1016/bs.irn.2017.04.003
35. Schestatsky P, Valls-Sole J, Ehlers JA, Rieder CR, Gomes I (2006) Hyperhidrosis in Parkinson's disease. Mov Disord 21(10):1744–1748. https://doi.org/10.1002/mds.21006
36. Shindo K, Iida H, Watanabe H, Ohta E, Nagasaka T, Shiozawa Z (2008) Sympathetic sudomotor and vasoconstrictive neural function in patients with Parkinson's disease. Parkinsonism Relat Disord 14(7):548–552. https://doi.org/10.1016/j.parkreldis.2007.12.004
37. Dabby R, Djaldetti R, Shahmurov M, Treves TA, Gabai B, Melamed E, Sadeh M, Avinoach I (2006) Skin biopsy for assessment of autonomic denervation in Parkinson's disease. J Neural Trans 113(9):1169–1176. https://doi.org/10.1007/s00702-005-0431-0
38. Wang N, Gibbons CH, Lafo J, Freeman R (2013) alpha-Synuclein in cutaneous autonomic nerves. Neurology 81(18):1604–1610. https://doi.org/10.1212/WNL.0b013e3182a9f449
39. Gibbons CH, Garcia J, Wang N, Shih LC, Freeman R (2016) The diagnostic discrimination of cutaneous alpha-synuclein deposition in Parkinson disease. Neurology 87(5):505–512. https://doi.org/10.1212/wnl.0000000000002919
40. Doppler K, Ebert S, Uceyler N, Trenkwalder C, Ebentheuer J, Volkmann J, Sommer C (2014) Cutaneous neuropathy in Parkinson's disease: a window into brain pathology. Acta Neuropathol 128(1):99–109. https://doi.org/10.1007/s00401-014-1284-0
41. Siepmann T, Penzlin AI, Illigens BM, Reichmann H (2017) Should skin biopsies be performed in patients suspected of having Parkinson's disease? Parkinsons Dis 2017:6064974. https://doi.org/10.1155/2017/6064974
42. Politis M, Piccini P, Pavese N, Koh SB, Brooks DJ (2008) Evidence of dopamine dysfunction in the hypothalamus of patients with Parkinson's disease: an in vivo 11C-raclopride PET study. Exp Neurol 214(1):112–116. https://doi.org/10.1016/j.expneurol.2008.07.021
43. Sandyk R, Iacono RP, Bamford CR (1987) The hypothalamus in Parkinson disease. Ital J Neurol Sci 8(3):227–234
44. McDonald C, Winge K, Burn DJ (2017) Lower urinary tract symptoms in Parkinson's disease: prevalence, aetiology and management. Parkinsonism Relat Disord 35:8–16. https://doi.org/10.1016/j.parkreldis.2016.10.024
45. Uchiyama T, Sakakibara R, Yamamoto T, Ito T, Yamaguchi C, Awa Y, Yanagisawa M, Higuchi Y, Sato Y, Ichikawa T, Yamanishi T, Hattori T, Kuwabara S (2011) Urinary dysfunction in early and untreated Parkinson's disease. J Neurol Neurosurg Psychiatry 82(12):1382–1386. https://doi.org/10.1136/jnnp.2011.241075
46. Sakakibara R, Tateno F, Yamamoto T, Uchiyama T, Yamanishi T (2018) Urological dysfunction in synucleinopathies: epidemiology, pathophysiology and management. Clin Auton Res 28(1):83–101. https://doi.org/10.1007/s10286-017-0480-0
47. Borghammer P, Knudsen K, Fedorova TD, Brooks DJ (2017) Imaging Parkinson's disease below the neck. NPJ Parkinsons Dis. https://doi.org/10.1038/s41531-017-0017-1
48. Seki S, Igawa Y, Kaidoh K, Ishizuka O, Nishizawa O, Andersson KE (2001) Role of dopamine D1 and D2 receptors in the micturition reflex in conscious rats. Neurourol Urodyn 20(1):105–113
49. Winge K, Friberg L, Werdelin L, Nielsen KK, Stimpel H (2005) Relationship between nigrostriatal dopaminergic degeneration, urinary symptoms, and bladder control in Parkinson's

disease. Eur J Neurol 12(11):842–850. https://doi.org/10.1111/j.1468-1331.2005.01087.x
50. Del Tredici K, Braak H (2012) Spinal cord lesions in sporadic Parkinson's disease. Acta Neuropathol 124(5):643–664. https://doi.org/10.1007/s00401-012-1028-y
51. VanderHorst VG, Samardzic T, Saper CB, Anderson MP, Nag S, Schneider JA, Bennett DA, Buchman AS (2015) alpha-Synuclein pathology accumulates in sacral spinal visceral sensory pathways. Ann Neurol 78(1):142–149. https://doi.org/10.1002/ana.24430
52. Armstrong R (2015) Oculo-visual dysfunction in Parkinson's disease. J Parkinsons Dis 5:715–726. https://doi.org/10.3233/jpd-150686
53. Giza E, Fotiou D, Bostantjopoulou S, Katsarou Z, Karlovasitou A (2011) Pupil light reflex in Parkinson's disease: evaluation with pupillometry. Int J Neurosci 121(1):37–43. https://doi.org/10.3109/00207454.2010.526730
54. Stergiou V, Fotiou D, Tsiptsios D, Haidich B, Nakou M, Giantselidis C, Karlovasitou A (2009) Pupillometric findings in patients with Parkinson's disease and cognitive disorder. Int J Psychophysiol 72(2):97–101. https://doi.org/10.1016/j.ijpsycho.2008.10.010
55. Yamashita F, Hirayama M, Nakamura T, Takamori M, Hori N, Uchida K, Hama T, Sobue G (2010) Pupillary autonomic dysfunction in multiple system atrophy and Parkinson's disease: an assessment by eye-drop tests. Clin Auton Res 20(3):191–197. https://doi.org/10.1007/s10286-009-0051-0
56. Hunter S (1985) The rostral mesencephalon in Parkinson's disease and Alzheimer's disease. Acta Neuropathol 68(1):53–58
57. Del Tredici K, Hawkes CH, Ghebremedhin E, Braak H (2010) Lewy pathology in the submandibular gland of individuals with incidental Lewy body disease and sporadic Parkinson's disease. Acta Neuropathol 119(6):703–713. https://doi.org/10.1007/s00401-010-0665-2
58. Srivanitchapoom P, Pandey S, Hallett M (2014) Drooling in Parkinson's disease: a review. Parkinsonism Relat Disord 20(11):1109–1118. https://doi.org/10.1016/j.parkreldis.2014.08.013
