Review

Neuropathological Staging of Brain Pathology in Sporadic Parkinson's disease: Separating the Wheat from the Chaff

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Abstract. A relatively small number of especially susceptible nerve cell types within multiple neurotransmitter systems of the human central, peripheral, and enteric nervous systems (CNS, PNS, ENS) become involved in the degenerative process underlying sporadic Parkinson's disease (sPD). The six-stage model we proposed for brain pathology related to sPD (*Neurobiol Aging* 2003) was a retrospective study of incidental and clinically diagnosed cases performed on unconventionally thick tissue sections (100 μm) from a large number of brain regions. The staging model emphasized what we perceived to be a sequential development of increasing degrees of Lewy pathology in anatomically interconnected regions together with the loss of aminergic projection neurons in, but not limited to, the locus coeruleus and substantia nigra. The same weight was assigned to axonal and somatodendritic Lewy pathology, and the olfactory bulb was included for the first time in a sPD staging system. After years of research, it now appears that the earliest lesions could develop at nonnigral (dopamine agonist nonresponsive) sites, where the surrounding environment is potentially hostile: the olfactory bulb and, possibly, the ENS. The current lack of knowledge regarding the development of Lewy pathology within the peripheral autonomic nervous system, however, means that alternative extra-CNS sites of origin cannot be disregarded as possible candidates. The PD staging system not only caused controversy but contributed a framework for (1) assessing pathology in the spinal cord, ENS, and PNS in relationship to that evolving in the brain, (2) defining prodromal disease and cohorts of at-risk individuals, (3) developing potential prognostic biomarkers for very early disease, (4) testing novel hypotheses and experimental models of α-synuclein propagation and disease progression, and (5) finding causally-oriented therapies that intervene before the substantia nigra becomes involved. The identification of new disease mechanisms at the molecular and cellular levels indicates that physical contacts (transsynaptic) and transneuronal transmission between vulnerable nerve cells are somehow crucial to the pathogenesis of sPD.

Keywords: α-synuclein, autonomic nervous system, cell-to-cell transfer, central nervous system, dorsal motor nucleus of the vagal nerve, enteric nervous system, Lewy body disease, locus coeruleus, Parkinson's disease, olfactory bulb, peripheral nervous system, prion-like, protein aggregation, protein misfolding, spinal cord, substantia nigra

"It therefore is worthwhile to examine the Lewy bodies, find out what they are composed of, and what molecular events precede and accompany their formation. Once we know that, will we be able to prevent Lewy bodies from forming? And if Lewy bodies do not form, will we then have no substantia nigra degeneration and no Parkinson's disease? Perhaps that is too much to expect from Lewy's peculiar cellular inclusions." L.S. Forno [1].

Fredrick Lewy's descriptions of the pathology associated with *paralysis agitans* were not confined to the substantia nigra [2], and these were expanded upon by later investigators, who recognized that Parkinson's disease is a multisystem and autonomic system disorder, during the course of which circumscribed subcortical nuclei, cortical areas, spinal cord structures, and portions of the peripheral and enteric nervous system become involved [3–10]. In 1997, the presynaptic protein α-synuclein was discovered to be a major component of Lewy bodies and neurites in the substantia nigra of sPD and dementia with Lewy bodies (DLB) [11]. Reports of α-synuclein in pale bodies, axons [12, 13], dot-like structures [14], and in punctate cytoplasmic inclusions [15] rapidly followed.

In Frankfurt, our group had been studying sPD since the early 1990's with a focus on the lesions in the amygdala and other extranigral regions of the human brain [16–18]. Gradually, three questions

emerged: (1) Does sPD begin in the substantia nigra or elsewhere [17, 19]? (2) Do vulnerable regions in all divisions of the human nervous system become involved at the same time? (3) Does the distribution of Lewy pathology in susceptible nonnigral regions follow a recognizable pattern or sequence [20]?

These questions can be answered only when biomarkers of the underlying degenerative process [21, 22], electrophysiological testing, and imaging modalities make it possible to assess and reassess one and the same individual at ongoing time points in life [23–26]. Neuropathologists necessarily perform cross-sectional studies that (ideally) include not only clinically diagnosed sPD but also prodromal sPD and incidental cases [27–29] to gain knowledge about the regional distribution and severity of the pathology, its progression and possible spreading, neurodegeneration, and nerve cell loss. The same limitations inherent in cross-sectional studies also apply to the procedures proposed for the neuropathological diagnosis and staging of Lewy body disease [20, 30–35].

