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EDITORIAL

# Special issue "Parkinson's disease"

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## General introduction

More than 200 years after its initial description by James Parkinson (1817), the disease that now bears his name is still a topic of intense research. Despite remarkable progress in the management of its motor symptoms by pharmacologic dopamine replacement or deep brain stimulation, there is still no cure and all attempts to develop treatments that halt or slow down the relentless progression of the disease have so far failed. Ironically, it is the progress in management of motor symptoms that have made us painfully aware of the huge impact of non-motor symptoms—autonomic disturbances, pain, depression and particularly cognitive decline— have on quality of life in the course of the disease. Given the changing age structure of our society, the number of patients with Parkinson's disease will inevitably increase greatly over the coming decades (Dorsey and Bloem 2018). A better understanding of the complex pathogenetic networks that contribute to disease risk, progression and the development of late complications is therefore urgently needed in order to develop novel effective treatment strategies that go beyond mere amelioration of the consequences of disturbed motor circuits.

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## Section 1: molecules and cells

Arguably, the most significant single quantum leap in the understanding of Parkinson's disease since the discovery of the role of the neurotransmitter dopamine in the motor system by Arvid Carlsson (Polymeropoulos et al. 1997; Fahn 2015) has been the finding that a single missense mutation in the gene encoding a predominantly presynaptic protein, α-synuclein, causes an autosomal-dominant form of Parkinson's disease (Polymeropoulos et al. 1997) and the subsequent identification of this protein as the major component of the characteristic abnormal filaments (fibrils) that constitute the synucleinopathies (Spillantini et al. 1998a). Although even today we are still far from a full comprehension of the complete sequence of events that lead from the mutation to the many manifestations of the disorder, this discovery has been the basis of many subsequent milestones, including the staging of PD within the central nervous system on the basis of the topographical extent of α-synuclein aggregation (Braak et al. 2003; Del Tredici and Braak 2012) and leading up to first clinical trials aimed at reducing α-synuclein burden.

## Genetic entry points into the pathogenesis of Parkinson's disease

Since this breakthrough, Parkinson's genetics, including studies in sporadic PD, have proven to be an extremely fruitful path, providing multiple entry points to a better understanding of the disorder (Klemann et al. 2017). In this issue, current concepts of the complex genetic architecture of PD are reviewed in the contribution by Billingsley et al. (2018), emphasizing that those networks that have originally been based on the identification of rare Mendelian mutations causing hereditary forms of PD are also playing a major role in the common sporadic forms of the disease.

Each of the major Mendelian genes turned out to lead to distinct pathways to disease that are described in depth in this issue: loss of function mutations in *parkin* and *PINK1* cause autosomal-recessive PD with early onset by a disruption of mitochondrial quality control systems (Larsen et al. 2018); mutations in LRRK2, the most common cause of autosomal-dominant PD, are thought to lead to increases of the kinase function of the encoded multidomain protein, thereby disrupting crucial pathways of cytoskeletal integrity and organelle transport (Price et al. 2018). Heterozygous variants in the GBA gene, encoding the lysosomal enzyme glucocerebrosidase, were found to be the most common genetic risk factor for PD in many populations (Sidransky et al. 2009). This finding highlighted the role of lysosomal protein degradation in the pathogenesis of PD. Recent evidence has closely linked lysosomal function to α-synuclein degradation (Stojkovska et al. 2018).

Still, there is a major gap to be closed between identifying relevant gene mutations and understanding their functional consequences. An important breakthrough that has transformed the investigation of molecular pathways leading to neurodegenerative disorders has been the Nobel prize-winning discovery that differentiated cells, for example skin-derived fibroblasts, can be "reprogrammed" to gain stem cell-like properties of practically limitless proliferation and pluripotency, the so-called induced pluripotent stem cells (iPSCs) (Takahashi et al. 2007). Within only a few years, this technology has matured to a standard laboratory procedure and protocols to differentiate iPSCs into a multitude of cell types including mid-brain dopaminergic neurons and even organoids as well as to analyze a host of mutation-associated phenotypes have been perfected to a remarkable degree. In this issue, Cobb et al. provide a brilliant overview of the current technological possibilities and review the cellular and molecular phenotypes that have been observed in neurons derived from iPSs harboring PD mutations (Cobb et al. 2018).

While the careful analysis of the molecular pathways leading to rare genetic forms of PD has generated a wealth of knowledge, it is still a major challenge to explain why disturbances of seemingly distinct pathways lead to an overlapping spectrum of pathologic and clinical changes and why—cum *grano salis*—the dopaminergic system features so prominently in the evolution of the disease. The convergence of pathways, as described in the contribution by Cherubini and Wade-Martins, may hold at least a partial answer to this fascinating question (Cherubini and Wade-Martins 2018).

