100 years of Lewy pathology

Michel Goedert, Maria Grazia Spillantini, Kelly Del Tredici and Heiko Braak

Abstract | In 1817, James Parkinson described the symptoms of the shaking palsy, a disease that was subsequently defined in greater detail, and named after Parkinson, by Jean-Martin Charcot. Parkinson expected that the publication of his monograph would lead to a rapid elucidation of the anatomical substrate of the shaking palsy; in the event, this process took almost a century. In 1912, Fritz Heinrich Lewy identified the protein aggregates that define Parkinson disease (PD) in some brain regions outside the substantia nigra. In 1919, Konstantin Nikolaevich Tretiakoff found similar aggregates in the substantia nigra and named them after Lewy. In the 1990s, α-synuclein was identified as the main constituent of the Lewy pathology, and its aggregation was shown to be central to PD, dementia with Lewy bodies, and multiple system atrophy. In 2003, a staging scheme for idiopathic PD was introduced, according to which α-synuclein pathology originates in the dorsal motor nucleus of the vagal nerve and progresses from there to other brain regions, including the substantia nigra. In this article, we review the relevance of Lewy's discovery 100 years ago for the current understanding of PD and related disorders.

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Introduction

In 1912, Fritz Jakob Heinrich Lewy (1885–1950) described the cellular inclusions that are characteristic of Parkinson disease (PD; originally known as the shaking palsy).[1] Konstantin Nikolaevich Tretiakoff (1892–1956) named them after Lewy ('corps de Lewy',[2] or Lewy bodies) in 1919. Besides describing abnormal inclusions in nerve cell bodies, Lewy also reported their presence in nerve cell processes (later called Lewy neurites[3]).

The centenary of Lewy's discovery gives us an opportunity to review his contributions in the light of what we know about the aetiology and pathogenesis of PD and related disorders. For example, it is now clear that the formation of Lewy pathology is central to the neurodegenerative process, but for many years the significance of the inclusions described by Lewy was unknown. This changed in 1997, when two findings brought the little-studied protein α-synuclein to the fore.[4,5] First, a missense mutation in *SNCA*, the α-synuclein gene, was found to cause a rare, familial form of PD. Second, Lewy bodies and Lewy neurites of idiopathic PD were shown to be immunoreactive for α-synuclein. Three different missense mutations in *SNCA*, as well as various genomic duplications and triplications, have been described in patients with dominantly inherited PD. Moreover, genome-wide association studies have shown that sequence variation in *SNCA* is an important risk factor for idiopathic PD.[6,7]

Lewy bodies and Lewy neurites were long known to be found outside the substantia nigra in patients with PD, but the temporal sequence of their emergence was unclear. In 2003, this issue was addressed by the introduction of a staging scheme based on the distribution of α-synuclein inclusions over time.[8]

In this article, we present an overview of Lewy's life, including the events that led up to the discovery of the inclusion bodies that now bear his name (Figure 1). We then discuss the central role of Lewy pathology in PD and other neurodegenerative disorders, and the research that has elucidated the mechanisms through which α-synuclein aggregation causes neuronal dysfunction and death.

Historical overview

Lewy was born on 28th January 1885 in Berlin, Germany, where his father worked as a physician.[9,10] He studied medicine at the Universities of Berlin and Zurich, Switzerland, and obtained his medical degree in Berlin in 1910. From 1908–1910, Lewy was based at the Institute of Physiology of the University of Breslau, Germany (now Wroclaw, Poland). From 1910–1912, he worked with Alois Alzheimer (1864–1915) at the Royal Psychiatric Clinic of the University of Munich, Germany (Figure 2). In 1912, Alzheimer was appointed to the Chair of Psychiatry and the Directorship of the Psychiatric Institute at the University of Breslau. Lewy moved with him back to Breslau, to take charge of the anatomical laboratory.

During World War I, Lewy served as medical officer of the German army in France, Russia and Turkey. In 1919, he became staff neurologist at the Charité Hospital in Berlin, where he was appointed to an Associate Professorship in Neurology and Internal Medicine in 1923. From 1928, Lewy was busy establishing a neurological institute in Berlin. At the time, neurology was

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Key points

- 100 years ago, Fritz Heinrich Lewy used light microscopy to describe the nerve cell inclusions that are characteristic of Parkinson disease (PD)
- The Lewy pathology consists of the protein α-synuclein in an insoluble form
- Missense and gene dosage mutations in *SNCA*, the α-synuclein gene, cause inherited cases of PD and dementia with Lewy bodies
- In PD, α-synuclein pathology is widespread in the CNS and PNS
- α-Synuclein pathology originates in a small number of nerve cells, from which it spreads in a prion-like fashion
- Clinically, the development of the pathological changes of PD is reflected by the presence of nonmotor and motor symptoms

still subsumed under psychiatry in Prussia, and Lewy's plan was for a new building consisting of a clinic with 100–150 beds and several research departments, including a neuropathology laboratory led by Max Bielschowsky (1869–1940). Lewy also wanted the Institute to become an integral part of Berlin University. He was able to move into the former clinic of the AEG (Allgemeine Elektrizitätswerke), but a University affiliation was not forthcoming, due in large part to strong opposition from the medical faculty of the Charité, in particular the psychiatrist Karl Bonhoeffer.

The Institute of Neurology opened its doors on 1st July 1932, but it remained under Lewy's directorship for only a year. On 30th January 1933, Adolf Hitler became Reich Chancellor, and on 7th April 1933 the so-called 'Reich Law for the Restoration of a Professional Civil Service' was passed by the Nazis. This law led to the summary dismissal of most 'non-Aryan' civil servants. On 2nd August 1933, Lewy was informed that he had been dismissed from his position on racial grounds, with retroactive effect to 1st July 1933. By the beginning of the academic year 1933–1934, approximately one-third of the Professors of Berlin University had lost their positions. Lewy's Institute was incorporated into the Charité in April 1934, and was destroyed during World War II.

During the summer of 1933, at the age of 48 years, Lewy left Germany.[11] He spent a year in the UK, where he worked on the effects of lead on the human body at the Chloride Electric Storage Company in Manchester, before emigrating to the USA. He became a Rockefeller Fellow and visiting Professor of Neurophysiology at the Hospital of the University of Pennsylvania in Philadelphia, PA in 1934. He changed his name from Fritz Heinrich Lewy (he had dropped his middle name in 1912) to Frederic Henry Lewey when he became an American citizen in 1940. During World War II, Lewey served in the US Army Medical Corps, where he was neurologist to the Surgeon General's Office. In 1947, he became Professor of Neuroanatomy and Associate Professor in Neuropathology at the University of Pennsylvania. During these years, he continued to work on basal ganglia and developed an interest in peripheral nerve injuries. Lewey died suddenly on 5th October 1950, at 65 years of age.