59. Proulx M, de Courval FP, Wiseman MA, Panisset M (2005) Salivary production in Parkinson's disease. Mov Disord 20(2):204–207. https://doi.org/10.1002/mds.20189
60. Heetun ZS, Quigley EM (2012) Gastroparesis and Parkinson's disease: a systematic review. Parkinsonism Relat Disord 18(5):433–440. https://doi.org/10.1016/j.parkreldis.2011.12.004
61. Pazo JH, Belforte JE (2002) Basal ganglia and functions of the autonomic nervous system. Cell Mol Neurobiol 22(5–6):645–654
62. Fasano A, Visanji NP, Liu LW, Lang AE, Pfeiffer RF (2015) Gastrointestinal dysfunction in Parkinson's disease. Lancet Neurol 14(6):625–639. https://doi.org/10.1016/S1474-4422(15)00007-1
63. Mu L, Sobotka S, Chen J, Su H, Sanders I, Nyirenda T, Adler CH, Shill HA, Caviness JN, Samanta JE, Sue LI, Beach TG (2013) Parkinson disease affects peripheral sensory nerves in the pharynx. J Neuropathol Exp Neurol 72(7):614–623. https://doi.org/10.1097/NEN.0b013e3182965886
64. Cersosimo MG, Benarroch EE (2012) Autonomic involvement in Parkinson's disease: pathology, pathophysiology, clinical features and possible peripheral biomarkers. J Neurol Sci 313(1–2):57–63. https://doi.org/10.1016/j.jns.2011.09.030
65. Di Maio R, Barrett PJ, Hoffman EK, Barrett CW, Zharikov A, Borah A, Hu X, McCoy J, Chu CT, Burton EA, Hastings TG, Greenamyre JT (2016) alpha-Synuclein binds to TOM20 and inhibits mitochondrial protein import in Parkinson's disease. Sci Transl Med 8(342):342ra378. https://doi.org/10.1126/scitranslmed.aaf3634
66. Arai E, Arai M, Uchiyama T, Higuchi Y, Aoyagi K, Yamanaka Y, Yamamoto T, Nagano O, Shiina A, Maruoka D, Matsumura T, Nakagawa T, Katsuno T, Imazeki F, Saeki N, Kuwabara S, Yokosuka O (2012) Subthalamic deep brain stimulation can improve gastric emptying in Parkinson's disease. Brain 135(Pt 5):1478–1485. https://doi.org/10.1093/brain/aws086
67. Yu QJ, Yu SY, Zuo LJ, Lian TH, Hu Y, Wang RD, Piao YS, Guo P, Liu L, Jin Z, Li LX, Chan P, Chen SD, Wang XM, Zhang W (2018) Parkinson disease with constipation: clinical features and relevant factors. Sci Rep 8(1):567. https://doi.org/10.1038/s41598-017-16790-8
68. Knudsen K, Haase AM, Fedorova TD, Bekker AC, Ostergaard K, Krogh K, Borghammer P (2017) Gastrointestinal transit time in Parkinson's disease using a magnetic tracking system. J Parkinsons Dis 7(3):471–479. https://doi.org/10.3233/jpd-171131
69. Yu T, Wang Y, Wu G, Xu Q, Tang Y, Lin L (2016) High-resolution anorectal manometry in Parkinson disease with defecation disorder: a comparison with functional defecation disorder. J Clin Gastroenterol 50(7):566–571. https://doi.org/10.1097/mcg.0000000000000469
70. Singaram C, Ashraf W, Gaumnitz EA, Torbey C, Sengupta A, Pfeiffer R, Quigley EM (1995) Dopaminergic defect of enteric nervous system in Parkinson's disease patients with chronic constipation. Lancet 346(8979):861–864
71. Annerino DM, Arshad S, Taylor GM, Adler CH, Beach TG, Greene JG (2012) Parkinson's disease is not associated with gastrointestinal myenteric ganglion neuron loss. Acta Neuropathol 124(5):665–680. https://doi.org/10.1007/s00401-012-1040-2
72. Corbille AG, Coron E, Neunlist M, Derkinderen P, Lebouvier T (2014) Appraisal of the dopaminergic and noradrenergic innervation of the submucosal plexus in PD. J Parkinsons Dis 4(4):571–576. https://doi.org/10.3233/jpd-140422
73. Barrenschee M, Zorenkov D, Bottner M, Lange C, Cossais F, Scharf AB, Deuschl G, Schneider SA, Ellrichmann M, Fritscher-Ravens A, Wedel T (2017) Distinct pattern of enteric phospho-alpha-synuclein aggregates and gene expression profiles in patients with Parkinson's disease. Acta Neuropathol Commun 5(1):1. https://doi.org/10.1186/s40478-016-0408-2
74. Petrovitch H, Abbott RD, Ross GW, Nelson J, Masaki KH, Tanner CM, Launer LJ, White LR (2009) Bowel movement frequency in late-life and substantia nigra neuron density at death. Mov Disord 24(3):371–376. https://doi.org/10.1002/mds.22360
75. Hinkle JT, Perepezko K, Mills KA, Mari Z, Butala A, Dawson TM, Pantelyat A, Rosenthal LS, Pontone GM (2018) Dopamine transporter availability reflects gastrointestinal dysautonomia in early Parkinson disease. Parkinsonism Relat Disord. https://doi.org/10.1016/j.parkreldis.2018.08.010
76. Edwards LL, Quigley EM, Harned RK, Hofman R, Pfeiffer RF (1993) Defecatory function in Parkinson's disease: response to apomorphine. Ann Neurol 33(5):490–493. https://doi.org/10.1002/ana.410330512
77. Pellegrini C, Colucci R, Antonioli L, Barocelli E, Ballabeni V, Bernardini N, Blandizzi C, de Jonge WJ, Fornai M (2016) Intestinal dysfunction in Parkinson's disease: lessons learned from translational studies and experimental models. Neurogastroenterol Motil 28(12):1781–1791. https://doi.org/10.1111/nmo.12933
78. Killinger BA, Madaj Z, Sikora JW, Rey N, Haas AJ, Vepa Y, Lindqvist D, Chen H, Thomas PM, Brundin P, Brundin L, Labrie V (2018) The vermiform appendix impacts the risk of developing Parkinson's disease. Sci Transl Med. https://doi.org/10.1126/scitranslmed.aar5280
79. Blesa J, Przedborski S (2014) Parkinson's disease: animal models and dopaminergic cell vulnerability. Front Neuroanat 8:155. https://doi.org/10.3389/fnana.2014.00155

