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NEUROLOGY AND PRECLINICAL NEUROLOGICAL STUDIES - REVIEW ARTICLE

The brain-first vs. body-first model of Parkinson's disease with comparison to alternative models

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Abstract

The ultimate origin of Lewy body disorders, including Parkinson's disease (PD) and Dementia with Lewy bodies (DLB), is still incompletely understood. Although a large number of pathogenic mechanisms have been implicated, accumulating evidence support that aggregation and neuron-to-neuron propagation of alpha-synuclein may be the core feature of these disorders. The synuclein, origin, and connectome (SOC) disease model of Lewy body disorders was recently introduced. This model is based on the hypothesis that in the majority of patients, the first alpha-synuclein pathology arises in single location and spreads from there. The most common origin sites are the enteric nervous system and the olfactory system. The SOC model predicts that gut-first pathology leads to a clinical body-first subtype characterized by prodromal autonomic symptoms and REM sleep behavior disorder. In contrast, olfactory-first pathology leads to a brain-first subtype with fewer non-motor symptoms before diagnosis. The SOC model further predicts that body-first patients are older, more commonly develop symmetric dopaminergic degeneration, and are at increased risk of dementia—compared to brain-first patients. In this review, the SOC model is explained and compared to alternative models of the pathogenesis of Lewy body disorders, including the Braak staging system, and the Unified Staging System for Lewy Body Disorders. Postmortem evidence from brain banks and clinical imaging data of dopaminergic and cardiac sympathetic loss is reviewed. It is concluded that these datasets seem to be more compatible with the SOC model than with those alternative disease models of Lewy body disorders.

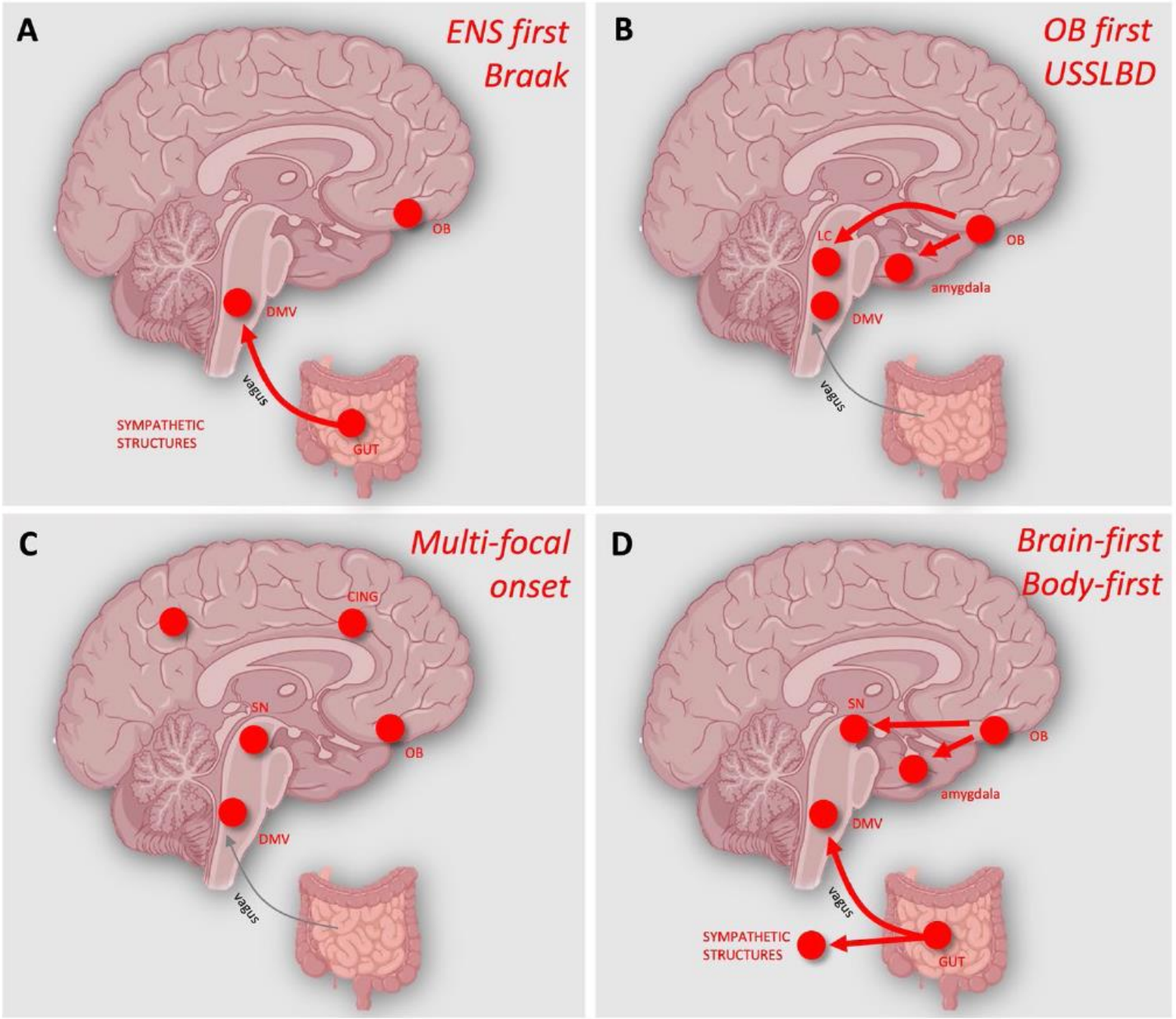
A
ENS first
Braak
OB
DMV
vagus
SYMPATHETIC
STRUCTURES
GUT
B
OB first
USSLBD
LC
OB
amygdala
DMV
vagus
C
Multi-focal
onset
CING
SN
OB
DMV
vagus
D
Brain-first
Body-first
SN
OB
amygdala
DMV
vagus
SYMPATHETIC
STRUCTURES
GUT