Lewy and Parkinson disease

Lewy initially examined the brains of 25 individuals with PD from the Städtisches Siechenhaus der Stadt Berlin and published his findings in Volume 3 of the *Handbuch der Neurologie* in 1912.[1] He then examined a further 60 brains obtained from the same institution, using more-sophisticated histological techniques. This work was presented at the annual meeting of the German Association of Psychiatrists and Neurologists in 1913.[12] Lewy described the characteristic inclusions in the dorsal motor nucleus of the vagus nerve, the basal nucleus of Meynert, the globus pallidus, the lateral nucleus of the thalamus, and the periventricular nucleus of the thalamus. He noticed similarities—but also some differences—with inclusions that Gonzalo Rodriguez Lafora (1886–1971) had described in 1911 in patients with progressive myoclonic epilepsy.[13] The inclusions described by Lewy were eosinophilic, and were insoluble in alcohol, chloroform and benzene, consistent with the presence of a major protein component. Lafora bodies are made of hyperphosphorylated forms of insoluble glycogen.

In 1919, Tretiakoff reported the presence of Lewy bodies in the substantia nigra in PD.[2] He also showed degeneration of the substantia nigra and postulated a connection between nerve cell loss, rigidity and tremor. This discovery followed earlier work by Paul Blocq (1860–1896) and Georges Marinesco (1863–1938), who had reported a case of parkinsonian tremor caused by a tumour of the substantia nigra.[14] In 1923, Lewy published a monograph of 673 pages on the shaking palsy (Figure 3).[15] He confirmed Tretiakoff's findings in only 11 out of 50 cases of PD, and he suspected that parkinsonism originated in the globus pallidus. In 1938, however, Rolf Hassler (1914–1984) confirmed Tretiakoff's observation that degeneration of the substantia nigra was the cause of parkinsonism.[16] He also demonstrated the focal distribution of pathology, with the most pronounced nerve cell loss being found in the caudal and ventrolateral parts of the substantia nigra. The fact that nerve cells in the ventrolateral part of the pars compacta of the substantia nigra are severely affected in PD is now well-established. These cells project mainly to the dorsal putamen, which is the most severely dopamine-depleted region of the striatum in PD.

Prior to Hassler's publication, Lewy had revisited the issue of inclusion bodies in a talk given at the first International Congress of Neurology in 1931, where he emphasized the similarities between the Negri bodies of rabies and the inclusions of the shaking palsy.[17] This is interesting in the light of recent work suggesting that the pathological inclusions of PD may spread through the brain via a prion-like mechanism.[18] In 1942, Lewy reviewed the history of research into basal ganglia diseases, but failed to attach much importance to either the inclusion bodies he had discovered, or the later findings of Tretiakoff and Hassler.[19]

Lewy body Parkinson disease

PD is the second most common neurodegenerative disorder of the human brain, after Alzheimer disease.[20] PD is not known to affect any other vertebrates besides humans and, provided that it is not arrested by death from other causes, it progresses relentlessly for decades.[21] Unlike Alzheimer disease, the pathological process of idiopathic

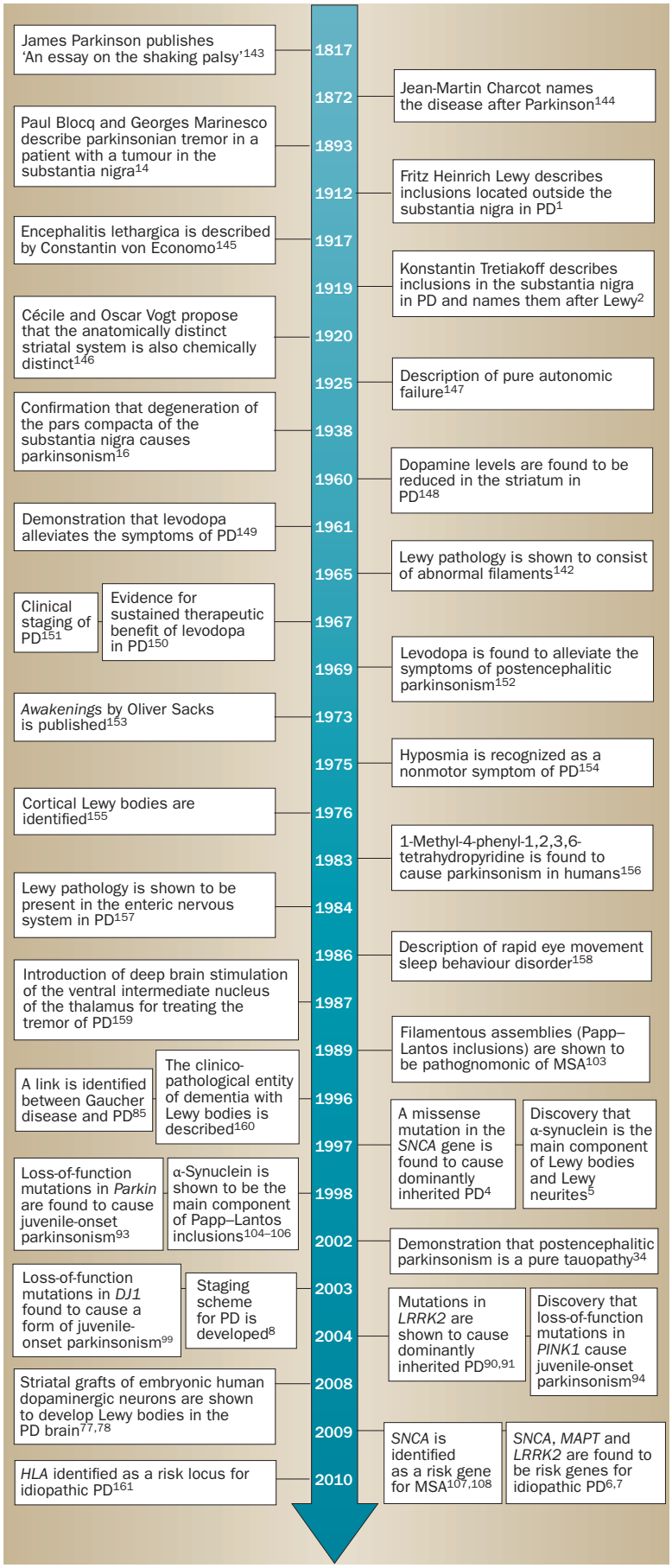


Figure 1 | 100 years of Lewy pathology: timeline of discoveries. Abbreviations: PD, Parkinson disease; MSA, multiple system atrophy; *SNCA*, α-synuclein gene; *LRRK2*, leucine-rich repeat kinase 2 gene; *MAPT*, microtubule-associated protein tau gene; *PINK1*, PTEN-induced kinase-1 gene.