Rapidly growing multiomics datasets require a whole new approach to extract biological meaning and, eventually, to transform them into new diagnostic tools and novel treatments. Computational system biology approaches have been developed in recent years to study multifaceted molecular alterations in complex disorders. Strengths and weaknesses of different analyses and multivariate machine learning techniques for investigating PD-related omics data are discussed in the article by Glaab (2018).

The year 2017 marked not only the 200th anniversary of James Parkinson's essay but also 50 years since the introduction of high-dosed oral L-DOPA therapy (Lees et al. 2015) and 20 years since the discovery that Lewy pathology in PD and dementia with Lewy bodies (DLB) is immunoreactive for α-synuclein (Spillantini et al. 1997). In the present issue, Spillantini and Goedert (2018) review these early discoveries as well as the physiological functions of the protein, genetic risk factors for PD and DLB (chiefly mutations in *SNCA*, the α-synuclein gene) and the propagation of α-synuclein aggregates to distant brain sites following intracerebral injection from diseased human brains or following the inoculation of aggregated recombinant α-synuclein into experimental animal models.

Although the speed of the growth of our knowledge and understanding of the molecular basis of PD has gained unprecedented momentum, the disease can still not be cured, nor are we able to slow its progression to a clinically meaningful degree. Pharmacologic dopamine replacement has been the mainstay of treatment. And in fact, often in the first years of therapy, the success is no less than spectacular, so that patients are almost free of symptoms and experience what is called a "honeymoon period" of their disease. Later, however, pharmacological treatment inevitably becomes less efficient and more prone to sometimes serious side effects. For many years, attempts to manage these late-disease stages were based on a "trial and error" approach. Today, there is a growing understanding of the molecular basis of pharmacologic dopamine replacement. You et al. show in this issue that a deep understanding of these molecular events provides the opportunity to better tailor the symptomatic treatments that are still fundamentally important to the vast majority of patients (You et al. 2018).

## The role of α-synuclein aggregation and Lewy pathology: neuroprotective or lethal?

The ongoing debate is addressed by Chartier and Duyckaerts (2018), who, from a variety of angles, take a close look at the intracellular aggregations of the protein α-synuclein that develop during PD and DLB in a few but specific, types of nerve cells. The emergence of the aggregates points to disturbances in protein metabolism that result from protein misfolding and produce an accumulation of harmful species that cannot be eliminated from the cytoplasm. The existence of intraaxonal Lewy pathology (i.e., Lewy neurites) also suggests that Lewy pathology is unlikely to be benign (Goedert et al. 2017a).

However, as in other fields of endeavor, the strategy of "splendid isolation" does not rescue involved cells in the long run, inasmuch as they ultimately degenerate and perish. Thus, Lewy body formation appears to be closely linked to cellular toxicity. Moreover, in experiments, the misfolded aggregates can organize into fibrils that corrupt additional normal α-synuclein molecules into misfolded molecules that also aggregate and spread from neuron to neuron.

In MSA, it is still unknown why oligodendrocytes develop α-synuclein inclusions (Spillantini et al. 1998b) and whether they are toxic. It may be that oligodendrocytes produce α-synuclein but that these non-neuronal cells either overexpress the protein and/or cannot eliminate the aggregates, or it is possible that the aggregates propagate from nerve cells to oligodendrocytes. In slice models, α-synuclein aggregates can transfer (or propagate) from neurons via the extracellular space to oligodendrocytes, astrocytes and microglia (Reyes et al. 2014; Steiner et al. 2018).

Here, the issue whether abnormal aggregation combined with the propagation of α-synuclein in currently available models correlates with increased α-synuclein aggregation and the severity of PD clinical symptomatology is also addressed by Steiner et al. (2018). The authors find much of the current experimental evidence conflicting and inconclusive but point out that recent findings regarding different strains (conformers, polymorphs) of recombinant aggregated α-synuclein might provide some clues: the oligomeric (Cremades et al. 2012) and filamentous as opposed to ribbon-like strains (Bousset et al. 2013; Peelaerts et al. 2015) appear to be especially toxic. If such polymorphs also were to exist in clinical PD and MSA, they could partially account for the seeding propensity of α-synuclein and the apparent discrepancy between symptom severity of and the presence (ribbons) or absence (fibrils) of Lewy pathology combined with cell loss.