Fig. 1 Different disease models of Lewy body disorders. Prion-like spreading is denoted by red arrows. **A** The Braak staging scheme posits that Lewy pathology arises simultaneously in the ENS and OB, but only the former is important in subsequent propagation of pathology. This model is, therefore, exclusively a bottom-up propagation hypothesis. **B** The authors behind the Unified Staging System of Lewy body Disorders (USSLBD) propose that Lewy pathology almost always starts in the OB, which is then followed by either a brainstem-predominant stage or a limbic stage. The model posits that Lewy pathology never starts in the gut. The model is, therefore, essentially a top-down propagation model. **C** Some investigators suggest that prion-like spreading perhaps does not occur. Instead, inherent variations in cellular vulnerability determine when cells develop pathology. Other investigators posit that Lewy pathology can be triggered by blood-borne factors. Some of these concepts can be considered multi-focal models without neuron-to-neuron spreading of aSyn pathology. **D** The SOC model posits that the majority of patients develop uni-focal pathology. The two most common onset sites are the ENS with spreading via vagal and sympathetic connections (body-first), or the OB and/or amygdala with spreading to limbic structures and the SN. A minority of uni-focal cases (10–15%) may have a different origin site, particularly the LC or SN (not shown). Cases originating in the OB, amygdala, SN, or LC are all considered brain-first. The model also posits that a small minority (perhaps 10–15%) of all Lewy body cases may be multi-focal