80. Blesa J, Trigo-Damas I, Quiroga-Varela A, Rey NLGd (2016) Animal Models of Parkinson's Disease. In: Kozubski JDaW (ed) Challenges in Parkinson's Disease. IntechOpen, London. https://doi.org/10.5772/63328
81. Bove J, Perier C (2012) Neurotoxin-based models of Parkinson's disease. Neuroscience 211:51–76. https://doi.org/10.1016/j.neuroscience.2011.10.057
82. Joers V, Seneczko K, Goecks NC, Kamp TJ, Hacker TA, Brunner KG, Engle JW, Barnhart TE, Nickles RJ, Holden JE, Emborg ME (2012) Nonuniform cardiac denervation observed by 11C-meta-hydroxyephedrine PET in 6-OHDA-treated monkeys. PLoS One 7(4):e35371. https://doi.org/10.1371/journal.pone.0035371
83. Metzger JM, Jones CA, Emborg ME (2018) Parkinson's disease in humans and in non-human primate aging and neurotoxin models. In: Conn JRaPM (ed) Conn's Handbook of Models for Human Aging, 2nd edn. Academic Press, London, pp 617–640
84. Johnson ME, Bobrovskaya L (2015) An update on the rotenone models of Parkinson's disease: their ability to reproduce the features of clinical disease and model gene-environment interactions. Neurotoxicology 46:101–116. https://doi.org/10.1016/j.neuro.2014.12.002
85. Richardson JR, Quan Y, Sherer TB, Greenamyre JT, Miller GW (2005) Paraquat neurotoxicity is distinct from that of MPTP and rotenone. Toxicol Sci 88(1):193–201. https://doi.org/10.1093/toxsci/kfi304
86. Rodriguez-Pallares J, Parga JA, Muñoz A, Rey P, Guerra MJ, Labandeira-Garcia JL (2007) Mechanism of 6-hydroxydopamine neurotoxicity: the role of NADPH oxidase and microglial activation in 6-hydroxydopamine-induced degeneration of dopaminergic neurons. J Neurochem 103(1):145–156. https://doi.org/10.1111/j.1471-4159.2007.04699.x
87. Meredith GE, Rademacher DJ (2011) MPTP mouse models of Parkinson's disease: an update. J Parkinsons Dis 1(1):19–33. https://doi.org/10.3233/jpd-2011-11023
88. Purisai MG, McCormack AL, Langston WJ, Johnston LC, Di Monte DA (2005) Alpha-synuclein expression in the substantia nigra of MPTP-lesioned non-human primates. Neurobiol Dis 20(3):898–906. https://doi.org/10.1016/j.nbd.2005.05.028
89. Kowall NW, Hantraye P, Brouillet E, Beal MF, McKee AC, Ferrante RJ (2000) MPTP induces alpha-synuclein aggregation in the substantia nigra of baboons. Neuro Rep 11(1):211–213
90. Betarbet R, Canet-Aviles RM, Sherer TB, Mastroberardino PG, McLendon C, Kim JH, Lund S, Na HM, Taylor G, Bence NF, Kopito R, Seo BB, Yagi T, Yagi A, Klinefelter G, Cookson MR, Greenamyre JT (2006) Intersecting pathways to neurodegeneration in Parkinson's disease: effects of the pesticide rotenone on DJ-1, alpha-synuclein, and the ubiquitin-proteasome system. Neurobiol Dis 22(2):404–420. https://doi.org/10.1016/j.nbd.2005.12.003
91. Polymeropoulos MH, Lavedan C, Leroy E, Ide SE, Dehejia A, Dutra A, Pike B, Root H, Rubenstein J, Boyer R, Stenroos ES, Chandrasekharappa S, Athanassiadou A, Papapetropoulos T, Johnson WG, Lazzarini AM, Duvoisin RC, Di Iorio G, Golbe LI, Nussbaum RL (1997) Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. Science 276(5321):2045–2047
92. Spillantini MG, Crowther RA, Jakes R, Hasegawa M, Goedert M (1998) alpha-synuclein in filamentous inclusions of Lewy bodies from Parkinson's disease and dementia with lewy bodies. Proc Natl Acad Sci USA 95(11):6469–6473
93. Narhi L, Wood SJ, Steavenson S, Jiang Y, Wu GM, Anafi D, Kaufman SA, Martin F, Sitney K, Denis P, Louis JC, Wypych J, Biere AL, Citron M (1999) Both familial Parkinson's disease mutations accelerate alpha-synuclein aggregation. J Biol Chem 274(14):9843–9846
94. Deng H, Wang P, Jankovic J (2018) The genetics of Parkinson disease. Ageing Res Rev 42:72–85. https://doi.org/10.1016/j.arr.2017.12.007
95. Kordower JH, Chu Y, Hauser RA, Freeman TB, Olanow CW (2008) Lewy body-like pathology in long-term embryonic nigral transplants in Parkinson's disease. Nat Med 14(5):504–506. https://doi.org/10.1038/nm1747
96. Li JY, Englund E, Holton JL, Soulet D, Hagell P, Lees AJ, Lashley T, Quinn NP, Rehncrona S, Bjorklund A, Widner H, Revesz T, Lindvall O, Brundin P (2008) Lewy bodies in grafted neurons in subjects with Parkinson's disease suggest host-to-graft disease propagation. Nat Med 14(5):501–503. https://doi.org/10.1038/nm1746
97. Brundin P, Melki R (2017) Prying into the prion hypothesis for Parkinson's disease. J Neurosci 37(41):9808–9818. https://doi.org/10.1523/jneurosci.1788-16.2017
98. Recasens A, Ulusoy A, Kahle PJ, Di Monte DA, Dehay B (2018) In vivo models of alpha-synuclein transmission and propagation. Cell Tissue Res 373(1):183–193. https://doi.org/10.1007/s00441-017-2730-9
99. Fuller RW, Hahn RA, Snoddy HD, Wikel JH (1984) Depletion of cardiac norepinephrine in rats and mice by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Biochem Pharmacol 33(19):2957–2960
100. Joers V, Emborg ME (2014) Modeling and imaging cardiac sympathetic neurodegeneration in Parkinson's disease. Am J Nucl Med Mol Imaging 4(2):125–159
101. Jiang YH, Jiang P, Yang JL, Ma DF, Lin HQ, Su WG, Wang Z, Li X (2015) Cardiac dysregulation and myocardial injury in a 6-hydroxydopamine-induced rat model of sympathetic denervation. PLoS One 10(7):e0133971. https://doi.org/10.1371/journal.pone.0133971