PD develops not only in the CNS, but also in the PNS and enteric nervous system.[22]

Definition as a synucleinopathy

In 1997, a missense mutation (Ala53Thr) in *SNCA* was shown to cause a dominantly inherited form of PD with Lewy pathology.[4] Two additional missense mutations (Ala30Pro and Glu46Lys) were subsequently identified in families with PD or dementia with Lewy bodies (DLB).[23,24] All three mutations are located in the amino-terminal repeat region of α-synuclein, which consists of seven imperfect 11-amino-acid repeats with the consensus sequence KTKEGV (Figure 4).[25] In the presence of negatively charged lipids, the natively unfolded α-synuclein folds into amphipathic α-helices through its amino-terminal repeats.

Overexpression of wild-type α-synuclein has also been identified as a cause of PD in families with heterozygous triplications or duplications of the region of chromosome 4 that comprises *SNCA*, with disease penetrance being highest for triplication cases (Figure 4).[26–28] Moreover, genome-wide association studies identified sequence variation in the regulatory region of *SNCA* as the most important genetic risk factor for idiopathic PD,[6,7] in confirmation of previous findings.[29]

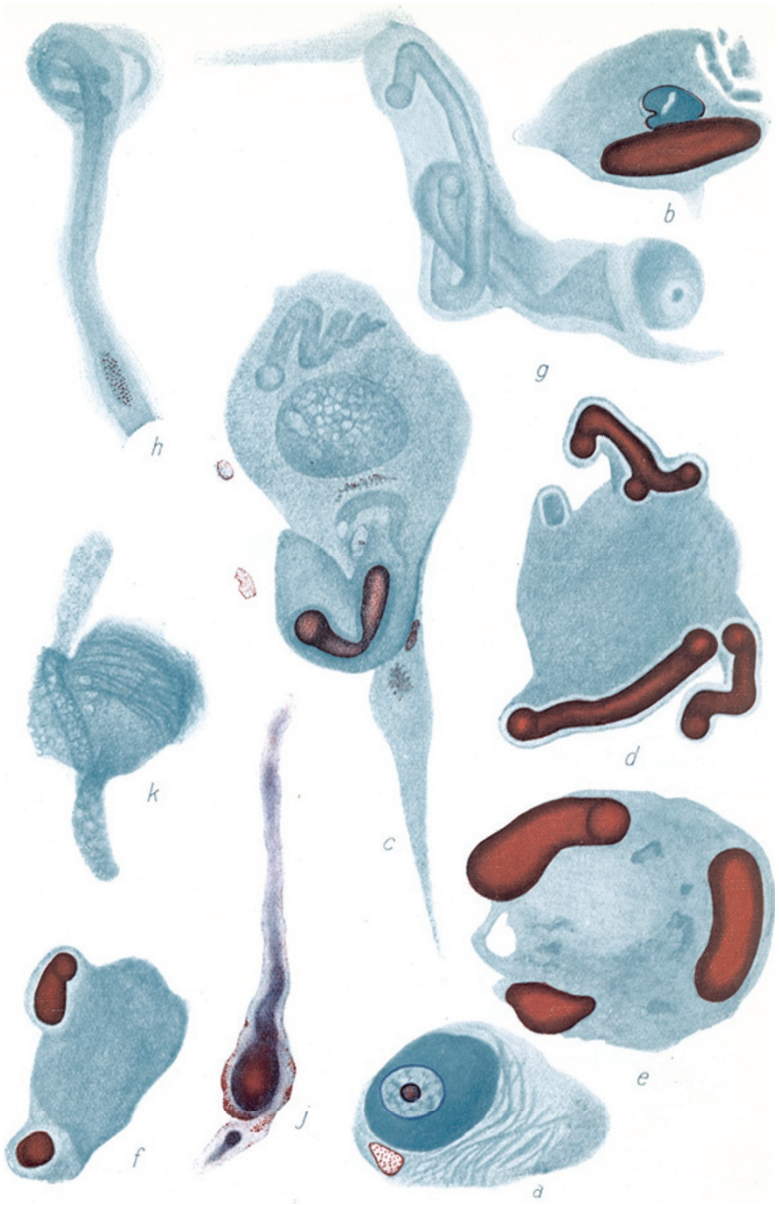
In 1997, Lewy bodies and Lewy neurites from cases of idiopathic PD were shown to be immunoreactive for α-synuclein.[5] Abundant α-synuclein inclusions are also characteristic of the diseases caused by *SNCA* mutations.[30] These findings established the central importance of α-synuclein aggregation for all cases of Lewy body PD. α-Synuclein-positive aggregates appear in neurites before they appear in nerve cell bodies, and may contain oligomeric assemblies that increase the production of reactive oxygen species.[31,32]

Lewy pathology is also the defining feature of several rarer diseases, including pure autonomic failure, in which Lewy bodies and Lewy neurites are mostly restricted to the PNS.[25] In incidental Lewy body disease, a condition that is characteristic of 5–10% of individuals over the age of 60 years and may be a preclinical form of PD,[33] small numbers of Lewy bodies and Lewy neurites are present in the absence of clinical symptoms. By contrast, abundant filamentous tau aggregates, in the absence of α-synuclein inclusions, are typical of postencephalitic parkinsonism.[34]

Lewy pathology

Electron microscopy revealed that Lewy bodies and Lewy neurites are made of unbranched α-synuclein filaments, with a length of 200–600 nm and a width of 5–10 nm.[35] The core of the filament extends over 70 amino acids and overlaps with the repeat region of α-synuclein. Like other amyloids, these filaments have a cross-β structure.[36] On

Figure 2 | Members of Alois Alzheimer's research group at the Royal Psychiatric Clinic of the University of Munich, Germany in 1910. Back row: Fritz Jakob Heinrich Lewy (circled) is on the far right, Alois Alzheimer is third from the right.



the basis of a model derived from solid-state nuclear magnetic resonance, the core of the α-synuclein filament comprises five β-strands reminiscent of a five-layered β-sandwich.[37] Hyperphosphorylation of Ser129 by G-protein-coupled receptor kinases is the main post-translational modification of filamentous α-synuclein,[38,39] and the α-synuclein filaments become ubiquitinated after assembly.[25]

Although Lewy bodies have been the most widely studied pathological feature of PD, aggregated α-synuclein also appears in a particulate form in nerve cell bodies (Figure 5a–c).[40] Some nerve cells develop multiple Lewy bodies. Pale bodies form occasionally in neuromelanin-containing cells and are probably precursors of Lewy bodies (Figure 5c).