## Tissular propagons, prions, prionoids (like prions)?

Four additional articles in this special volume focus on the mechanisms of intercellular spreading by α-synuclein aggregates in what often is termed a "prion-like" manner (Grozdanov and Danzer 2018; Recasens et al. 2018; Peelaerts et al. 2018; Tamgüney and Korczyn 2018). Nerve cells possess three strategies for dealing with abnormal proteins, including α-synuclein: degradation and elimination, inclusion body formation (protein deposition), or release into the extracellular space (Grozdanov and Danzer 2018). The authors recount the conditions under which monomeric α-synuclein can passively diffuse through the cell membrane into the extracellular space and the conditions under which monomeric, oligomeric and, possibly, aggregated α-synuclein, which form a continuum (Pieri et al. 2016), can be actively released (secreted) by cells via exocytosis or in a vesicle-associated manner, e.g., in exosomes. α-Synuclein uptake from the extracellular space can also take place passively via diffusion or actively via endocytosis and the uptake of aggregates can seed anew the aggregation of endogenous α-synuclein. If aggregated α-synuclein is internalized by receptor-mediated endocytosis (Lee et al. 2008), then the identities and exact functions (binding affinity, internalization) of these receptors are important because they might be subject to modification, thereby interrupting α-synuclein uptake and the process of its cell-to-cell transmission. On the output side, only a portion of α-synuclein is released in exosomes (Danzer et al. 2012) and more studies are needed to see to what extent α-synuclein, which is seed-competent, may be released in exosomes and taken up by other cells (Tofaris 2017).

Although multiple lines of evidence support the hypothesis of the self-propagating (prion-like) spread of aggregates as a major pathogenic mechanism in Lewy body disorders, it is important to point out that this may not reflect the entire story, as some in vivo models, including those using viral vector-mediated overexpression of α-synuclein to induce pathology, do not appear to involve this process, as discussed by Recasens et al. (2018). Does human-derived α-synuclein possess the same pathogenic properties observed in synthetic recombinant α-synuclein aggregates (Osterberg et al. 2015) and in rodent-derived forms? The authors carefully review the latest findings regarding potential toxic effects of intracerebrally administered human-derived samples from patients with DLB (Masuda-Suzukake et al. 2013), PD (Luk et al. 2012; Recasens et al. 2014), incidental Lewy body disease (Bernis et al. 2015) and MSA (Watts et al. 2013; Bernis et al. 2015; Woerman et al. 2015; Prusiner et al. 2015). A balancing act between success and setbacks becomes evident. For instance, in contrast to intracerebral injection, intranasal administration of DLB-derived α-synuclein insoluble fractions failed to produce phosphorylated α-synuclein histopathology in DLB and the inoculates from PD brains failed to induce histopathological changes in every study. The factors that could account for these puzzling differences and/or setbacks are discussed. Note: Animal models displaying α-synuclein transmission and neurological changes dysfunction are also reviewed in Steiner et al. (2018).

Based in part on their own work (Bousset et al. 2013), Peelaerts et al. (2018) explain and elaborate on the concept of α-synuclein strains, i.e., how α-synuclein assembles into distinct polymorphisms that can contribute to the pathogenesis of synucleinopathies and that specific strains with their structural variations may also be responsible for causing the distinctive pathological features associated with the phenotypes of human synucleinopathies. The existence of α-synuclein strains has also been shown by others (Uchihara

et al. 2005; Peng et al. 2018), although these strains do not always lead to the formation of Lewy pathology (Peelaerts et al. 2015; Prusiner et al. 2015). The surfaces of different pathogenic strains determine their ability not only to evade elimination but also to interact with the cell membrane and to propagate transsynaptically. Strain differences, their concentrations and lifespans, in addition to the size of α-synuclein aggregates, could influence the speed with which the aggregates are transported anterogradely and retrogradely within axons, thus determining the tempo of disease progression. If "strainotyping" was to become possible, development of conformation-specific therapies would be the next goal.

Despite pathbreaking work and convincing arguments from studies dealing with the prion-like properties of α-synuclein assemblies (Kordower et al. 2008; Li et al. 2008; Brundin et al. 2008; Peelaerts and Baekelandt 2016; Brundin and Melki 2017), these assemblies have not yet been proved to be transmitted between individuals (Irwin et al. 2013). For this but also for other reasons (Tamgüney and Korczyn 2018), researchers, some of them coming from the prion field, still prefer to distinguish human synucleinopathies from prions, "proteinaceous infectious particles" (Prusiner 1982; Aguzzi and Lakkaraju 2016; Goedert et al. 2017b) in infectious transmissible encephalopathies (TSE).

## Section 2: Circuitries

In PD, the disease process appears to spread gradually and continuously along neural pathways in the brain and it influences all portions of the human nervous system (central, peripheral and enteric nervous system), including motor and non-motor circuitries. The vital importance of the nigrostriatal system cannot detract from the early involvement and role of the locus coeruleus-norepinephrine system (LC-NE) in PD. Here, E.E. Benarroch (2018) delineates both the non-motor and motor contributions of the LC-NE and directs the reader's attention to diagnostic methods especially geared to revealing LC-NE dysfunctions and expanding the range of options for the early diagnosis of PD. At the same time, the numerous possibilities for influencing this system also substantially enrich existing therapeutic instruments (Benarroch 2018).