102. Goldstein DS, Grossman E, Tamrat M, Chang PC, Eisenhofer G, Bacher J, Kirk KL, Bacharach S, Kopin IJ (1991) Positron emission imaging of cardiac sympathetic innervation and function using 18F-6-fluorodopamine: effects of chemical sympathectomy by 6-hydroxydopamine. J Hypertens 9(5):417–423
103. Joers V, Dilley K, Rahman S, Jones C, Shultz J, Simmons H, Emborg ME (2014) Cardiac sympathetic denervation in 6-OHDA-treated nonhuman primates. PLoS One 9(8):e104850. https://doi.org/10.1371/journal.pone.0104850
104. Metzger JM, Moore CF, Boettcher CA, Brunner KG, Fleddermann RA, Matsoff HN, Resnikoff HA, Bondarenko V, Kamp TJ, Hacker TA, Barnhart TE, Lao PJ, Christian BT, Nickles RJ, Gallagher CL, Holden JE, Emborg ME (2018) In vivo imaging of inflammation and oxidative stress in a nonhuman primate model of cardiac sympathetic neurodegeneration. NPJ Parkinsons Dis 4:22. https://doi.org/10.1038/s41531-018-0057-1
105. Ariza D, Lopes FN, Crestani CC, Martins-Pinge MC (2015) Chemoreflex and baroreflex alterations in Parkinsonism induced by 6-OHDA in unanesthetized rats. Neurosci Lett 607:77–82. https://doi.org/10.1016/j.neulet.2015.09.024
106. Silva AS, Ariza D, Dias DP, Crestani CC, Martins-Pinge MC (2015) Cardiovascular and autonomic alterations in rats with Parkinsonism induced by 6-OHDA and treated with L-DOPA. Life Sci 127:82–89. https://doi.org/10.1016/j.lfs.2015.01.032
107. Yu JG, Wu J, Shen FM, Cai GJ, Liu JG, Su DF (2008) Arterial baroreflex dysfunction fails to mimic Parkinson's disease in rats. J Pharmacol Sci 108(1):56–62
108. Ben V, Bruguerolle B (2000) Effects of bilateral striatal 6-OHDA lesions on circadian rhythms in the rat: a radiotelemetric study. Life Sci 67(13):1549–1558
109. Boulamery A, Simon N, Vidal J, Bruguerolle B (2010) Effects of L-Dopa on circadian rhythms of 6-OHDA striatal lesioned rats: a radiotelemetric study. Chronobiol Int 27(2):251–264. https://doi.org/10.3109/07420521003664213

110. Falquetto B, Tuppy M, Potje SR, Moreira TS, Antoniali C, Takakura AC (2017) Cardiovascular dysfunction associated with neurodegeneration in an experimental model of Parkinson's disease. Brain Res 1657:156–166. https://doi.org/10.1016/j.brainres.2016.12.008
111. Sakata M, Sei H, Toida K, Fujihara H, Urushihara R, Morita Y (2002) Mesolimbic dopaminergic system is involved in diurnal blood pressure regulation. Brain Res 928(1–2):194–201
112. Zhang Z, Du X, Xu H, Xie J, Jiang H (2015) Lesion of medullary catecholaminergic neurons is associated with cardiovascular dysfunction in rotenone-induced Parkinson's disease rats. Eur J Neurosci 42(6):2346–2355. https://doi.org/10.1111/ejn.13012
113. Hallett PJ, McLean JR, Kartunen A, Langston JW, Isacson O (2012) alpha-Synuclein overexpressing transgenic mice show internal organ pathology and autonomic deficits. Neurobiol Dis 47(2):258–267. https://doi.org/10.1016/j.nbd.2012.04.009
114. Fleming SM, Jordan MC, Mulligan CK, Masliah E, Holden JG, Millard RW, Chesselet MF, Roos KP (2013) Impaired baroreflex function in mice overexpressing alpha-synuclein. Front Neurol 4:103. https://doi.org/10.3389/fneur.2013.00103
115. Griffioen KJ, Rothman SM, Ladenheim B, Wan R, Vranis N, Hutchison E, Okun E, Cadet JL, Mattson MP (2013) Dietary energy intake modifies brainstem autonomic dysfunction caused by mutant alpha-synuclein. Neurobiol Aging 34(3):928–935. https://doi.org/10.1016/j.neurobiolaging.2012.07.008
116. Kuo YM, Li Z, Jiao Y, Gaborit N, Pani AK, Orrison BM, Bruneau BG, Giasson BI, Smeyne RJ, Gershon MD, Nussbaum RL (2010) Extensive enteric nervous system abnormalities in mice transgenic for artificial chromosomes containing Parkinson disease-associated alpha-synuclein gene mutations precede central nervous system changes. Hum Mol Genet 19(9):1633–1650. https://doi.org/10.1093/hmg/ddq038
117. Billia F, Hauck L, Grothe D, Konecny F, Rao V, Kim RH, Mak TW (2013) Parkinson-susceptibility gene DJ-1/PARK7 protects the murine heart from oxidative damage in vivo. Proc Natl Acad Sci USA 110(15):6085–6090. https://doi.org/10.1073/pnas.1303444110
118. Dorn GW (1857) 2nd (2016) central Parkin: the evolving role of Parkin in the heart. Biochim Biophys Acta 8:1307–1312. https://doi.org/10.1016/j.bbabio.2016.03.014
119. Billia F, Hauck L, Konecny F, Rao V, Shen J, Mak TW (2011) PTEN-inducible kinase 1 (PINK1)/Park6 is indispensable for normal heart function. Proc Natl Acad Sci USA 108(23):9572–9577. https://doi.org/10.1073/pnas.1106291108
120. Baptista MA, Dave KD, Frasier MA, Sherer TB, Greeley M, Beck MJ, Varsho JS, Parker GA, Moore C, Churchill MJ, Meshul CK, Fiske BK (2013) Loss of leucine-rich repeat kinase 2 (LRRK2) in rats leads to progressive abnormal phenotypes in peripheral organs. PLoS One 8(11):e80705. https://doi.org/10.1371/journal.pone.0080705
121. Algeri S, Ambrosio S, Garofalo P, Gerli P (1987) Peripheral effects of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and its main metabolite 1-methyl-4-phenylpyridinium ion (MPP+) in the rat. Eur J Pharmacol 141(2):309–312