Reactions to the six-stage grading model have been essentially encouraging [36–40], although the following anecdote is illustrative of the climate in which some of the earlier differences of opinion took place. In August 2009, we received an email from an American colleague of a newly published experimental study: "In the discussions with the authors and editors, it was suggested to take out the references to your work so that our paper could be published . . . . I am not sure why your findings are

so controversial and bring up such strong emotions." Controversies surrounding the staging publication [20] crystalized chiefly around the following points:

1. Inasmuch as DLB belongs to the spectrum of Lewy body diseases, the staging should have been performed not only on sPD but also on DLB cases. The staging of sPD does not 'fit' DLB.

We ventured to postulate that DLB cases might overlap with sPD stages 5 and 6 [41; see also 42] and that a phase of mild cognitive impairment could precede overt dementia in sPD [41, 43, 44], which can be accompanied by the presence of severe Alzheimer's-related pathology. Nevertheless, the sPD staging concept was never intended for DLB [45, 46], and during the peer review process, we were explicitly requested to include the following caveats for the reader: "... the study sample does not include cases clinically diagnosed as diffuse Lewy body disease... It remains to be seen whether deviations from the proposed staging scheme exist in cases of advanced AD with Lewy bodies or in cases of clinically assessed diffuse Lewy body disease" [20].

2. PD staging does not apply to 'amygdala-predominant' cases.

Within the context of approximately 43–60% of late-stage AD cases, Lewy pathology can be mainly or even solely confined to the amygdala [47–50], especially in the 'corticomedial' regions of the amygdala, including the central and cortical subnuclei [47]. The basolateral subnuclei (which become involved during stage 3 after the central subnucleus in sPD; see [20]) were also evaluated, but the degree of the involvement there was not further specified [47]. Later, it could be seen that, in 17/66 AD cases with NFT stages V-VI and amygdala-predominant Lewy pathology, anterior olfactory structures, including the olfactory bulb, were α-synuclein-immunoreactive [51–53]. Inasmuch as it is unlikely that such amygdala-predominant cases represent prodromal sPD [54] and probably constitute a neuropathologically distinct synucleinopathy [47], it is not surprising that they are not stageable – nor, in retrospect, were cases of amygdala-predominant pathology included in our sPD staging study sample [20].

3. Clinical symptoms and the clinical course of disease do not correspond to the proposed neuropathological stages and it is unlikely that older persons with incidental Lewy pathology would have gone on to be diagnosed with PD.

Most individuals in our sample with Lewy pathology corresponding to stages 1–3 were older than 60 years of age and, thus, on average older than those representing sPD stages 4–6, where neurological impairment was present or would be expected [20, 38]. The assumption, however, that at least some of those at stages 1–3 who were between 54 and 71 years of age [20] would have developed sPD had they survived longer is in line with the results and demographics from several other cross-sectional or prospective hospital- and university-based cohorts [55–59] as well as a study of 139 longitudinally followed elderly controls [60] (Fig. 1a-d). For the first time, the olfactory bulb was included as a diagnostic region for staging sPD [20], and in more recent studies of at-risk or prodromal persons, e.g., with olfactory lesions and hyposmia compared to controls, as well as of individuals with Lewy pathology in gastrointestinal biopsies and/or constipation (i.e., autonomic dysregulation), some not only were older than 60 but subsequently converted to sPD [61–65; see also 66, 67].

Gibb and Lees [68] pointed out that some of the most influential neuropathological studies on sPD provided too little, if any, clinical data, and this also applied to Lewy's own studies. For staging purposes, we had access to neuropathological and clinical datasets, including the cause of death, for the majority of cases with clinically diagnosed sPD, whereas for a few cases with incidental Lewy pathology this information was unavailable [20]. Because sPD as a cause of death may be underreported [69], it cannot be ruled out that some of these 'incidental' cases were at or beyond the threshold to early but yet undiagnosed sPD with subtle motor symptoms.