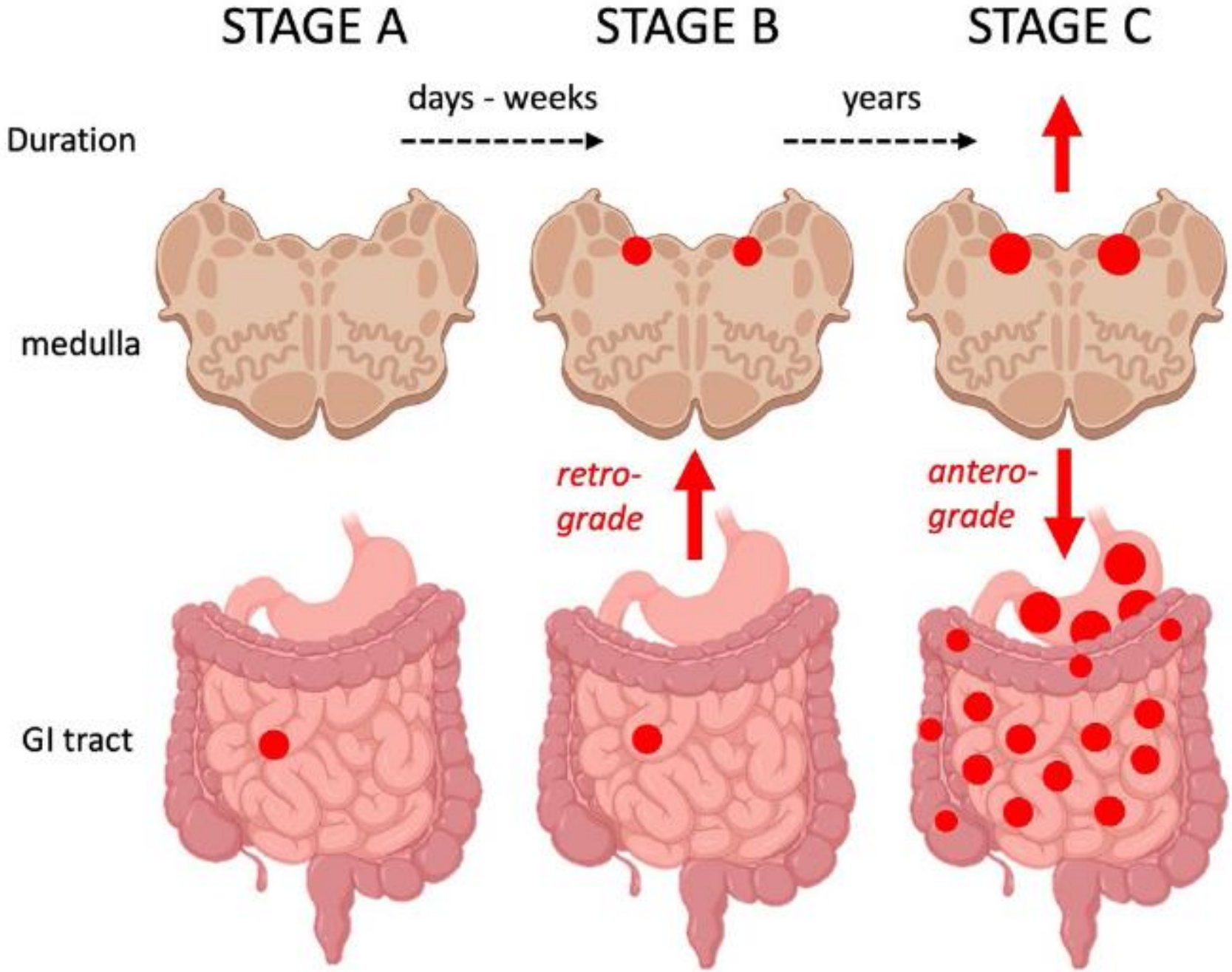
STAGE A
STAGE B
STAGE C
Duration
days - weeks
years
medulla
retro-
grade
antero-
grade
GI tract

Fig. 2 Hypothetical illustration of the possible start and evolution of gut-first Lewy body disease. Stage A depicts a hypothetical gut-only phase of Lewy pathology. The initial patch of pathology could be very small and might arise anywhere in the GI tract. If randomly located, reliable detection of such spatially restricted pathology requires many hundreds of tissue sections throughout the 8–10 m length of the human GI tract. Stage B depicts the hypothetical early CNS disease phase. Alpha-synuclein seeds have now spread retrogradely through autonomic nerves and Lewy pathology is now detectable in the DMV and in sympathetic ganglia (not shown). Since the first Lewy pathology in the ENS is always in close proximity to parasympathetic terminals, or indeed may have arisen inside those very terminals, the CNS phase may materialize simultaneously with or only days-to-weeks after the gut-only phase. The temporal window for detection of gut-only pathology might, therefore, be extremely narrow or even non-existent. Stage C depicts later disease stages. A rostral-caudal gradient of Lewy pathology, mirroring vagal innervation density, is now evident in the GI tract (Beach et al. 2010; Gelpi et al. 2014; Wakabayashi et al. 1988). The most parsimonious explanation for the appearance of this pattern is secondary anterograde DMV-to-gut propagation of pathology. In short, neurons inside the DMV nucleus could easily infect the neighboring DMV neurons. Subsequent anterograde spreading of alpha-synuclein seeds would then lead to ENS Lewy pathology mirroring the pattern of vagal innervation