122. Johnson ME, Lim Y, Senthilkumaran M, Zhou XF, Bobrovskaya L (2015) Investigation of tyrosine hydroxylase and BDNF in a low-dose rotenone model of Parkinson's disease. J Chem Neuroanat 70:33–41. https://doi.org/10.1016/j.jchemneu.2015.11.002
123. Farrell KF, Krishnamachari S, Villanueva E, Lou H, Alerte TN, Peet E, Drolet RE, Perez RG (2014) Non-motor parkinsonian pathology in aging A53T alpha-synuclein mice is associated with progressive synucleinopathy and altered enzymatic function. J Neurochem 128(4):536–546. https://doi.org/10.1111/jnc.12481
124. Suaudeau C, Dourmap N, Costentin J (1995) Rapid and long lasting reduction of the hypothermic effect of a D2 dopamine agonist after an intracerebroventricular injection of 6-hydroxydopamine. Neuropharmacology 34(1):101–105
125. Jiao Y, Dou Y, Lockwood G, Pani A, Jay Smeyne R (2015) Acute effects of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) or paraquat on core temperature in C57BL/6 J mice. J Parkinsons Dis 5(2):389–401. https://doi.org/10.3233/jpd-140424
126. Kamberov YG, Karlsson EK, Kamberova GL, Lieberman DE, Sabeti PC, Morgan BA, Tabin CJ (2015) A genetic basis of variation in eccrine sweat gland and hair follicle density. Proc Natl Acad Sci USA 112(32):9932–9937. https://doi.org/10.1073/pnas.1511680112
127. Rao MS, Jaszczak E, Landis SC (1994) Innervation of footpads of normal and mutant mice lacking sweat glands. J Comp Neurol 346(4):613–625. https://doi.org/10.1002/cne.903460412
128. Yodlowski ML, Fredieu JR, Landis SC (1984) Neonatal 6-hydroxydopamine treatment eliminates cholinergic sympathetic innervation and induces sensory sprouting in rat sweat glands. J Neurosci 4(6):1535–1548
129. Soler R, Fullhase C, Santos C, Andersson KE (2011) Development of bladder dysfunction in a rat model of dopaminergic brain lesion. Neurourol Urodyn 30(1):188–193. https://doi.org/10.1002/nau.20917
130. Yoshimura N, Kuno S, Chancellor MB, De Groat WC, Seki S (2003) Dopaminergic mechanisms underlying bladder hyperactivity in rats with a unilateral 6-hydroxydopamine (6-OHDA) lesion of the nigrostriatal pathway. Br J Pharmacol 139(8):1425–1432. https://doi.org/10.1038/sj.bjp.0705388
131. Kitta T, Chancellor MB, de Groat WC, Shinohara N, Yoshimura N (2016) Role of the anterior cingulate cortex in the control of micturition reflex in a rat model of Parkinson's disease. J Urol 195(5):1613–1620. https://doi.org/10.1016/j.juro.2015.11.039
132. Campeau L, Soler R, Sittadjody S, Pareta R, Nomiya M, Zarifpour M, Opara EC, Yoo JJ, Andersson KE (2014) Effects of allogeneic bone marrow derived mesenchymal stromal cell therapy on voiding function in a rat model of Parkinson disease. J Urol 191(3):850–859. https://doi.org/10.1016/j.juro.2013.08.026
133. Albanese A, Jenner P, Marsden CD, Stephenson JD (1988) Bladder hyperreflexia induced in marmosets by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. Neurosci Lett 87(1–2):46–50
134. Yoshimura N, Mizuta E, Yoshida O, Kuno S (1998) Therapeutic effects of dopamine D1/D2 receptor agonists on detrusor hyperreflexia in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned parkinsonian cynomolgus monkeys. J Pharmacol Exp Ther 286(1):228–233
135. Mitra R, Aronsson P, Winder M, Tobin G, Bergquist F, Carlsson T (2015) Local change in urinary bladder contractility following CNS dopamine denervation in the 6-OHDA rat model of Parkinson's disease. J Parkinsons Dis 5(2):301–311. https://doi.org/10.3233/jpd-140509
136. Pritchard S, Jackson MJ, Hikima A, Lione L, Benham CD, Chaudhuri KR, Rose S, Jenner P, Iravani MM (2017) Altered detrusor contractility in MPTP-treated common marmosets with bladder hyperreflexia. PLoS One 12(5):e0175797. https://doi.org/10.1371/journal.pone.0175797
137. Hamill RW, Tompkins JD, Girard BM, Kershen RT, Parsons RL, Vizzard MA (2012) Autonomic dysfunction and plasticity in micturition reflexes in human alpha-synuclein mice. Dev Neurobiol 72(6):918–936. https://doi.org/10.1002/dneu.20978
138. Tereshchenko LV, Anisimov VN, Shul'govsky VV, Latanov AV (2015) Early changes in saccadic eye movement in hemiparkinsonian MPTP-treated monkeys. Perception 44(8–9):1054–1063. https://doi.org/10.1177/0301006615596868
139. Lawrence MS, Redmond DE Jr (1991) MPTP lesions and dopaminergic drugs alter eye blink rate in African green monkeys. Pharmacol Biochem Behav 38(4):869–874

140. Wu XH, Qian KW, Xu GZ, Li YY, Ma YY, Huang F, Wang YQ, Zhou X, Qu J, Yang XL, Zhong YM, Weng SJ (2016) The role of retinal dopamine in C57BL/6 mouse refractive development as revealed by intravitreal administration of 6-hydroxydopamine. Invest Ophthalmol Vis Sci 57(13):5393–5404. https://doi.org/10.1167/iovs.16-19543
141. Cuenca N, Herrero MT, Angulo A, de Juan E, Martinez-Navarrete GC, Lopez S, Barcia C, Martin-Nieto J (2005) Morphological impairments in retinal neurons of the scotopic visual pathway in a monkey model of Parkinson's disease. J Comp Neurol 493(2):261–273. https://doi.org/10.1002/cne.20761
142. Cavallotti C, Frati A, Sagnelli P, Pescosolido N (2005) Re-evaluation and quantification of the different sources of nerve fibres supplying the rat eye. J Anat 206(3):217–224. https://doi.org/10.1111/j.1469-7580.2005.00390.x