We emphasized that a biological *continuum* exists from the preclinical (silent) through the prodromal to the clinical phase [20, 45, 70, 71]. Do the sPD neuropathological stages we proposed have any bearing on the clinical symptoms and disease courses seen by neurologists in their patients? Our impression is yes, and we see the staging model as a useful framework for longitudinal autopsy-controlled correlation studies [72–74], for models of possible propagation and routes of spreading (see below), for the development of possible biomarkers during the preclinical and prodromal phases [61, 75–77], and for potential therapeutic strategies of symptoms consistent with early pathology and with even earlier changes within the protein α-synuclein [38, 75, 78–82]. As new research results continue to emerge, other groups inevitably will winnow out and discard what is incorrect or
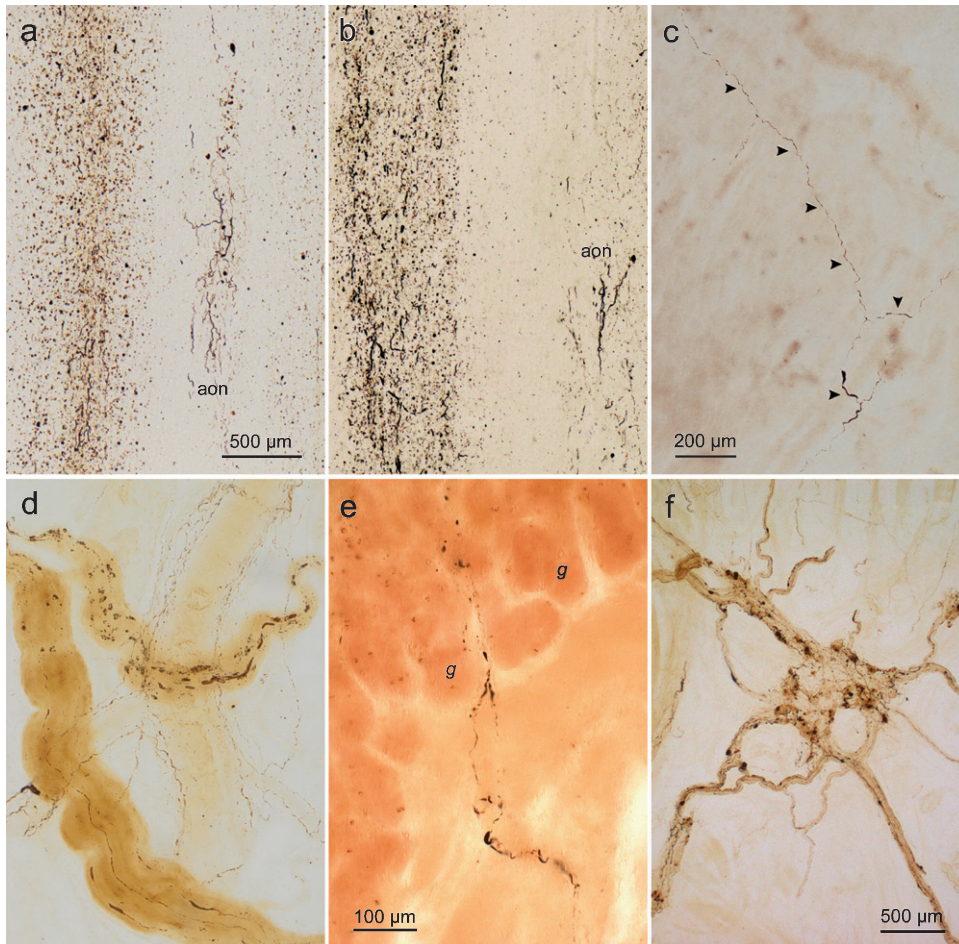
Fig. 1. **(a-f)** Lewy pathology in the olfactory bulb and gastric Auerbach plexus visualized in α-synuclein immunohistochemistry (100 μm polyethylene glycol sections). **a.** Olfactory bulb and anterior olfactory nucleus (aon) (50-year-old male, stage 2). The dorsal motor nucleus of the vagal nerve and intermediate reticular zone in the medulla also contained Lewy neurites and Lewy bodies. Presumably, this non-demented individual would have gone on to develop PD had he lived longer. **b.** Olfactory bulb and aon (63-year-old female, stage 2). Much less severe pathology was also present in the dorsal motor nucleus of the vagal nerve, intermediate reticular zone, nucleus raphes magnus, and locus coeruleus. **c.** Tangential section from the gastric cardia showing Lewy neurites (*arrowheads*, same case as in **b**). Again, it is presumed that, had she lived longer, this cognitively intact individual would have been diagnosed with PD. **d.** Intramural Lewy pathology in a section cut tangentially to the surface of the gastric cardia. Also visible (*in background*) is a large, branching blood vessel lined by thread-like immunoreactive sympathetic nerve fibers. In addition to the occurrence of Lewy neurites and Lewy bodies in the dorsal motor nucleus of the vagal nerve, intermediate reticular zone, nucleus raphes magnus, locus coeruleus, and substantia nigra, some nigral cell loss was also evident in the pars compacta (65-year-old male, stage 3). **e.** Detail of Lewy neurites in PD penetrating the muscularis mucosa and reaching upwards into the lamina propria (mucosa) where they extend between the gastric glands (*g*) in a perpendicularly cut section (69-year-old female, stage 4). **f.** Tangential section from the gastric cardia of a PD patient with disease duration of 11 years (78-year-old female, stage 5). Scale bars: **a** is valid for **b; c** also applies to **d**. Stages in parentheses refer to neuropathological stages 1–6 of sporadic PD. Micrographs **e, f** reproduced with permission from [70].