α-Synuclein lesions occur with a high degree of specificity in the olfactory bulb and some of the very earliest α-synuclein aggregates within the central nervous system develop there (Beach et al. 2009). In her article, M.G. Cersósimo (2018) tracks down the possibilities that could arise for the further progression (or spreading) of the pathology, in the event that PD was to begin in the olfactory bulb. After treating the anatomy and components of the olfactory system in detail, she turns to its role in PD and DLB. The potential pathways she describes explain some of the non-motor symptoms associated with these disorders and lead her to a consideration of the possible impairment of regions (both cortical and subcortical) outside the nigrostriatal system.

Although acknowledged as a separate disease (Schenk et al. 1986), REM sleep behavior disorder (RBD) is frequently associated with or paves the way for PD or another synucleinopathy (Boeve et al. 2013; Ehrminger et al. 2016; Iranzo et al. 2013; Vilas et al. 2016). The connection between RBD and the pathological process associated with PD emerged as it gradually became clear that PD involved a very large number of non-nigral subcortical centers, including some of those responsible for the regulation of REM sleep. The author reviews many of these centers and also discusses the debate about the origin of movements in RBD, i.e., the "cortical" vs. the "brainstem" hypothesis (Iranzo 2018). Although no animal model presently exists to prove that following the injection of aggregated recombinant α-synuclein into key REM sleep-related regions clinical RBD develops or the pathology spreads from there to other structures, some preliminary evidence does exist following injection of a recombinant adeno-associated virus expressing human α-synuclein into the REM sleep circuit in mice for the pathological aggregation of Lewy-like pathology in REM sleep-generating cells and for elevated levels of phasic motor activity during REM sleep (McKenna and Peever 2017).

As pointed out above, sporadic PD is characterized by the presence of Lewy pathology in and the dysfunction of the central, peripheral and enteric nervous systems. In their review titled Peripheral and central autonomic nervous system: Does the sympathetic or parasympathetic nervous system bear the brunt of the pathology during the course of sporadic PD? (Orimo et al. 2018), the authors provide an overview of the findings related to known and soon to be published original neuropathological changes within the peripheral and enteric autonomic nervous system and some of the related functional disturbances. Such work is important because at autopsy tissue samples from the peripheral organs often are not routinely examined for the presence of α-synuclein inclusions. Given its complexity, which is also related to the vast size of the autonomic nervous system, this task and new advances will likely come from studies performed in large tissue banks and anatomical institutes. Equally difficult to study at autopsy are the pathological changes that can occur in circumscribed brain areas of PD patients with a history of successful and unsuccessful deep brain stimulation (DBS) surgical interventions. Reddy and Lozano tackle this task in their review and provide insights into the downside of a procedure that is considered the most successful therapeutic advancement in the treatment of PD-related motor disability since dopamine replacement therapy (Reddy and Lozano 2018).

The initial motor symptoms that provide reasonable grounds for suspecting the presence of sporadic PD are frequently lateralized to only one side of the body (Fahn 2003).

Surprisingly, little is known about the neuropathology underlying this phenomenon (Hobson 2012). In their review, Riederer et al. (2018) explain the reasons for the asymmetrical onset of PD and point out the asymmetrical development of the pathological process involved in nuclei and cortical fields. In addition to motor manifestations, they also analyze the non-motor aspects and discuss many of the unanswered questions arising in this connection. Recognition of the lateralization of initial symptoms may help to secure a PD diagnosis and to better characterize PD subforms (Riederer et al. 2018).

Despite the ongoing interest in the PD community in the role of the enteric nervous system (ENS) in the possible pathogenesis and/or progression of PD, the authors Shannon and Vanden Berghe (2018) believe that (too) many issues remain unclear or contradictory. Even if it could be shown that Lewy pathology in the ENS is a biomarker of PD, how solid is the available evidence that it influences the disease (e.g., gastrointestinal dysmotility or delayed transit) there or elsewhere in humans? The same applies to the proposed possible prion-like spread of α-synuclein aggregates from the ENS to the CNS as a potential disease mechanism: Do experimental models of α-synuclein transfer (Ulusoy et al. 2013; Holmqvist et al. 2014) accurately reflect what happens during PD? The authors conclude by posing a series of open-ended questions, e.g., what is the potential role of microbial changes or abnormalities in PD (Scheperjans et al. 2015; Sampson et al. 2016)? Or, is Lewy pathology in the ENS (and, by extension, the possible spread of Lewy pathology from the ENS to the lower brainstem) applicable only to one group of individuals, namely, those with sporadic PD possibly corresponding to the caudorostral brain staging model proposed by Braak et al. (2003)? In other words, some subsets of PD patients would never develop the ENS Lewy pathology in the ENS reported by previous researchers (Wakabayashi et al. 1988; Beach et al. 2010; Stokholm et al. 2016).