143. Luthman J, Sundstrom E (1990) No apparent difference in the effects of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) on the sympathetic system in NMRI and C57 BL/6 mice. Toxicol Lett 54(1):83–92
144. Ghilardi MF, Bodis-Wollner I, Onofrj MC, Marx MS, Glover AA (1988) Spatial frequency-dependent abnormalities of the pattern electroretinogram and visual evoked potentials in a parkinsonian monkey model. Brain 111(Pt 1):131–149
145. Colasanti BK, Kosa JE, Trotter RR (1978) Responsiveness of the rabbit eye to adrenergic and cholinergic agonists after treatment with 6-hydroxydopamine or alpha-methyl-para-tyrosine: part I-Pupillary changes. Ann Ophthalmol 10(8):1067–1074
146. Ghilardi MF, Marx MS, Bodis-Wollner I, Camras CB, Glover AA (1989) The effect of intraocular 6-hydroxydopamine on retinal processing of primates. Ann Neurol 25(4):357–364. https://doi.org/10.1002/ana.410250407
147. Surguchov A, McMahan B, Masliah E, Surgucheva I (2001) Synucleins in ocular tissues. J Neurosci Res 65(1):68–77. https://doi.org/10.1002/jnr.1129
148. Price DL, Rockenstein E, Mante M, Adame A, Overk C, Spencer B, Duong-Polk KX, Bonhaus D, Lindsey J, Masliah E (2016) Longitudinal live imaging of retinal alpha-synuclein:GFP deposits in a transgenic mouse model of Parkinson's disease/dementia with lewy bodies. Sci Rep 6:29523. https://doi.org/10.1038/srep29523
149. Nuckolls AL, Worley C, Leto C, Zhang H, Morris JK, Stanford JA (2012) Tongue force and tongue motility are differently affected by unilateral vs bilateral nigrostriatal dopamine depletion in rats. Behav Brain Res 234(2):343–348. https://doi.org/10.1016/j.bbr.2012.07.003
150. Cullen KP, Grant LM, Kelm-Nelson CA, Brauer AFL, Bickelhaupt LB, Russell JA, Ciucci MR (2018) Pink1 -/- rats show early-onset swallowing deficits and correlative brainstem pathology. Dysphagia. https://doi.org/10.1007/s00455-018-9896-5
151. Yang KM, Blue KV, Mulholland HM, Kurup MP, Kelm-Nelson CA, Ciucci MR (2018) Characterization of oromotor and limb motor dysfunction in the DJ1 -/- model of Parkinson disease. Behav Brain Res 339:47–56. https://doi.org/10.1016/j.bbr.2017.10.036
152. Zheng LF, Wang ZY, Li XF, Song J, Hong F, Lian H, Wang Q, Feng XY, Tang YY, Zhang Y, Zhu JX (2011) Reduced expression of choline acetyltransferase in vagal motoneurons and gastric motor dysfunction in a 6-OHDA rat model of Parkinson's disease. Brain Res 1420:59–67. https://doi.org/10.1016/j.brainres.2011.09.006
153. Pan-Montojo F, Schwarz M, Winkler C, Arnhold M, O'Sullivan GA, Pal A, Said J, Marsico G, Verbavatz JM, Rodrigo-Angulo M, Gille G, Funk RH, Reichmann H (2012) Environmental toxins trigger PD-like progression via increased alpha-synuclein release from enteric neurons in mice. Sci Rep 2:898. https://doi.org/10.1038/srep00898
154. Zheng LF, Song J, Fan RF, Chen CL, Ren QZ, Zhang XL, Feng XY, Zhang Y, Li LS, Zhu JX (2014) The role of the vagal pathway and gastric dopamine in the gastroparesis of rats after a 6-hydroxydopamine microinjection in the substantia nigra. Acta Physiol (Oxf) 211(2):434–446. https://doi.org/10.1111/apha.12229
155. Zhu HC, Zhao J, Luo CY, Li QQ (2012) Gastrointestinal dysfunction in a Parkinson's disease rat model and the changes of dopaminergic, nitric oxidergic, and cholinergic neurotransmitters in myenteric plexus. J Mol Neurosci 47(1):15–25. https://doi.org/10.1007/s12031-011-9560-0
156. Toti L, Travagli RA (2014) Gastric dysregulation induced by microinjection of 6-OHDA in the substantia nigra pars compacta of rats is determined by alterations in the brain-gut axis. Am J Physiol Gastrointest Liver Physiol 307(10):G1013–1023. https://doi.org/10.1152/ajpgi.00258.2014
157. Anselmi L, Toti L, Bove C, Hampton J, Travagli RA (2017) A Nigro–vagal pathway controls gastric motility and is affected in a rat model of parkinsonism. Gastroenterology 153(6):1581–1593. https://doi.org/10.1053/j.gastro.2017.08.069
158. Tian YM, Chen X, Luo DZ, Zhang XH, Xue H, Zheng LF, Yang N, Wang XM, Zhu JX (2008) Alteration of dopaminergic markers in gastrointestinal tract of different rodent models of Parkinson's disease. Neuroscience 153(3):634–644. https://doi.org/10.1016/j.neuroscience.2008.02.033
159. Anderson G, Noorian AR, Taylor G, Anitha M, Bernhard D, Srinivasan S, Greene JG (2007) Loss of enteric dopaminergic neurons and associated changes in colon motility in an MPTP mouse model of Parkinson's disease. Exp Neurol 207(1):4–12. https://doi.org/10.1016/j.expneurol.2007.05.010
160. Greene JG, Noorian AR, Srinivasan S (2009) Delayed gastric emptying and enteric nervous system dysfunction in the rotenone model of Parkinson's disease. Exp Neurol 218(1):154–161. https://doi.org/10.1016/j.expneurol.2009.04.023
161. Tasselli M, Chaumette T, Paillusson S, Monnet Y, Lafoux A, Huchet-Cadiou C, Aubert P, Hunot S, Derkinderen P, Neunlist M (2013) Effects of oral administration of rotenone on gastrointestinal functions in mice. Neurogastroenterol Motil 25(3):e183–193. https://doi.org/10.1111/nmo.12070