Two types of Lewy bodies have been described: a brainstem type and a cortical type. The brainstem type has an acidophilic and argyrophilic core, and a pale-staining halo; the latter is strongly immunoreactive for α-synuclein. The cortical type is less well-defined and lacks a halo. Spindle-like or thread-like Lewy neurites (Figure 5d–f) occur in axons and dendrites of affected neurons.[3] Lewy plaques consist of a core of aggregated extracellular amyloid-β (Aβ) that is surrounded by dystrophic α-synuclein-immunoreactive neurites (Figure 5g). Cortical deposits of Aβ are required for the formation of Lewy plaques.[22]

Dementia is common in PD, especially in advanced cases.[21] A diagnosis of PD dementia (PDD) is made when cognitive impairment develops in a patient with long-standing idiopathic PD, whereas dementia develops within a year of the appearance of parkinsonian signs in cases of DLB.[41] PDD and DLB show similar neuropathological profiles, including the presence of widespread cortical α-synuclein-positive Lewy pathology. Many cases also have Alzheimer-type plaques and tangles.[42] Conversely, a substantial number of individuals with Alzheimer disease develop Lewy pathology, especially in the amygdala.[43] Some individuals with *SNCA* mutations develop both PD and DLB.[24,26]

Nerve cells can survive for decades in the presence of multiple Lewy bodies and Lewy neurites, raising the question of whether α-synuclein aggregates are harmless, neuroprotective[44] or detrimental to nerve cell function.[45–47] In the CNS, they form along the entire neuraxis, including the spinal cord (Figure 6a).[48,49] α-Synuclein aggregates are also found in the ganglia of Meissner's and Auerbach's plexuses in the gastrointestinal tract (Figure 6c,d),[50,51] as well as in sympathetic ganglia (Figure 6b) and the sympathetic trunk,[49,52] the adrenal medulla,[53] the submandibular gland,[54] and the heart,[55,56] including the cardiac conduction system.[57] Consequently, specific neurotransmitter systems are

◀ **Figure 3** | Abnormal nerve cell bodies and processes in the dorsal motor nucleus of the vagal nerve in Parkinson disease. Some filamentous inclusions appear as elongated eosinophilic bodies (red). With kind permission of Springer Science+Business Media © Lewy, F. H. *Die Lehre vom Tonus und der Bewegung*. (Springer-Verlag, Berlin, 1923).[15]

insufficient for identifying neurons that are prone to develop Lewy pathology, and PD can no longer be viewed as a monosystemic disease that predominantly affects the nigrostriatal dopaminergic system. Instead, PD is a multisystem disorder that affects many different regions of the nervous system (Figures 5 and 6).[58–62]

Disease staging

Idiopathic PD constitutes over 90% of PD cases. Extensive studies of normal and diseased human brains have shown that α-synuclein inclusions emerge in a predictable order in different parts of the brain, making it possible to distinguish six stages of α-synuclein deposition (Figures 7 and 8).[8,22]

The first α-synuclein-positive structures in the brain usually occur in the olfactory bulb and/or the dorsal motor nucleus of the glossopharyngeal and vagal nerves (stage 1). In stage 2, Lewy pathology develops in the medulla oblongata and the pontine tegmentum. By stage 3, pathology has reached the amygdala and the substantia nigra. Generally, at some point during this stage, the motor symptoms of PD (bradykinesia, with at least one of the three features of rigidity, rest tremor or gait disturbance) begin to appear. The pathology worsens and the α-synuclein inclusions reach the temporal cortex (stage 4). During stages 5 and 6, Lewy bodies and Lewy neurites appear in the neocortex, accounting for many of the cognitive problems associated with advanced PD.

Other groups have confirmed the accuracy of this staging scheme.[63–65] Exceptions have been reported in 10–20% of cases, which have included an amygdala plus olfactory variant[66] and an amygdala variant.[67] Discrepant results[68,69] may be attributable to section thickness[8] or variable protocols for processing and analysing tissues,[64,70] and also to the fact that not all brain regions included in the staging system[8] are assessed routinely by all laboratories, making it difficult to compare results.

α-Synuclein deposits may form early in the enteric nervous system—which is connected to the brain via the the vagal nerve—and in the PNS.[71] The mechanism through which the disease process spreads remains unclear: it could begin in the gut and move retrogradely to the brain via the vagal nerve; it could start in the vagal dorsal motor nucleus and move from there to the spinal cord and gut in an anterograde fashion;[48] or it could begin in the periphery at multiple autonomic sites and subsequently be transmitted to the spinal cord.[49,72] The distribution of Lewy pathology in the gut parallels the input from the vagal dorsal motor nucleus;[73] this occurs in the absence of myenteric ganglion cell loss, indicating that the contribution of cell dysfunction to the pathological process underlying PD should not be underestimated. Accumulation of α-synuclein has been described in some nerve cell bodies and processes in Meissner's plexus of the large intestine several years before the appearance of the first motor symptoms of PD.[74] The presence of α-synuclein inclusions in the large intestine may, therefore, be a useful biomarker of PD.

The staging system described by Braak *et al.*[8] has been expanded in an attempt to incorporate not only the α-synuclein deposits in postganglionic neurons of part of the enteric nervous system,[71] but also those in the coeliac and superior cervical ganglia and in the spinal cord.[48,49,54,72] Spinal cord lesions are first seen during stage 2 in sympathetic and sacral parasympathetic preganglionic nerve cells and, during stage 3, in the motor neurons of Onuf's nucleus and the ventral horn, as well as in layer 1 nociceptive neurons of the dorsal horn.[48]

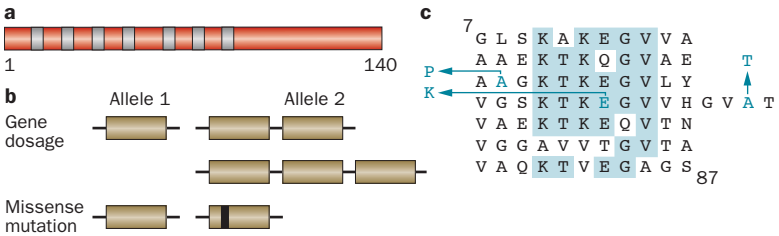


Figure 4 | Human α-synuclein and its disease-causing mutations. **a** | Diagram of the 140-amino-acid human α-synuclein protein. The core regions of the amino-terminal repeats are shown as blue bars. **b** | An increase in gene dosage (duplication or triplication) of the chromosomal region containing *SNCA* or missense mutations in *SNCA* cause dominantly inherited forms of Parkinson disease and dementia with Lewy bodies. **c** | The seven repeats (residues 7–87) of human α-synuclein are shown, with the disease-causing missense mutations (Ala30Pro, Glu46Lys and Ala53Thr) indicated in blue text. Amino acids that are identical in at least five of the seven repeats are shaded in blue. Abbreviation: *SNCA*, α-synuclein gene.