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Parkinson's Disease Is Not Simply a Prion Disorder

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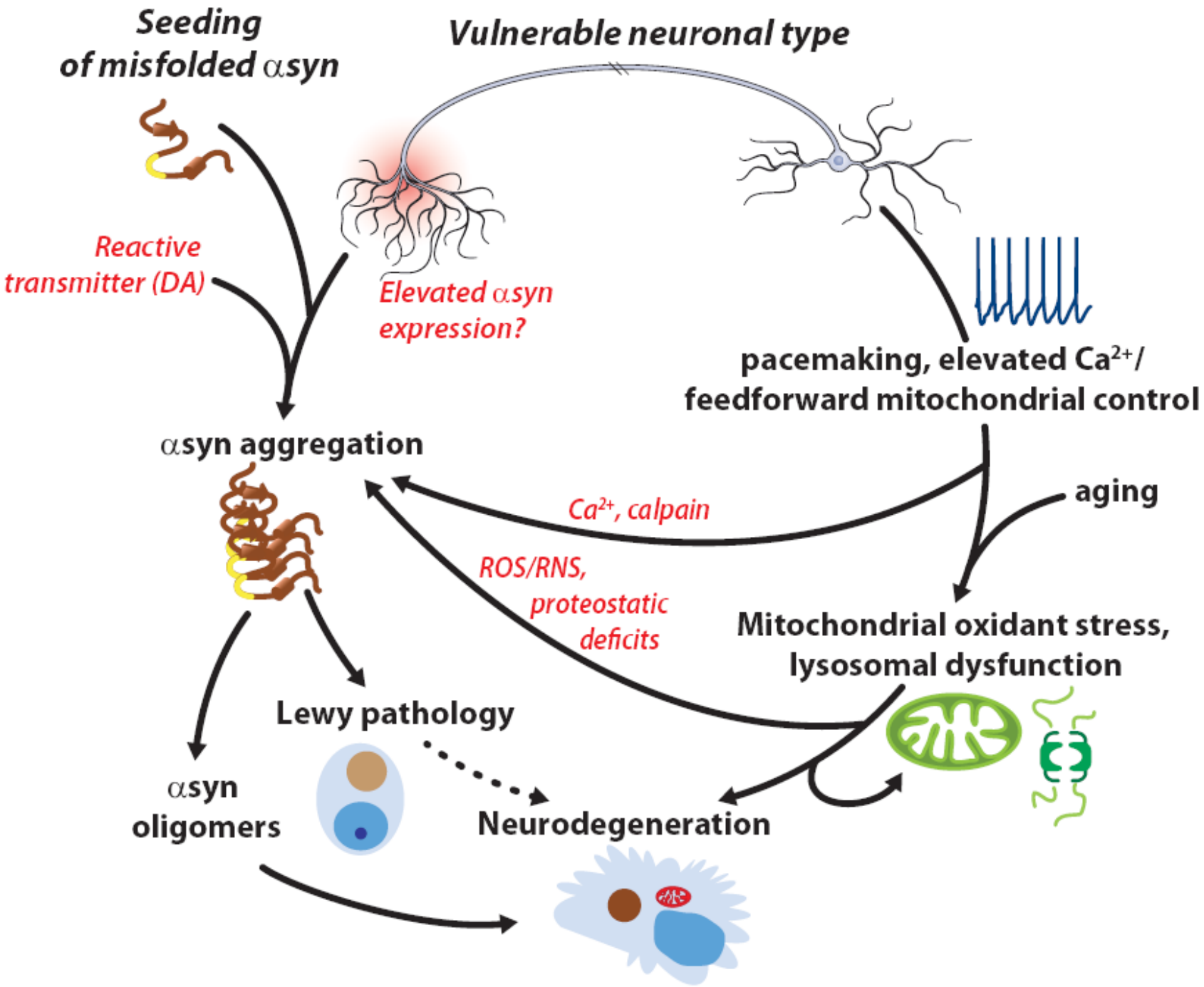
Seeding of misfolded αsyn
Vulnerable neuronal type
Reactive transmitter (DA)
Elevated αsyn expression?
pacemaking, elevated Ca2+/ feedforward mitochondrial control
αsyn aggregation
aging
Ca2+, calpain
ROS/RNS, proteostatic deficits
Mitochondrial oxidant stress, lysosomal dysfunction
Lewy pathology
αsyn oligomers
Neurodegeneration