obsolete while keeping the relevant and valid aspects of the staging system.

4. Staging based on the presence of Lewy pathology (e.g., pale bodies, Lewy bodies, Lewy neurites) rather than on neuronal loss or other evidence of neurodegenerative change is not admissible. The presence and distribution patterns of Lewy pathology in nondopaminergic neurons during sPD could be attributable to localized, regional vulnerabilities and the Lewy pathology might be neuroprotective rather than deleterious.

Inasmuch as the prodromal symptoms and vulnerable neuronal types in sPD and DLB are remarkably similar, i.e., Lewy pathology in limbic and neocortical regions correlate equally well with dementia in sPD and in DLB [12, 83, 84], it is odd that the

pathological status of Lewy pathology is questioned within the context of sPD but not DLB. Similarly, why do clinical symptoms in DLB (but not those in sPD-related dementia) reportedly parallel the numbers of Lewy bodies rather than nerve cell loss in the limbic system and, above all, in the neocortex [85, 86]?

That the protein α-synuclein is pathogenic in sPD is shown by the fact that duplication or triplication of the wild-type α-synuclein gene also causes a familial form of PD, in which increased levels of even the normal protein are sufficient to trigger disease accompanied by Lewy body formation [87, 88]. Postmitotic cells may produce somatic Lewy bodies as an adaptive measure [89]. If so, however, this presumably is not because the nerve cells with such inclusions fail to recognize them as abnormal (and, thus, destined for elimination) but because the physiological cellular systems responsible for clearing soluble defective proteins and fibrillar aggregates probably become dysfunctional during sPD [90–95]. Multiple Lewy bodies that nearly fill a single cell soma are unlikely, in the long term, to be 'protective'. Moreover, depletion of cytoplasmic tyrosine hydroxylase or of choline acetyltransferase and their sequestration within Lewy bodies [96] make these enzymes unavailable for the neuromodulation of essential brain functions [97, 98]. Too little is currently known about the stages at which neurotransmitter deficits develop or when they manifest themselves clinically [99]. Postural instability and gait problems in sPD, for example, appear to be related to cholinergic and glutaminergic rather than dopaminergic nerve cell and neurotransmitter loss [100, 101].

The presence of α-synuclein aggregates in the *somatodendritic compartment* represents an *abnormal localization* of a protein that physiologically occurs in presynaptic terminals [102, 103] following its production in the neuronal soma [81, 104]. Lewy neurites in the axoplasm may interfere with cellular homeostasis [105, 106] and, although it is unknown to what extent animal models of Lewy-like neurodegeneration accurately reflect mechanisms of the sPD disease process within the human nervous system [107–113], it has been shown that synthetic α-synuclein fibrils as well as Lewy pathology extracts derived from human brains contribute to punctate changes in wild-type mice and in rhesus monkeys without the genetic overexpression of α-synuclein [114, 115].