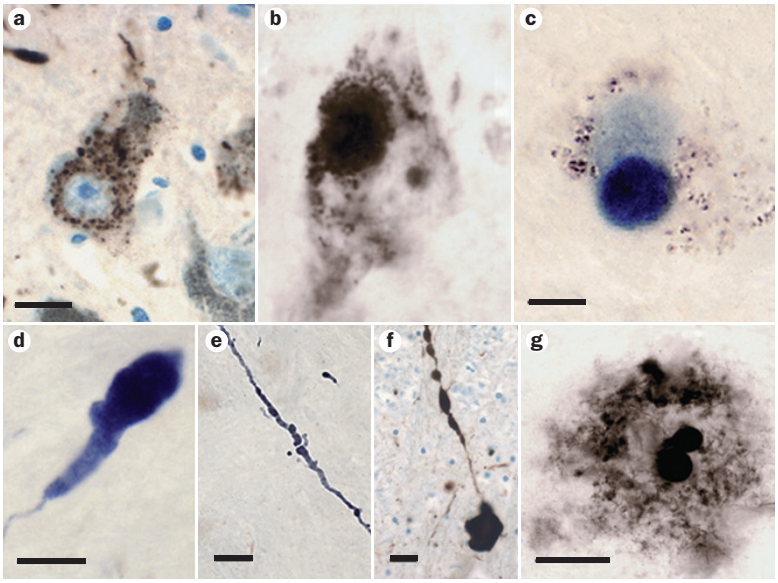


Figure 5 | Synuclein-immunoreactive Lewy pathology in the Parkinson disease brain. **a** | Particulate aggregates (punctate inclusions) in dopaminergic nerve cells of the substantia nigra, which probably precede Lewy body formation. **b** | Mossy cell with Lewy body in sector CA4 of Ammon's horn of the hippocampus. **c** | Lewy bodies in dopaminergic nerve cells of the substantia nigra. Pale body in the background (pale blue area) and Lewy body (dark blue) in a neuromelanin-containing cell in the foreground. **d** | Club-shaped, **e** | filiform and **f** | varicose Lewy neurites. **g** | Lewy plaque consisting of an extracellular Aβ core that is surrounded by a perimeter of α-synuclein-immunoreactive dystrophic neurites. Sections are immunostained for α-synuclein, with the addition of Campbell–Switzer silver staining for Aβ in part g. Scale bars, 20 μm. Abbreviation: Aβ, amyloid-β. With kind permission of Springer Science+Business Media © Braak, H. & Del Tredici, K. Neuroanatomy and pathology of sporadic Parkinson's disease. *Adv. Anat. Embryol. Cell Biol.* **201**, 1–119 (2009).[22]

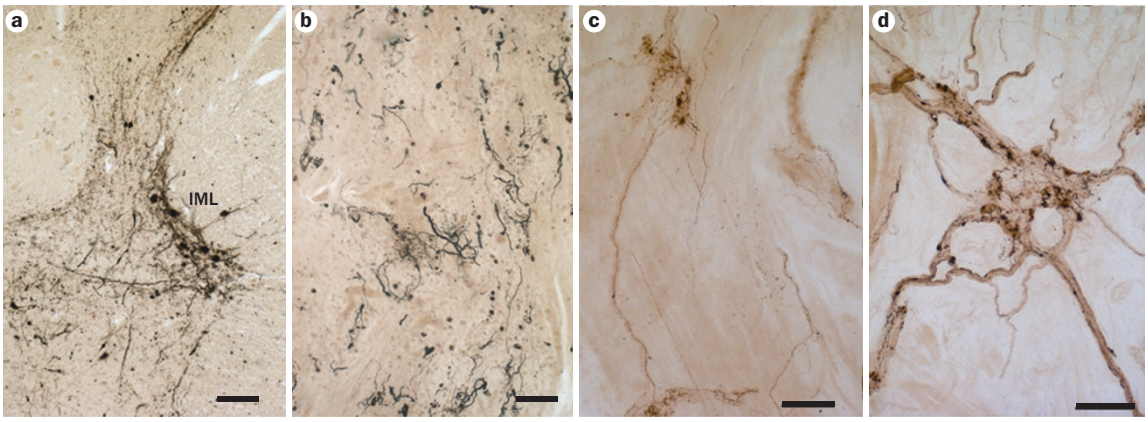


Figure 6 | Synuclein-immunoreactive Lewy pathology in the PD spinal cord, coeliac ganglion and gastrointestinal tract. **a** | IML with affected preganglionic sympathetic neurons. The dorsal nucleus (pale round area at upper right) is virtually uninvolved. **b** | Lewy bodies and Lewy neurites are widespread in nerve cells of the coeliac ganglion (postganglionic sympathetic neurons), shown here from a case at stage 6 of PD pathology. Scale bars in a and b, 200 μm. **c** | Auerbach's plexus of the stomach from an asymptomatic individual at stage 3 of PD pathology. Aggregates are seen in axons of the fibre bundles that connect individual ganglia. **d** | At stage 6 of PD pathology, heavy involvement of the enteric nervous system is a major reason why many patients experience gastrointestinal dysfunction. Scale bars in c and d, 500 μm. Abbreviations: IML, interomediolateral column; PD, Parkinson disease. With kind permission of Springer Science+Business Media © Braak, H. & Del Tredici, K. Neuroanatomy and pathology of sporadic Parkinson's disease. *Adv. Anat. Embryol. Cell Biol.* **201**, 1–119 (2009).[22]

Together with previous findings, this report indicates that the disease process within the CNS does not originate in the spinal cord.[63,75]

The staging scheme is consistent with the fact that most PD patients have nonmotor symptoms that appear before motor dysfunction. Autonomic dysfunction, hyposmia, depression and rapid eye movement sleep behaviour disorder can precede the motor symptoms by many years.[76] These symptoms are consistent with the distribution of Lewy bodies and Lewy neurites in the brain during the early pathological stages.[60,76] Incidental Lewy body disease may be at one end of the Lewy body disease spectrum, with DLB at the other end, and with Lewy body dysphagia, pure autonomic failure and PD in between.