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Prying into the Prion Hypothesis for Parkinson's Disease

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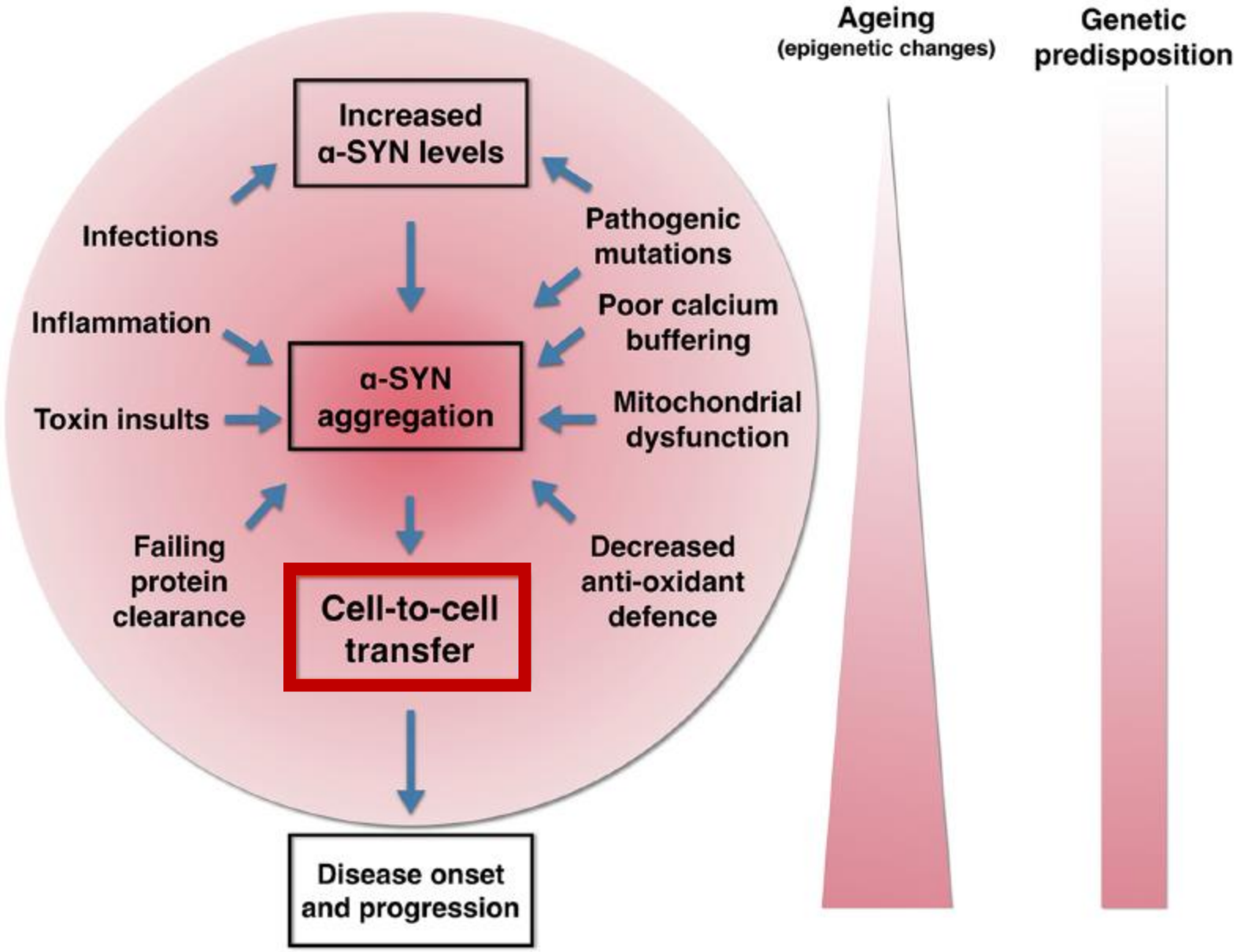