That Lewy pathology (particularly Lewy neurites) are closely associated with neurodegeneration in sPD is evident in that nonnigral regions with susceptible nerve cell types are subject to premature neuronal loss [20, 71]: These include the dorsal motor nucleus of the vagal nerve, with its preganglionic neurons that supply dense parasympathetic innervation of the distal esophagus and stomach [116], the locus coeruleus [6, 20, 117–121], the pedunculopontine nucleus [118, 121, 122], and Meynert's nucleus in the basal forebrain [6, 123]. Attenuated sPD staging protocols are practical and perhaps unavoidable for routine diagnostic use on thin tissue sections (6–10 μm) but they can make it possible to underestimate Lewy pathology severity and the degree of nerve cell loss within distinct regions (e.g., the interstitial nucleus of the diagonal band) at different stages [20].

We ascribed the same weight to axonopathy and nerve cell dysfunction (presumably attributable, but not limited, to the presence of Lewy pathology) as to neuronal death [20, 46] because the development of pathology together with neurotransmitter loss [96, 121, 124–132], axonal, and somatodendritic dysfunction in multiple neuronal populations could prove to be more stressful for involved neurons over time than premature cell death within a select neuronal population [46, 71, 133]. Viewed from this perspective, the thick network of Lewy neurites that gradually forms during sPD in the CA2/CA3 sectors of the Ammon's horn [20, 71, 134] and the severe Lewy pathology seen in the lower and upper raphe systems, magnocellular nuclei of the basal forebrain, the hypothalamic tuberomamillary nucleus, and the intralaminar nuclei of the thalamus are not negligible lesions [71]. Staging based on the presence and distribution of Lewy pathology rather than on nerve cell loss also makes sense for another reason: Effective longterm neuron-to-neuron spreading of α-synuclein [135–137] presupposes the existence of sufficient numbers of at least minimally intact nerve cells and intact circuitries [138, 139].

One of the most controversial aspects of the staging classification is the concept of a caudorostral trajectory of pathology in the brain [20, 38, 70] – although, upon somewhat closer inspection, our concept and that of McKeith et al. [32] can be seen to rest on the same basic assumption as Kosaka's tripartite model [30]: namely, that Lewy pathology progresses systematically and topographically in a generally caudal to rostral trajectory [33]. An important difference between our staging model and that proposed for DLB, however, is that we included the presence of cortical Lewy neurites and not only cortical Lewy bodies [20]. Although the staging concept cannot

answer the important question whether dopaminergic and susceptible nonnigral neurons are all subject to the same pathogenic mechanisms in sPD [38, 140–142], we believe that the study of regional vulnerabilites is meaningful only within the context of neuronal networks (connectivities) and not in isolation. Were it to become possible one day to 'rescue' somehow dopaminergic neurons, the neuronal dysfunction and nerve cell loss within other involved susceptible long-axoned nonnigral projection cells would remain, presumably, unabated [71, 143].

Once the disease process begins, it may not proceed as a sweeping 'wave' to end-stage sPD [144, 145] but with a degree of inter-individual variability that partially depends on the rate at which seeding of very small α-synuclein aggregates and, above all, the rate at which regional spread of Lewy pathology occurs within the nervous system of each individual. After α-synuclein seeding, the neuropathology that emerges probably develops over a much longer time period, thereby implying a timelag or threshold between the development of Lewy pathology in a given nucleus or neuronal population and the emergence of detectable functional deficits [75, 146]. Thus, nonunitary (nonlinear) rates of progression do not necessarily imply a nonunitary pathogenesis of sPD [147].

In the same year that our group's staging article appeared, we speculated in a second publication that a neurotropic pathogen, possibly a virus, with access to the olfactory bulb and gastrointestinal tract, might trigger abnormal changes in the protein α-synuclein: "Such a pathogen could possess unconventional prion-like properties and might consist of misfolded α-synuclein molecular fragments [148]." At that time, the idea was so speculative we thought it might never be published.