162. Pan-Montojo F, Anichtchik O, Dening Y, Knels L, Pursche S, Jung R, Jackson S, Gille G, Spillantini MG, Reichmann H, Funk RH (2010) Progression of Parkinson's disease pathology is reproduced by intragastric administration of rotenone in mice. PLoS One 5(1):e8762. https://doi.org/10.1371/journal.pone.0008762
163. Anselmi L, Bove C, Coleman FH, Le K, Subramanian MP, Venkiteswaran K, Subramanian T, Travagli RA (2018) Ingestion of subthreshold doses of environmental toxins induces ascending Parkinsonism in the rat. NPJ Parkinsons Dis 4:30. https://doi.org/10.1038/s41531-018-0066-0
164. Noorian AR, Rha J, Annerino DM, Bernhard D, Taylor GM, Greene JG (2012) Alpha-synuclein transgenic mice display age-related slowing of gastrointestinal motility associated with transgene expression in the vagal system. Neurobiol Dis 48(1):9–19. https://doi.org/10.1016/j.nbd.2012.06.005
165. Wang L, Magen I, Yuan PQ, Subramaniam SR, Richter F, Chesselet MF, Taché Y (2012) Mice overexpressing wild-type human alpha-synuclein display alterations in colonic myenteric ganglia and defecation. Neurogastroenterol Motil 24(9):e425–436. https://doi.org/10.1111/j.1365-2982.2012.01974.x
166. Chesselet MF, Richter F, Zhu C, Magen I, Watson MB, Subramaniam SR (2012) A progressive mouse model of Parkinson's disease: the Thy1-aSyn ("Line 61") mice. Neurotherapeutics 9(2):297–314. https://doi.org/10.1007/s13311-012-0104-2
167. Holmqvist S, Chutna O, Bousset L, Aldrin-Kirk P, Li W, Bjorklund T, Wang ZY, Roybon L, Melki R, Li JY (2014) Direct evidence of Parkinson pathology spread from the gastrointestinal

tract to the brain in rats. Acta Neuropathol 128(6):805–820. https://doi.org/10.1007/s00401-014-1343-6
168. Uemura N, Yagi H, Uemura MT, Hatanaka Y, Yamakado H, Takahashi R (2018) Inoculation of alpha-synuclein preformed fibrils into the mouse gastrointestinal tract induces lewy body-like aggregates in the brainstem via the vagus nerve. Mol Neurodegener 13(1):21. https://doi.org/10.1186/s13024-018-0257-5
169. Fornai M, Pellegrini C, Antonioli L, Segnani C, Ippolito C, Barocelli E, Ballabeni V, Vegezzi G, Al Harraq Z, Blandini F, Levandis G, Cerri S, Blandizzi C, Bernardini N, Colucci R (2016) Enteric dysfunctions in experimental Parkinson's disease: alterations of excitatory cholinergic neurotransmission regulating colonic motility in rats. J Pharmacol Exp Ther 356(2):434–444. https://doi.org/10.1124/jpet.115.228510
170. Levandis G, Balestra B, Siani F, Rizzo V, Ghezzi C, Ambrosi G, Cerri S, Bonizzi A, Vicini R, Vairetti M, Ferrigno A, Pastoris O, Blandini F (2015) Response of colonic motility to dopaminergic stimulation is subverted in rats with nigrostriatal lesion: relevance to gastrointestinal dysfunctions in Parkinson's disease. Neurogastroenterol Motil 27(12):1783–1795. https://doi.org/10.1111/nmo.12691
171. Colucci M, Cervio M, Faniglione M, De Angelis S, Pajoro M, Levandis G, Tassorelli C, Blandini F, Feletti F, De Giorgio R, Dellabianca A, Tonini S, Tonini M (2012) Intestinal dysmotility and enteric neurochemical changes in a Parkinson's disease rat model. Auton Neurosci 169(2):77–86. https://doi.org/10.1016/j.autneu.2012.04.005
172. Blandini F, Balestra B, Levandis G, Cervio M, Greco R, Tassorelli C, Colucci M, Faniglione M, Bazzini E, Nappi G, Clavenzani P, Vigneri S, De Giorgio R, Tonini M (2009) Functional and neurochemical changes of the gastrointestinal tract in a rodent model of Parkinson's disease. Neurosci Lett 467(3):203–207. https://doi.org/10.1016/j.neulet.2009.10.035
173. Zhang X, Li Y, Liu C, Fan R, Wang P, Zheng L, Hong F, Feng X, Zhang Y, Li L, Zhu J (2015) Alteration of enteric monoamines with monoamine receptors and colonic dysmotility in 6-hydroxydopamine-induced Parkinson's disease rats. Transl Res 166(2):152–162. https://doi.org/10.1016/j.trsl.2015.02.003
174. Liu Y, Sun JD, Song LK, Li J, Chu SF, Yuan YH, Chen NH (2015) Environment-contact administration of rotenone: a new rodent model of Parkinson's disease. Behav Brain Res 294:149–161. https://doi.org/10.1016/j.bbr.2015.07.058
175. Arnhold M, Dening Y, Chopin M, Arevalo E, Schwarz M, Reichmann H, Gille G, Funk RH, Pan-Montojo F (2016) Changes in the sympathetic innervation of the gut in rotenone treated mice as possible early biomarker for Parkinson's disease. Clin Auton Res 26(3):211–222. https://doi.org/10.1007/s10286-016-0358-6
176. Lai F, Jiang R, Xie W, Liu X, Tang Y, Xiao H, Gao J, Jia Y, Bai Q (2018) Intestinal pathology and gut microbiota alterations in a methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model of Parkinson's disease. Neurochem Res. https://doi.org/10.1007/s11064-018-2620-x
177. Shultz JM, Resnikoff H, Bondarenko V, Joers V, Meija A, Simmons H, Emborg ME (2016) Neurotoxin-induced catecholaminergic loss in the colonic myenteric plexus of rhesus monkeys. J Alzheimers Dis Parkinsonism. https://doi.org/10.4172/2161-0460.1000279
178. Natale G, Kastsiushenka O, Fulceri F, Ruggieri S, Paparelli A, Fornai F (2010) MPTP-induced parkinsonism extends to a subclass of TH-positive neurons in the gut. Brain Res 1355:195–206. https://doi.org/10.1016/j.brainres.2010.07.076