The presence of Lewy bodies in human fetal brain cells a decade or more following their transplantation into the striatum of patients with PD is consistent with the spreading of α-synuclein inclusions from the host brain to the grafted cells,[77,78] although the microenvironment of the graft may also play a role.[79] In the grafts, up to 5% of dopaminergic neurons contained Lewy bodies, similar to the proportion of Lewy body-bearing neurons in the substantia nigra of patients with PD.[80,81] It has been suggested that nerve cells with Lewy bodies might die within 6 months of inclusion formation, with Lewy bodies and nerve cell loss ultimately reaching a steady state.[81]

Recent work has led to the development of a unifying mechanism of neurodegeneration.[18,82] According to this view, protein aggregation is a relatively common event, with cells efficiently removing early aggregates in the vast majority of cases. Following a rare successful aggregation event, the prion-like replication and intercellular transfer of pathology may provide a mechanism for the rapid propagation of protein inclusions. A stochastic misfolding event may be the primary cause, with the subsequent influence of more-deterministic processes. The early misfolding of a given disease protein is not entirely random, however, in that it tends to develop in a predictable manner within a given brain region. The causal relationships between α-synuclein aggregation, spreading and neurodegeneration are unknown. In particular, the relative contributions of Lewy bodies and Lewy neurites remain to be established.[83]

Other forms of Parkinson disease

Following the discovery of *SNCA*, additional PD-associated genetic loci were identified, raising the question of whether multiple forms of PD exist or whether a single pathway can account for all cases. As discussed above, the aggregation of α-synuclein is central to at least one form of PD, and its relevance has been reinforced with the demonstration of a progressive and spreading disease, encompassing widespread pathology and a long presymptomatic phase.[84] It seems unlikely that the same pathogenic process is central to forms of clinical PD that lack Lewy bodies and Lewy neurites at autopsy.

Homozygous mutations in the gene encoding the enzyme glucocerebrosidase (*GBA*), resulting in the lysosomal accumulation of glucocerebroside, cause Gaucher disease; some patients with this condition develop PD. Heterozygous *GBA* mutation carriers (without Gaucher disease) also have an increased risk of developing PD.[85,86] Among individuals with Gaucher disease, the probability of developing PD before the age of 80 years is 9–12%, compared with 2.6% in the general population.[87] Moreover, patients with PD are over five times more likely to carry *GBA* mutations than are healthy controls. Patients with PD and *GBA* mutations exhibit an earlier age of onset and more-severe nonmotor symptoms, including autonomic dysfunction, neuropsychiatric symptoms and

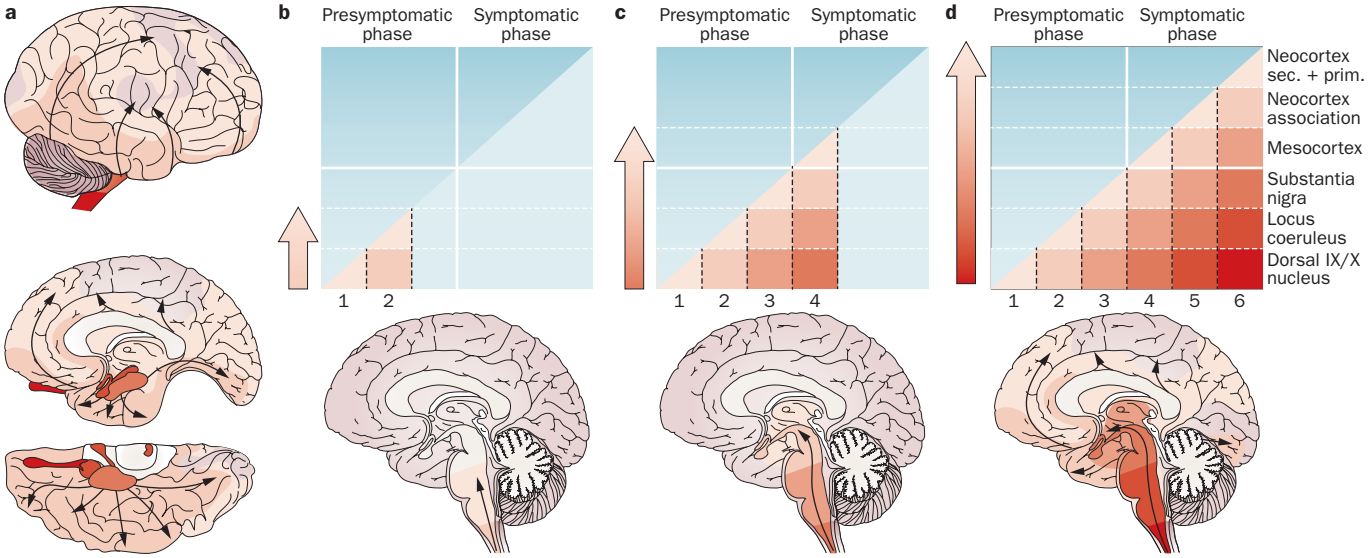


Figure 7 | Six stages of PD pathology. Cases with α-synuclein inclusions fall into one of six groups according to the brain regions involved. Progression between groups involves additional brain areas and worsening of pathology in previously affected brain regions. **a** | Rostrocaudal progression of the pathological process (arrows). Variable red shading reflects the ascending disease process and increasing severity of pathology. **b** | Stage 1: lesions occur in the olfactory bulb, the anterior olfactory nucleus and/or the dorsal motor nuclei of the vagal and glossopharyngeal nerves in the brainstem. Stage 2: lesions are observed in the pontine tegmentum (locus coeruleus, magnocellular nucleus of the reticular formation, and lower raphe nuclei). **c** | Stages 3 and 4: lesions reach the pedunculopontine nucleus, the cholinergic magnocellular nuclei of the basal forebrain, the pars compacta of the substantia nigra (stage 3), the hypothalamus, portions of the thalamus and, as the first cortical region, the anteromedial temporal mesocortex (stage 4). First clinical symptoms of PD appear during stage 3 or early stage 4. **d** | Stages 5 and 6: lesions reach neocortical high-order association areas (stage 5), followed by first-order association areas and primary fields (stage 6). Abbreviation: PD, Parkinson disease.

dementia, than do PD patients without *GBA* mutations. At autopsy, all cases with *GBA* mutations and PD exhibit abundant Lewy bodies and Lewy neurites, many of which also contain glucocerebrosidase.[88] Current models suggest that *GBA* mutations enhance, but do not initiate, the aggregation of α-synuclein.[89] This work has established a link between lysosomal dysfunction, α-synuclein aggregation and PD.