Vriend (2018) provides insights into the neurobiological aspects of impulse control disorders (ICD), e.g., compulsive shopping or internet use, binge eating, hypersexuality, pathological gambling, which some PD patients develop within the context of dopamine replacement therapy (Wu et al. 2014; Weintraub et al. 2010; Weintraub et al. 2015). In the first part of his review, Vriend summarizes the contributions of dopamine to ICD together with the dopaminergic vulnerability to ICD development. (It is of note that several animal models have been found to display "impulsivity-inducing" effects.) However, he also considers the possible roles of the serotonergic and noradrenergic systems in ICD and points to the value of functional neuroimaging techniques to study brain changes associated with ICD at the local and network levels.

Many pieces of the larger puzzle of PD have been found and described in unprecedented detail in recent years, as illustrated by the articles in this Special Issue. Nevertheless, many pieces are still missing and how exactly these fit together to create the full mosaic will require ongoing intense research efforts.

## References


Aguzzi A, Lakkaraju A (2016) Cell biology of prions and prionoids: a status report. Trends Cell Biol 26:40–51

Beach TG, White CL III, Hladik CL, Sabbagh MN, Connor DJ, Shill HA et al (2009) Olfactory bulb α-synucleinopathy has high specificity and sensitivity for Lewy body disorders. Acta Neuropathol 117: 169–174

Beach TG, Adler CH, Sue LI, Vedders L, Lue L, White CL III et al (2010) Multi-organ distribution of phosphorylated alpha synuclein histopathology in subjects with Lewy body disorders. Acta Neuropathol 119:689–702

Benarroch EE (2018) Locus coeruleus. Cell Tissue Res. https://doi.org/10.1007/s00441-017-2649-1

Bernis ME, Babila JT, Breid S, Wüsten KA, Wüllner U, Tamgüney G (2015) Prion-like propagation of human brain-derived alpha-synuclein in transgenic mice expressing human wild-type alpha-synuclein. Acta Neuropathol Commun 3:75

Billingsley KJ, Bandres-Ciga S, Saez-Atienzar S, Singleton AB (2018) Genetic risk factors in Parkinson's disease. Cell Tissue Res. https://doi.org/10.1007/s00441-018-2817-y

Boeve BF, Silber MH, Ferman TJ, Lin SC, Benarroch EE, Schmeichel AM et al (2013) Clinicopathologic correlations in 172 cases of rapid eye movement sleep behavior disorder with or without a coexisting neurologic disorder. Sleep Med 14:754–762

Bousset L, Peri L, Ruiz-Arlandis G, Gath J, Jensen PH, Habenstein B et al (2013) Structural and functional characterization of two alpha-synuclein strains. Nat Commun 4:2575

Braak H, Del Tredici K, Rüb U, de Vos RA, Jansen Steur EN, Braak E (2003) Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging 24:197–211

Brundin P, Melki R (2017) Prying into the prion hypothesis for Parkinson's disease. J Neurosci 37:9808–9818

Brundin P, Li J-Y, Holton JL, Lindvall O, Revesz T (2008) Research in motion: the enigma of Parkinson's disease pathology spread. Nat Rev Neurosci 9:741–745

Cersósimo MG (2018) Propagation of alpha-synuclein pathology from the olfactory bulb: possible role in the pathogenesis of dementia with Lewy bodies. Cell Tissue Res. https://doi.org/10.1007/s00441-017-2733-6

Chartier S, Duyckaerts C (2018) Is Lewy pathology in the human nervous system an indicator of neuronal protection or of toxicity? Cell Tissue Res. https://doi.org/10.1007/s00441-018-2854-6

Cherubini M, Wade-Martins R (2018) Convergent pathways in Parkinson's disease. Cell Tissue Res. https://doi.org/10.1007/s00441-017-2700-2

Cobb MM, Ravisankar A, Skibinski G, Finkbeiner S (2018) iPS cells in the study of PD molecular pathogenesis. Cell Tissue Res. https://doi.org/10.1007/s00441-017-2749-y

Cremades N, Cohen SIA, Deas E, Abramov AY, Chen AY, Orte A et al (2012) Direct observation of the interconversion of normal and toxic forms of α-synuclein. Cell 149:1048–1059