Figure 2. Schematic diagram depicting a possible central cascade leading to cell-to-cell transfer of α-SYN. The central process is likely affected by several other disease mechanisms that have already been implicated in PD (shown inside the circle) and that form an interdependent network of molecular events, which in combination or each on their own can promote the central cascade. Weak genetic risk factors and aging are depicted as potential triggers or promoters of cell-to-cell transfer of α-SYN (for details of the different mechanisms, see text).

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REVIEW

The concept of alpha-synuclein as a prion-like protein: ten years after

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Abstract

Parkinson's disease is characterized by the loss of nigrostriatal dopaminergic signaling and the presence of alpha-synuclein aggregates (also called Lewy bodies and neurites) throughout the brain. In 2003, Braak and colleagues created a staging system for Parkinson's disease describing the connection between the alpha-synuclein pathology and disease severity. Later, they suggested that the pathology might initially be triggered by exogenous insults targeting the gut and olfactory system. In 2008, we and other groups documented Lewy pathology in grafted neurons in people with Parkinson's disease who had been transplanted over a decade prior to autopsy. We proposed that the Lewy pathology in the grafted neurons was the result of permissive templating or prion-like spread of alpha-synuclein pathology from neurons in the host to those in the grafts. During the following ten years, several studies described the transmission of alpha-synuclein pathology between neurons, both in cell culture and in experimental animals. Recent research has also begun to identify underlying molecular mechanisms. Collectively, these experimental studies tentatively support the idea that the progression from one Braak stage to the next is the consequence of prion-like propagation of Lewy pathology. However, definitive proof that intercellular propagation of alpha-synuclein pathology occurs in Parkinson's disease cases has proven difficult to secure. In this review, we highlight several open questions that currently prevent us from concluding with certainty that prion-like transfer of alpha-synuclein contributes to the progression of Parkinson's disease.