Neuron-to-neuron transfer of pathogenic α-synuclein aggregates was demonstrated for the first time in humans when fetal neuronal grafts developed Lewy pathology more than a decade after surgery [135–137; see also 149] and when experimental models made it possible to detect seeding mechanisms of α-synuclein aggregates [109, 150–152]. The current and disputed hypothesis of a 'prion-like' dissemination of α-synuclein being explored by many PD research groups [153] is that a pathogenic (i.e., aggregation-prone) form of the protein can self-assemble into oligomers and fibrils, transfer into another nerve cell, recruit the endogenous α-synuclein there, and instigate the gradual but virtually indefinite self-propagation of new insoluble α-synuclein aggregates [146, 154–162]. The

existence of different conformers or 'strains' lends additional credence to the prion-like properties of α-synuclein [163, 164; but see 165]. It remains to be seen whether different strains also differ with respect to their pathogenicity, spreading propensities, and accumulation patterns.

Such neuron-to-neuron propagation of α-synuclein during aging may partially explain the predictable topographical distribution pattern of Lewy pathology and the neurodegeneration we described in different, but anatomically (axonally) interconnected, populations of susceptible projection neurons in the human brain [20, 166; see also 167]. The earliest sPD-related lesions within the nervous system appear to develop in the olfactory bulb, dorsal motor nucleus of the vagal nerve, and possibly also the ENS [19, 20, 56, 127, 133, 148, 168]. At two of these sites, the surrounding environment is potentially hostile to projection neurons with long unmyelinated axons [133, 148, 169–171, 171a] because both the olfactory bulb as well as the intramucosal nerve fibers of the gastrointestinal tract are easily accessible conduits for neurotropic viruses [172–174] that could cause the initial conformational change in a-synuclein.

We reasoned that, after entering vulnerable local projection neurons of the intramural plexuses (Fig. 1e, f), α-synuclein aggregates might reach unmyelinated axons of the vagal nerve and, from there, via retrograde axonal transport the preganglionic visceromotor neurons of the dorsal motor nucleus [148, 169, 170, 175]. In experiments with intraduodenal, intragastric, and peripheral vagal nerve inoculations [176–178], some of the results reported are consistent not only with regional spreading within the nervous system. Vagotomy, on the other hand, halted the progression [179]. Similarly, vagotomy severely reduced the innervation of the ENS in a study of normative and abnormal patterns of α-synuclein expression in specific subsets of enteric neurons and vagal efferents of the rat proximal myenteric plexus [180; see also 181, 182].

The results derived from experimental models have received support from epidemiologic evaluations of vagotomies, which formerly were performed to treat peptic ulcers [183]. Full vagotomy, with resection of both vagal trunks, differs from selective vagotomy, which involves resection of only terminal branches of the vagal nerve that supply the fundus and corpus of the stomach [183; see also 184–186]. This illustrates that the risk of having developed sPD at follow-up more than ten years after surgical intervention

was significantly reduced in individuals who had undergone full truncal vagotomy but remained nearly similar to the risk of the general population in persons with selective vagotomy [183].

Additional routes of Lewy pathology transmission from the intramural plexus of the ENS to the central nervous system are conceivable, including via retrograde axonal transport to postanglionic sympathetic projection neurons in the prevertebral celiac ganglion and from there to preganglionic sympathetic neurons in layer 7 (intermediolateral nucleus) and nociceptive neurons in layer 1 of the spinal cord dorsal horn [187; see also 9, 56, 176, 188]. Alternatively, α-synuclein aggregates originating in the ENS could be transmitted via the celiac ganglion and layer 7 to the level-setting nuclei of the lower brainstem and from there anterogradely to noradrenergic neurons within the dorsal vagal area (A1 group) and within the intermediate reticular zone (A2 group) [14, 71].

Whether the pathogenic process in incidental and prodromal cases proceeds in a retrograde direction (ENS > central nervous system), in an anterograde direction (CNS > ENS), or reciprocally, still has to be proved [188]. Presumably, however, inasmuch as seeding can take place in both retrograde and anterograde directions [109, 115, 189], anterograde prion-like propagation of Lewy pathology along preganglionic projection neurons of the dorsal motor nucleus of the vagal nerve via cholinergic vagal efferents to the intramural plexus of the gastrointestinal tract is anatomically conceivable [189a]. Until now, only a single study showing intraneuronal changes – first in the dorsal motor nucleus of the vagal nerve, followed by chiefly varicose neuritic changes in the myenteric plexus of the stomach and duodenum – exists [190]. Once again, however, vagotomy interrupted the anterograde spread of α-synuclein in this animal model [190].