Danzer KM, Kranich LR, Ruf WP, Cagsal-Getkin O, Winslow AR, Zhu L, Vanderburg CR, McLean PJ (2012) Exosomal cell-to-cell transmission of alpha synuclein oligomers. Mol Neurodegener 7:42

Del Tredici K, Braak H (2012) Spinal cord lesions in sporadic Parkinson's disease. Acta Neuropathol 124:643–664

Dorsey ER, Bloem BR (2018) The Parkinson pandemic—a call to action. JAMA Neurol 75:9–10

Ehrminger M, Latimier A, Pyatigorskya N, Garcia-Lorenzo D, Leu-Semenescu S, Vidailhet M et al (2016) The coeruleus/subcoeruleus complex in idiopathic rapid eye movement sleep behaviour disorder. Brain 139:1180–1188

Fahn S (2003) Description of Parkinson's disease as a clinical syndrome. Ann N Y Acad Sci 991:1–14

Fahn S (2015) The medical treatment of Parkinson disease from James Parkinson to George Cotzias. Mov Disord 30:4–18

Glaab E (2018) Computational systems biology approaches for Parkinson's disease. Cell Tissue Res. https://doi.org/10.1007/s00441-017-2734-5

Goedert M, Jakes R, Spillantini MG (2017a) The synucleinopathies: twenty years on. J Parkinsons Dis 7(s1):S51–S69

Goedert M, Masuda-Suzukake M, Falcon B (2017b) Like prions: the propagation of aggregated tau and alpha-synuclein in neurodegeneration. Brain 140:266–278

Grozdanov V, Danzer KM (2018) Release and uptake of pathologic alpha-synuclein. Cell Tissue Res. https://doi.org/10.1007/s00441-017-2775-9

Hobson DE (2012) Asymmetry in parkinsonism, spreading pathogens and the nose. Parkinsonism Relat Disord 18:1–9

Holmqvist S, Chutna O, Bousset L, Aldrin-Kirk P, Li W, Bjorklund T et al (2014) Direct evidence of Parkinson pathology spread from the gastrointestinal tract to the brain in rats. Acta Neuropathol 128:805–820

Iranzo A (2018) The REM sleep circuit and how its impairment leads to REM sleep behavior disorder. Cell Tissue Res. https://doi.org/10.1007/s00441-018-2852-8

Iranzo A, Tolosa E, Gelpi E, Molinuevo L, Valldeoriola F, Serradell M et al (2013) Neurodegenerative status and postmortem pathology in idiopathic rapid-eye movement behavior disorder: an observational cohort study. Lancet Neurol 12:443–453

Irwin DJ, Abrams JY, Schonberger LB, Leschek EW, Mills JL, Lee VM et al (2013) Evaluation of potential infectivity of Alzheimer and Parkinson disease proteins in recipients of cadaver-derived human growth hormone. JAMA Neurol 70:462–468

Klemann CJHM, Martens GJM, Sharma M, Martens MB, Isacson O, Gasser T et al (2017) Integrated molecular landscape of Parkinson's disease. NPJ Parkinson's Dis 3:14

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 14:504–506

Larsen SB, Hanss Z, Krüger R (2018) The genetic architecture of mitochondrial dysfunction in Parkinson's disease. Cell Tissue Res. https://doi.org/10.1007/s00441-017-2768-8

Lee HJ, Suk JE, Bae EJ, Lee JH, Paik SR, Lee SJ (2008) Assembly-dependent endocytosis and clearance of extracellular alpha-synuclein. Int J Biochem Cell Biol 40:1835–1849

Lees AJ, Tolosa E, Olanow CW (2015) Four pioneers of L-dopa treatment: Arvid Carlsson, Oleh Hornykiewicz, George Cotzias, and Melvin Yahr. Mov Disord 30:19–36

Li J-Y, Englund E, Holton JL, Soulet D, Hagell P, Lees AJ et al (2008) Lewy bodies in grafted neurons in subjects with Parkinson's disease suggest host-to-graft disease propagation. Nat Med 14:501–503

Luk KC, Kehm VM, Zhang B, O'Brien P, Trojanowski JQ, Lee VMY (2012) Intracerebral inoculation of pathological α-synuclein initiates a rapidly progressive neurodegenerative α-synucleinopathy in mice. J Exp Med 209:975–986

Masuda-Suzukake M, Nonaka T, Hosokawa M, Oikawa T, Arai T, Akiyama H et al (2013) Prion-like spreading of pathological α-synuclein in brain. Brain 136:1128–1138

McKenna D, Peever J (2017) Degeneration of rapid eye movement sleep circuitry underlies rapid eye movement sleep behavior disorder. Mov Disord 32:636–644