179. Ellett LJ, Hung LW, Munckton R, Sherratt NA, Culvenor J, Grubman A, Furness JB, White AR, Finkelstein DI, Barnham KJ, Lawson VA (2016) Restoration of intestinal function in an MPTP model of Parkinson's disease. Sci Rep 6:30269. https://doi.org/10.1038/srep30269
180. Yang X, Qian Y, Xu S, Song Y, Xiao Q (2017) Longitudinal analysis of fecal microbiome and pathologic processes in a rotenone induced mice model of Parkinson's disease. Front Aging Neurosci 9:441. https://doi.org/10.3389/fnagi.2017.00441
181. Wang L, Fleming SM, Chesselet MF, Tache Y (2008) Abnormal colonic motility in mice overexpressing human wild-type alpha-synuclein. Neuro Rep 19(8):873–876. https://doi.org/10.1097/WNR.0b013e3282ffda5e
182. Vidal-Martinez G, Vargas-Medrano J, Gil-Tommee C, Medina D, Garza NT, Yang B, Segura-Ulate I, Dominguez SJ, Perez RG (2016) FTY720/fingolimod reduces synucleinopathy and improves gut motility in A53T mice: contributions of pro-brain-derived neurotrophic factor (PRO-BDNF) and mature BDNF. J Biol Chem 291(39):20811–20821. https://doi.org/10.1074/jbc.M116.744029
183. Manfredsson FP, Luk KC, Benskey MJ, Gezer A, Garcia J, Kuhn NC, Sandoval IM, Patterson JR, O'Mara A, Yonkers R, Kordower JH (2018) Induction of alpha-synuclein pathology in the enteric nervous system of the rat and non-human primate results in gastrointestinal dysmotility and transient CNS pathology. Neurobiol Dis 112:106–118. https://doi.org/10.1016/j.nbd.2018.01.008
184. Yamashiro K, Tanaka R, Shimo Y, Oyama G, Ogawa T, Umemura A, Hattori N (2018) Cerebral microbleeds and blood pressure abnormalities in Parkinson's disease. NeurologicalSci 10:5–11. https://doi.org/10.1016/j.ensci.2017.12.002
185. Salawu F, Olokoba A (2015) Excessive daytime sleepiness and unintended sleep episodes associated with Parkinson's disease. Oman Med J 30(1):3–10. https://doi.org/10.5001/omj.2015.02
186. Koller WC, Vetere-Overfield B, Williamson A, Busenbark K, Nash J, Parrish D (1990) Sexual dysfunction in Parkinson's disease. Clin Neuropharmacol 13(5):461–463
187. Olanow CW, Kieburtz K, Katz R (2017) Clinical approaches to the development of a neuroprotective therapy for PD. Exp Neurol 298(Pt B):246–251. https://doi.org/10.1016/j.expneurol.2017.06.018
188. Cummings JL, Morstorf T, Zhong K (2014) Alzheimer's disease drug-development pipeline: few candidates, frequent failures. Alzheimer's Res Ther 6(4):37. https://doi.org/10.1186/alzrt269
189. Radad K, Hassanein K, Moldzio R, Rausch WD (2013) Vascular damage mediates neuronal and non-neuronal pathology following short and long-term rotenone administration in Sprague-Dawley rats. Exp Toxicol Pathol 65(1–2):41–47. https://doi.org/10.1016/j.etp.2011.05.008
190. Killeen N (1997) T-cell regulation: Thy-1–hiding in full view. Curr Biol 7(12):R774–777
191. Rodriguez M, Rodriguez-Sabate C, Morales I, Sanchez A, Sabate M (2015) Parkinson's disease as a result of aging. Aging Cell 14(3):293–308. https://doi.org/10.1111/acel.12312
192. Li X, Yang W, Chen M, Liu C, Yu S (2018) Age-dependent elevations of oligomeric and phosphorylated alpha-synuclein synchronously occurs in the brain and gastrointestinal tract of cynomolgus monkeys. Neurosci Lett 662:276–282. https://doi.org/10.1016/j.neulet.2017.10.047
193. Chu Y, Kordower JH (2007) Age-associated increases of alpha-synuclein in monkeys and humans are associated with nigrostriatal dopamine depletion: is this the target for Parkinson's disease? Neurobiol Dis 25(1):134–149. https://doi.org/10.1016/j.nbd.2006.08.021
194. Miller TA (1997) Control of circulation in insects. Gen Pharmacol 29(1):23–38
195. Young HM, Cane KN, Anderson CR (2011) Development of the autonomic nervous system: a comparative view. Auton Neurosci 165(1):10–27. https://doi.org/10.1016/j.autneu.2010.03.002
196. Snyder JM, Hagan CE, Bolon B, Keene CD (2018) 20—Nervous System. In: Treuting PM, Dintzis SM, Montine KS (eds)

Comparative Anatomy and Histology, 2nd edn. Academic Press, San Diego, pp 403–444. https://doi.org/10.1016/B978-0-12-802900-8.00020-8
197. Furness JB (2015) Chapter 4—peripheral autonomic nervous system. In: Paxinos G (ed) The Rat Nervous System, 4th edn. Academic Press, London, pp 61–76
198. Becker RF, Grunt JA (1957) The cervical sympathetic ganglia. Anat Rec 127(1):1–14
199. Hassimoto M, Harada T (2002) Practical method for correcting QT intervals in experimental animals: QT correction formulas for beagle dogs and rhesus monkeys. Adv Anim Cardiol 35(2):119–123. https://doi.org/10.11276/jsvc.35.119
200. Manning-Bog AB, Langston JW (2007) Model fusion, the next phase in developing animal models for Parkinson's disease. Neurotox Res 11(3–4):219–240
201. Muthukumaran K, Smith J, Jasra H, Sikorska M, Sandhu JK, Cohen J, Lopatin D, Pandey S (2014) Genetic susceptibility model of Parkinson's disease resulting from exposure of DJ-1 deficient mice to MPTP: evaluation of neuroprotection by Ubisol-Q10. J Parkinsons Dis 4(3):523–530. https://doi.org/10.3233/jpd-140368
202. Niu Y, Guo X, Chen Y, Wang CE, Gao J, Yang W, Kang Y, Si W, Wang H, Yang SH, Li S, Ji W, Li XJ (2015) Early Parkinson's disease symptoms in alpha-synuclein transgenic monkeys. Hum Mol Genet 24(8):2308–2317. https://doi.org/10.1093/hmg/ddu748