Some of the earliest detectable Lewy pathology in stage 1 cases occurs in the olfactory bulb [20], and the finding that brain involvement can be confined to the olfactory bulb [34] or to anterior olfactory structures only (glomerula, olfactory mucosa) [168] prompted new hypotheses to test possible spreading routes in sPD. For instance, a recent axonal tracing study delineated the existence of an anterograde pathway between the substantia nigra and the olfactory bulb in rats [191]. In another scenario, retrograde transport and transsynaptic transmission of Lewy pathology could take place early in the disease course from anterior olfactory structures to the amygdala or to the level-setting nuclei, including the locus coeruleus

[192–194], possibly before pathology originating in the ENS could reach the dorsal motor nucleus of the vagal nerve. In stage 4 of our staging model, amgydala Lewy pathology is followed by the initial appearance of cortical lesions in the transentorhinal region [20], which is lacking in non-primates. This may account for why routes beyond the amygdala [169] taken by viruses or by α-synuclein inoculates in an animal model [195] are not directly comparable to the routes accessible in humans. Alternatively, a latent neurotropic virus in the locus coeruleus or amygdala might become reactivated there but use either site only as a 'transit center' with the initial development of Lewy pathology taking place elsewhere, i.e., in anterior olfactory structures [194, 196]. The theory of a neurotropic virus that utilizes a 'key-lock' mechanism to invade unprotected nerve cell fibers could explain why – among a multitude of vertebrates – only the human species develops sPD. The pathogen would need to deactivate endogenous chaperones and cause α-synuclein to undergo a stable (albeit pathological) conformation [197, 198] prior to prion-like propagation.

Knowledge about the distribution and development of Lewy pathology in the peripheral autonomic nervous system during sPD is still remarkably limited. Previous observers, however, reported in incidental sPD cases a differential distribution and density of α-synuclein aggregates in *sympathetic* (cardiac and vesicoprostatic) *versus* parasympathetic neurons or networks [10, 23, 56, 126, 127 129, 199, 200]. Thus, as further potential extra-CNS sites of disease origin, the cardiac sympathetic nerves and the postganglionic neurons of the paravertebral sympathetic ganglia, with possible subsequent prion-like spreading of α-synuclein to the spinal cord [201], require further investigation. Within the spinal cord, the Lewy pathology that develops in the preganglionic intermediolateral nucleus and the sacral parasympathetic nucleus of layer 7, beginning in PD stage 2, could also originate in neurons of the supraspinal level-setting nuclei, including the locus coeruleus, and terminate in the visceromotor autonomic centers of layer 7 via anterograde axonal transport [56, 188, 202].

In closing, we still have many unanswered questions and we see that many issues remain disputed. Nevertheless, there has also been progress, not the least owing to morphological and neuropathological studies, with implications and practical consequences for diagnostics and therapies of prodromal sPD symptoms. The more we understand about the mechanisms

underlying the conformational change and aggregation of the protein α-synuclein and about the anatomically interconnected regions with their susceptible nerve cells at all levels, the greater is our hope that a causal therapy (or therapies) for sPD can be found. Because experimental cell models approximate the milieu found in the human nervous system, where Lewy pathology develops in projection neurons with a long life expectancy, we wonder if a human ENS cell model might yield valuable insights into the mechanisms of α-synuclein aggregation and transmission [133]. Resected tissue culled from surgical interventions on the human gastrointestinal tract, for example, contains functional groups of susceptible post-mitotic myenteric plexus nerve cells [203; see also 204]. We also are interested to learn what results might be yielded by experiments and animal models involving human-derived α-synuclein and Lewy pathology from nonnigral sites. Do the seeding and spreading behaviors resemble or differ from those observed when using nigral extracts or inoculates?

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CONFLICTS OF INTEREST

The authors have no current or potential conflicts of interest to report.

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