Orimo S, Ghebremedhin E, Gelpi E (2018) Peripheral and central autonomic nervous system: does the sympathetic or parasympathetic nervous system bear the brunt of the pathology during the course of sporadic PD? Cell Tissue Res. https://doi.org/10.1007/s00441-018-2851-9

Osterberg VR, Spinelli KJ, Weston LJ, Luk KC, Woltjer RL, Unni VK (2015) Progressive aggregation of alpha-synuclein and selective degeneration of Lewy inclusion-bearing neurons in a mouse model of parkinsonism. Cell Rep 10:1252–1260

Parkinson J. (1817) Essay on the shaking palsy London: Sherwood, Nealy and Jones

Peelaerts W, Baekelandt V (2016) α-Synuclein strains and the variable pathologies of synucleinopathies. J Neurochem 139(Suppl 1):256–274

Peelaerts W, Bousset L, Van der Perren A, Moskalyuk A, Pulizzi R, Giugliano M et al (2015) α-Synuclein strains cause distinct synucleinopathies after local and systemic administration. Nature 522:340–344

Peelaerts W, Bousset L, Baekelandt V, Melki R (2018) α-Synuclein strains and seeding in Parkinson's disease, incidental Lewy body disease, dementia with Lewy bodies, and multiple system atrophy: similarities and differences. Cell Tissue Res. https://doi.org/10.1007/s00441-018-2839-5

Peng C, Gathagen RJ, Covell DJ, Medellin C, Stieber A, Robinson JL, Zhang B, Pitkin RM, Olufemi MF, Luk KC, Trojanowski JQ, Lee VM (2018) Cellular milieu imparts distinct pathological α-synuclein strains in α-synucleinopathies. Nature. https://doi.org/10.1038/s41586-018-0104-4

Pieri L, Madiona K, Melki R (2016) Structural and functional properties of prefibrillar alpha-synuclein oligomers. Sci Rep 6:24526

Polymeropoulos MH, Lavedan C, Leroy E, Ide SE, Dehejia A, Dutra A et al (1997) Mutation in the a-synuclein gene identified in families with Parkinson's disease. Science 276:2045–2047

Price A, Manzoni C, Cookson MR, Lewis PA (2018) The LRRK2 signalling system. Cell Tissue Res. https://doi.org/10.1007/s00441-017-2759-9

Prusiner SB (1982) Novel proteinaceous infectious particles cause scrapie. Science 216:136–144

Prusiner SB, Woerman AL, Mordes DA, Watts JC, Rampersaud R, Berry DB et al (2015) Evidence for α-synuclein prions causing multiple system atrophy in humans with parkinsonism. Proc Natl Acad Sci U S A 112:E5308–E5317

Recasens A, Dehay B, Bové J, Carballo-Carbajal I, Dovero S, Pérez-Villalba A et al (2014) Lewy body extracts from Parkinson disease brains trigger α-synuclein pathology and neurodegeneration in mice and monkeys. Ann Neurol 75:351–362

Recasens A, Ulusoy A, Kahle PJ, Di Monte DA, Dehay B (2018) In vivo models of alpha-synuclein transmission and propagation. Cell Tissue Res. https://doi.org/10.1007/s00441-017-2730-9

Reddy GD, Lozano AM (2018) Postmortem studies of deep brain stimulation for Parkinson's disease: a systematic review of the literature. Cell Tissue Res. https://doi.org/10.1007/s00441-017-2672-2

Reyes JF, Rey NL, Bousset L, Melki R, Brundin P, Angot E (2014) Alpha-synuclein transfers from neurons to oligodendrocytes. Glia 62:387–398

Riederer P, Jellinger KA, Kolber P, Hipp G, Sian-Hülsmann J, Krüger R (2018) Lateralisation in Parkinson disease. Cell Tissue Res. https://doi.org/10.1007/s00441-018-2832-z

Sampson TR, Debelius JW, Thron T, Janssen S, Shastri GG, Ilhan ZE et al (2016) Gut microbiota regulate motor deficits and neuroinflammation in a model of Parkinson's disease. Cell 167:1469–1480

Schenk CH, Bundlie SR, Ettinger MG, Mahowald MW (1986) Chronic behavioural disorders of human REM sleep: a new category of parasomnia. Sleep 9:293–308

Scheperjans F, Aho V, Pereira PA, Koskinen K, Paulin L, Pekkonen E et al (2015) Gut microbiota are related to Parkinson's disease and clinical phenotype. Mov Disord 30:350–358

Shannon K, Vanden Berghe P (2018) The Enteric Nervous System in PD: gateway, bystander victim or source of solutions. Cell Tissue Res. https://doi.org/10.1007/s00441-018-2856-4

Sidransky E, Nalls MA, Aasly JO, Aharon-Peretz J, Annesi G, Barbosa ER et al (2009) Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease. N Engl J Med 361:1651–1661