Heterozygous mutations in the leucine-rich repeat kinase 2 (*LRRK2*) gene are a common cause of PD.[90,91] The Gly2019Ser mutation in *LRRK2* is estimated to account for up 1% of idiopathic PD cases and 4% of familial PD cases. Although the physiological substrates of LRRK2 are not known, the Gly2019Ser mutation in the kinase domain is believed to increase its kinase activity. Disease penetrance in individuals with this mutation is age-dependent and ranges from 30–74%.

The neuropathology resulting from the presence of *LRRK2* mutations can be variable.[30,92] The majority of Gly2019Ser carriers with PD have typical Lewy bodies and Lewy neurites. However, some individuals with Gly2019Ser or other mutations in *LRRK2* develop a progressive supranuclear palsy-like syndrome with filamentous tau inclusions, and a third group with *LRRK2* mutations exhibits dopaminergic nerve cell death in the substantia nigra in the apparent absence of filamentous deposits.

Defects in mitochondrial damage repair cause recessive forms of juvenile-onset parkinsonism.[93,94] These forms of disease progress slowly, and the patients experience symptomatic improvements after sleep. The associated proteins Parkin (an E3 ubiquitin ligase) and PINK1 (a mitochondrial protein kinase) function in the same pathway.[95,96] Following the depolarization of mitochondria, PINK1 is stabilized and activated. It then recruits, phosphorylates and activates Parkin on the surface of mitochondria,[97] which results in the ubiquitination of a number of target proteins and the removal of defective mitochondria by autophagy.[98] In juvenile parkinsonism, this pathway is defective because of homozygous and compound heterozygous loss-of-function mutations in *Parkin* or *PINK1*.

Loss-of-function mutations in the *DJ1* gene also cause juvenile parkinsonism.[99] DJ1 may function in the same pathway as Parkin and PINK1, since it has been shown to translocate to mitochondria and to protect against oxidative stress.[100]

Most cases of juvenile parkinsonism with *Parkin* mutations lack α-synuclein inclusions. Of the nine cases examined, six lacked Lewy bodies, two had typical Lewy bodies, and one had Lewy body-like inclusions in the pedunculopontine nucleus and the anterior horn of the lumbar spinal cord.[30] All but the two cases with Lewy body pathology had more-severe nerve cell loss in the substantia nigra than in the locus coeruleus, in contrast to the typical pattern in idiopathic PD.[101] Only one autopsy case with a compound heterozygous mutation in *PINK1* has been reported.[102] Lewy body pathology

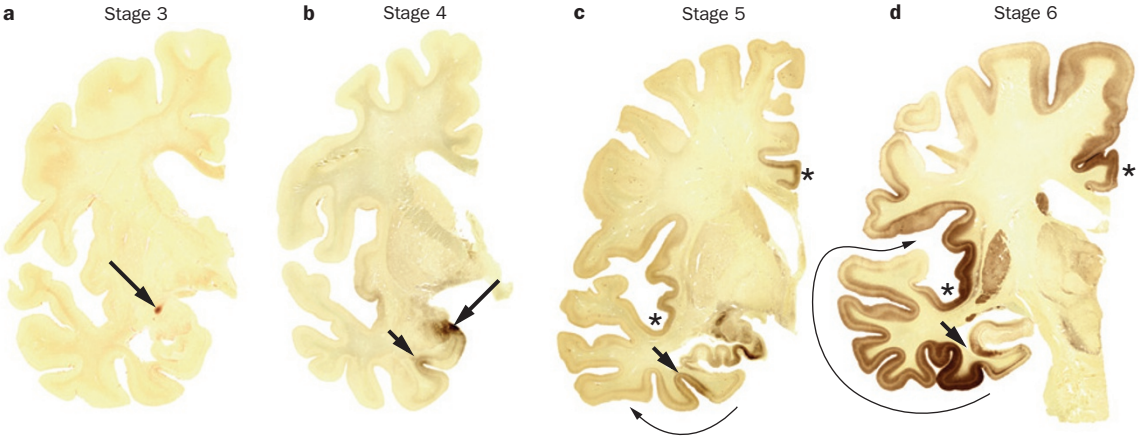


Figure 8 | Stages 3–6 of Parkinson disease pathology. **a** | Stage 3: α-synuclein staining in the central subnucleus of the amygdala (arrow). **b** | Stage 4: the amygdala is more severely affected (long arrow) and α-synuclein staining is also present in the anteromedial temporal transition zone between allocortex and neocortex (short arrow). **c** | Stage 5: a thick network of Lewy neurites is present in the superficial layers of the anteromedial temporal cortex, with Lewy bodies in the projection neurons of the deep layers (short arrow). The disease process encroaches on the insular and cingulate cortices (asterisks). From here, α-synuclein inclusions progress to high-order association fields of the neocortex. Immunoreactivity tapers off as it approaches the secondary and primary fields of the temporal cortex (long arrow). **d** | Stage 6: areas of the insular, cingulate (asterisks) and temporal mesocortex (short arrow) are strongly immunoreactive. Cortical staining increases in severity and extent. The disease process reaches secondary and, in advanced cases, primary neocortical fields, as indicated by staining of Heschl's gyrus (long arrow). Permission obtained from John Wiley and Sons © Braak, H. *et al. Mov. Disord.* **21**, 2042–2051 (2006).[162]

and nerve cell loss were present in the substantia nigra, but not in the locus coeruleus. The brainstem reticular formation and the nucleus basalis of Meynert were also affected. Information from additional autopsy cases is required to establish whether a mechanistic link exists between reduced turnover of defective mitochondria and α-synuclein aggregation.