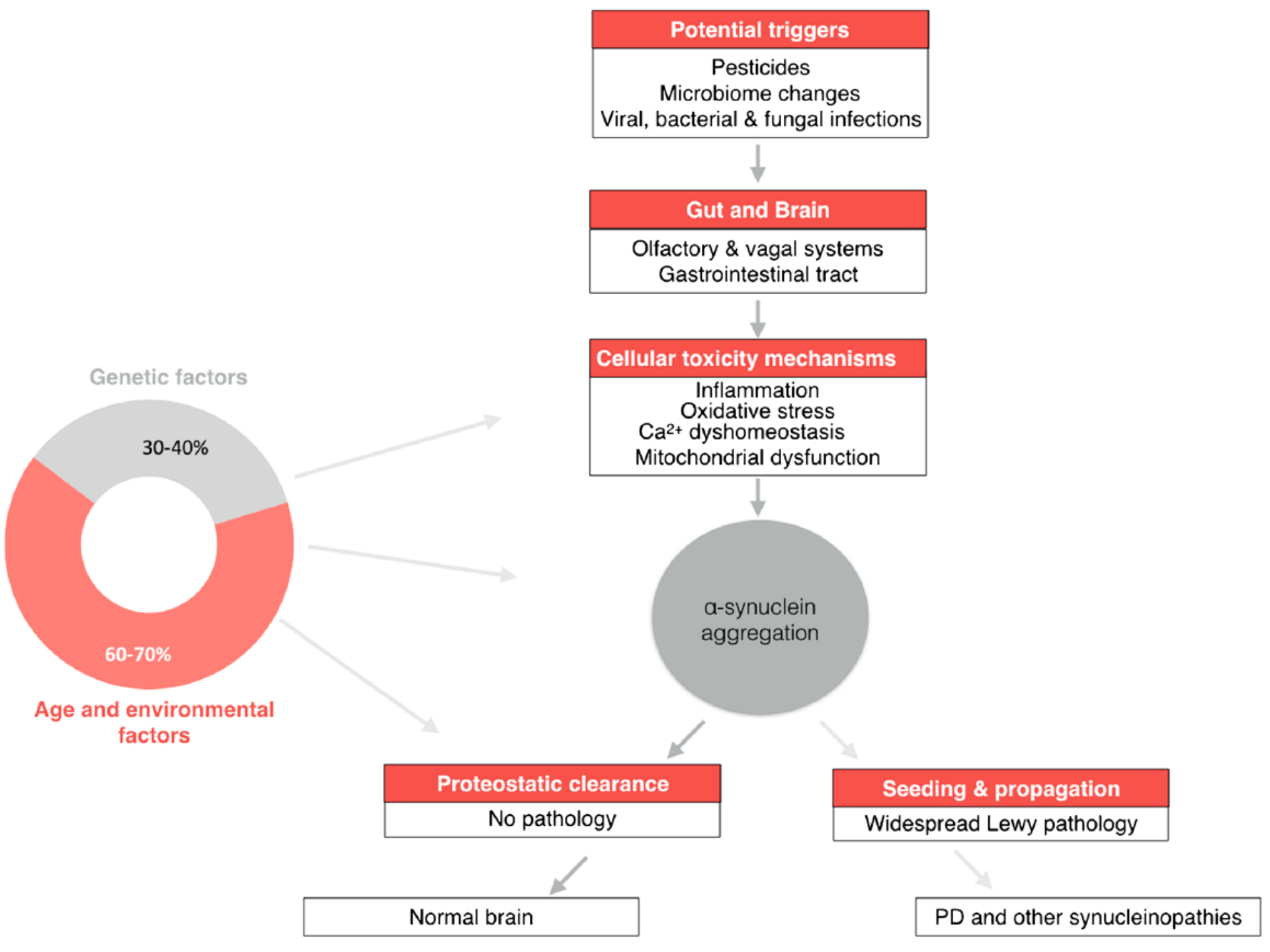
Potential triggers
Pesticides
Microbiome changes
Viral, bacterial & fungal infections
Gut and Brain
Olfactory & vagal systems
Gastrointestinal tract
Cellular toxicity mechanisms
Inflammation
Oxidative stress
Ca2+ dyshomeostasis
Mitochondrial dysfunction
Genetic factors
30-40%
60-70%
Age and environmental factors
α-synuclein aggregation
Proteostatic clearance
No pathology
Seeding & propagation
Widespread Lewy pathology
Normal brain
PD and other synucleinopathies

Fig. 1 Mechanisms of α-syn aggregation and propagation. Legend: (Left) Schematic showing presumed contributions of different factors to the development of Parkinson's disease and demonstrating how they influence various pieces of the pathway to Lewy pathology (Keller et al. 2012). (Right) Schematic of development of Lewy pathology by step-wise progression from potential triggers, proposed entry sites and mechanisms that may promote α-syn aggregation to the resultant effects of such aggregation. In a more likely scenario, the system can use proteostatic clearance successfully to remove aggregates. However, when proteostatic clearance is impaired and α-syn aggregation and accumulation proceeds unchecked, the initial aggregates may be transferred in a "prion-like" manner and may seed further aggregation, resulting in widespread Lewy pathology that contributes to the development of PD and other synucleinopathies