Spillantini MG, Goedert M (2018) Neurodegeneration and the ordered assembly of α-synuclein. Cell Tissue Res. https://doi.org/10.1007/s00441-017-2706-9

Spillantini MG, Schmidt ML, Lee VM, Trojanowski JQ, Jakes R, Goedert M (1997) Alpha-synuclein in Lewy bodies. Nature 388:839–840

Spillantini MG, Crowther RA, Jakes R, Hasegawa M, Goedert M (1998a) α-Synuclein in filamentous inclusions of Parkinson's disease and dementia with Lewy bodies. Proc Natl Acad Sci U S A 95:6469–6473

Spillantini MG, Crowther RA, Jakes R, Cairns NJ, Lantos PL, Goedert M (1998b) Filamentous α-synuclein inclusions link multiple system atrophy with Parkinson's disease and dementia with Lewy bodies. Neurosci Lett 251:205–208

Steiner JA, Quansah E, Brundin P (2018) The concept of alpha-synuclein as a prion-like protein: ten years after. Cell Tissue Res. https://doi.org/10.1007/s00441-018-2814-1

Stojkovska I, Krainc D, Mazzulli JR (2018) Molecular mechanisms of α-synuclein and GBA1 in Parkinson's disease. Cell Tissue Res. https://doi.org/10.1007/s00441-017-2704-y

Stokholm MS, Danielsen EH, Hamilton-Dutoit SJ, Borghammer P (2016) Pathological alpha-synuclein in gastrointestinal tissues from prodromal Parkinson's disease patients. Ann Neurol 79:940–949

Takahashi K, Tanabe K, Ohnuki M, Narita M, Ichisaka T, Tomoda K et al (2007) Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Cell 131:861–872

Tamgüney G, Korczyn AD (2018) A critical review of the prion hypothesis of human synucleinopathies. Cell Tissue Res. https://doi.org/10.1007/s00441-017-2712-y

Tofaris GK (2017) A critical assessment of exosomes in the pathogenesis and stratification of Parkinson's disease. J Parkinsons Dis 7:569–576

Uchihara T. Tsuchiya K, Nakamura A, Akiyama H. 2005. Argyrophilic grains are not always argyrophilic — distinction from neurofibrillary tangles of diffuse neurofibrillary tangles with calcification revealed by comparison between Gallyas and Campbell-Switzer methods. Acta Neuropathol 110:158–164

Ulusoy A, Rusconi R, Perez-Revuelta BI, Musgrove RE, Helwig M, Winzen-Reichert B et al (2013) Caudo-rostral brain spreading of alpha-synuclein through vagal connections. EMBO Mol Med 5:1119–1127

Vilas D, Iranzo A, Tolosa E, Aldecoa I, Berenguer J, Vilaseca I, Marti C et al (2016) Assessment of α-synuclein in submandibular glands of patients with idiopathic rapid-eye movement sleep behaviour disorder: a case-control study. Lancet Neurol 15:708–718 2016

Vriend C (2018) The neurobiology of impulse control disorders in Parkinson's disease: from neurotransmitters to neural networks. Cell Tissue Res. https://doi.org/10.1007/s00441-017-2771-0

Wakabayashi K, Takahashi H, Takeda S, Ohama E, Ikuta F (1988) Parkinson's disease: the presence of Lewy bodies in Auerbach's and Meissner's plexuses. Acta Neuropathol 76:217–221

Watts JC, Giles K, Oehler A, Middleton L, Dexter DT, Gentleman SM et al (2013) Transmission of multiple system atrophy prions to transgenic mice. Proc Natl Acad Sci U S A 110:19555–19560

Weintraub D, Koester J, Potenza MN, Siderowf AD, Stacy M, Voon V et al (2010) Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. Arch Neurol 67:589–595

Weintraub D, David AS, Evans AH, Grant JE, Stacy M (2015) Clinical spectrum of impulse control disorders in Parkinson's disease. Mov Disord 30:121–127

Woerman AL, Stöhr J, Aoyagi A, Rampersaud R, Krejciova Z, Watts JC et al (2015) Propagation of prions causing synucleinopathies in cultured cells. Proc Natl Acad Sci U S A 112:E4949–E4958

Wu K, Politis M, O'Sullivan SS, Lawrence AD, Warsi S, Lees A, Piccini P (2014) Problematic Internet use in Parkinson's disease. Parkinsonism Relat Disord 20:482–487

You H, Mariani L-L, Mangone G, Le Febvre de Nailly D, Charbonnier-Beaupel F, Corvol J-C (2018) Molecular basis of dopamine replacement therapy and its side effects in Parkinson's disease. Cell Tissue Res. https://doi.org/10.1007/s00441-018-2813-2