Multiple system atrophy

Glial cytoplasmic inclusions (GCIs, or Papp–Lantos inclusions) consist of abnormal filaments and are the defining neuropathological feature of multiple system atrophy (MSA), an atypical parkinsonian movement disorder.[103] GCIs are found mostly in the cytoplasm and, to a lesser extent, in the nucleus of oligodendrocytes. The inclusions are also present in some nerve cells. The substantia nigra, striatum, locus coeruleus, pontine nuclei, inferior olives, cerebellum and spinal cord are predominantly affected, and nerve cell loss and gliosis are widespread. The filamentous inclusions of MSA are made of α-synuclein[104–106], but filament morphologies differ between MSA and Lewy body diseases, suggesting that distinct conformers of assembled α-synuclein can give rise to different neurodegenerative diseases.[105] Sequence variation in *SNCA* is a risk factor for MSA, which is largely a sporadic disease.[107,108]

Animal models of synucleinopathies

Loss of function of α-synuclein is probably not pathogenic: α-synuclein-knockout mice do not develop neurodegeneration,[109,110] and mice with knockouts of all three synucleins (besides α-synuclein, vertebrates also express β-synuclein and γ-synuclein; only α-synuclein is found in the disease inclusions) do not exhibit any nerve cell loss.[111] Together with the fact that even a modest overexpression of α-synuclein is detrimental in humans, this identifies a reduction in the level of soluble α-synuclein as a promising approach for the development of mechanism-based therapies for PD and related diseases.[112,113]

Since the identification of the central role of α-synuclein aggregation in PD, DLB and MSA, the human diseases have been modelled in animals.[114] In mice transgenic for human mutant Glu46Lys or Ala53Thr α-synuclein, abundant α-synuclein filaments formed in the brain and spinal cord.[115,116] Surprisingly, in the Glu46Lys line, numerous inclusions consisting of filamentous hyperphosphorylated tau were present alongside α-synuclein inclusions.[116] The formation of α-synuclein inclusions correlated with the development of a movement disorder. In a mouse line transgenic for wild-type human α-synuclein, dephosphorylation of α-synuclein at Ser129 by protein phosphatase 2A protected against neurotoxicity.[117] In these and other models, a major difference with PD was the absence of significant pathology and neurodegeneration in dopaminergic nerve cells of the substantia nigra. This problem has been partly addressed through the production of transgenic mouse lines expressing carboxy-terminally truncated human α-synuclein under the control of the rat tyrosine hydroxylase promoter.[118,119] These mice developed α-synuclein aggregates, a striatal dopamine deficiency and reduced locomotion. However, a transgenic mouse line that fully recapitulates the behavioural phenotype, neuropathology and pathophysiology of PD remains to be produced.

One report described a neurotoxin model of α-synuclein pathology in the rat, which was generated through chronic intravenous administration of the pesticide rotenone, a high-affinity inhibitor of mitochondrial complex I of the respiratory chain.[120] Some rats developed inclusions that were immunoreactive

for α-synuclein and ubiquitin, and showed progressive degeneration of nigrostriatal neurons. The rats exhibited bradykinesia, postural instability and resting tremor. The inhibition of complex I was partial, suggesting that reactive oxygen species can link mitochondrial dysfunction and α-synuclein aggregation. Intragastric administration of rotenone has been reported to cause accumulation of α-synuclein in the enteric nervous system, the dorsal motor nucleus of the vagal nerve, the intermediolateral nucleus of the spinal cord, and the substantia nigra.[121]

Adeno-associated and lentiviral vectors have been used to express human wild-type and mutant α-synuclein in the rodent and primate substantia nigra,[122,123] leading to the formation of Lewy body-like inclusions and the degeneration of many nerve cells. In this system, aggregation of α-synuclein promoted the progressive degeneration of nigral dopaminergic neurons.[124,125]

Expression of human α-synuclein in *Drosophila melanogaster* resulted in the formation of filamentous Lewy body-like inclusions, age-dependent loss of some dopaminergic neurons, and locomotor deficits.[126] Aggregation of α-synuclein was necessary for neurodegeneration, and these effects were modulated by chaperones.[127,128] It is not clear which molecular species caused neurodegeneration, although a prevalent idea is that oligomeric species of α-synuclein are the most neurotoxic. Overexpression of human α-synuclein in *Caenorhabditis elegans* also resulted in dopaminergic nerve cell loss and motor deficits.[129]

Genome-wide screens have identified proteins involved in vesicle transport, lipid metabolism and protein degradation as modifiers of α-synuclein toxicity, indicating that lipid binding and vesicle transport are important for early toxic events.[130] Small organic compounds that inhibit the aggregation of α-synuclein *in vitro* have been identified,[131] but it remains to be seen whether they are beneficial in models of synucleinopathy.

Experimental evidence supports the intercellular transfer of α-synuclein and the seeding of aggregation. Internalized filaments made from recombinantly expressed α-synuclein induced the aggregation of endogenous α-synuclein in mouse primary hippocampal neurons, resulting in synaptic dysfunction and nerve cell death.[132] Moreover, human α-synuclein has been shown to transit from host cells to neurons grafted into the striatum.[133–135] Furthermore, injection of brain lysates from symptomatic mice transgenic for human mutant Ala53Thr α-synuclein into the cerebral cortex and striatum of asymptomatic transgenic mice accelerated the initiation of disease, even in brain regions that were at a distance from the injection sites.[136,137] The effects of brain lysates could be replicated by filaments made from recombinantly expressed α-synuclein. These findings indicate that immunotherapy with α-synuclein antibodies, which is likely to reduce the intercellular transfer of aggregates, may turn out to be an effective mechanism-based therapy for the synucleinopathies.[138,139]

Induced pluripotent stem cell (iPSC)-derived neurons from *SNCA* mutation carriers are likely to occupy an important place between humans and model organisms in future.[140,141] The application of iPSC technology to the modelling of diseases with a long latency and caused by a gain of toxic function mechanism, such as PD, may be challenging. In principle, the earliest pathogenic changes that lead to disease can be studied in these model systems. However, their interpretation may only be meaningful if end-stage pathology also develops over time.

Conclusions

Specific protein aggregates constitute the defining pathological characteristics of the most common neurodegenerative diseases. 100 years ago, Lewy used light microscopy and PD tissue sections to describe the inclusions that were subsequently named after him.[1,2] In the 1960s, electron microscopy showed that these inclusions are made of abnormal filaments.[142] In the 1990s, α-synuclein was identified as the main component of the Lewy pathology filaments.[5,35] A causal connection is believed to exist between inclusion body formation and the degenerative process.[4–7] As a result of these efforts, Lewy's name is better known now than during his lifetime. Prevention of the formation of the pathological inclusions that he first described is a major goal for the years to come.

Review criteria

For the historical parts of the Review, the PubMed database (all years) was searched using, for example, the terms: "dementia with Lewy bodies", "genetics of Parkinson's disease", "Lewy" ("Lewy body", "Lewy neurite", "Lewy pathology"), "multiple system atrophy", "Parkinson's disease" and "synucleins". Selected full-length papers and books available in English were used and articles from the reference lists of these items were used as further leads. Where deemed appropriate, papers and books written in German and French were also consulted. For the remaining parts of the review, literature was obtained from the PubMed database (all years). The authors attempted to achieve a judicious balance between original studies and timely reviews.

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Author contributions
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