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A Mechanistic Overview of the Cellular Pathology and Prion-Like Propagation of α-Synuclein in Parkinson's Disease: A Narrative Review

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Abstract

Introduction: Prions are quaternary protein complexes made up of misfolded protein isoforms (PrP^{Sc}) that are able to aggregate and self-replicate in the absence of nucleic acids. They do this by incorporating and inducing the misfolding of normally-folded protein isoforms (PrP^{C}) in a template-directed fashion, before fragmenting and continuing to propagate at increasingly greater concentrations in cells. Parkinson's disease (PD) is a disease affecting the central nervous system (CNS), primarily characterised by a marked loss of dopaminergic neurons from the pars compacta of the substantia nigra in the midbrain (snPC). Lewy bodies (LBs) and Lewy neurites (LNs) are protein inclusions made primarily of the protein α-synuclein (α-Syn) and are implicated in defective neural signalling and neuronal cell death in PD. LBs/LNs have been hypothesised to cause symptoms of PD via propagation throughout the CNS in a prion-like mechanism.

Methods: A narrative literature review was conducted to synthesise current and past research surrounding the prion-like propagation of α-Syn in PD, and models connecting cellular pathology to pathophysiology. Results were critically analysed and implications were determined.

Results: α-Syn is a conformationally flexible protein normally involved in presynaptic regulation and dopamine homeostasis. In PD, α-Syn takes on a pathogenic, β-sheet rich conformation resulting from random cellular events or inoculation, that acts in a prion-like manner, inducing the misfolding of normal protein isoforms. Pathogenic α-Syn is propagated between neurons via exosomal secretion and leads to neurotoxicity by loss-of-function causing disruption of dopamine homeostasis, and proteasomal saturation and inhibition. Due to prion-like propagation, and differential susceptibility of neurons to pathogenic α-Syn-mediated neurotoxicity, models of PD progression and symptomatology have been suggested with differing degrees of success.

Discussion: This narrative review aims to build on previous knowledge by clearly describing and evaluating the mechanisms of prion-like propagation and neurotoxicity of pathogenic α-Syn in PD, comparing them to traditional prion mechanisms observed for PrP^{Sc}, and models of PD which connect cellular pathology with pathophysiology.

Conclusion: This review provides insight into the cellular mechanisms behind PD and can be used to propel research in this areas via identification of future areas of inquiry and pharmacological targets, among others.

Keywords: prions; Parkinson's disease; prionopathies; α-synuclein; α-synucleinopathies; Lewy bodies; Lewy neurites; protein aggregation

Introduction

Prions (**Pr**oteinaceous **i**nfectious **on**ly particles) are quaternary protein complexes made up of misfolded protein isoforms that are able to aggregate and self-replicate in the absence of nucleic acids [1,2]. Prions were first identified as infectious agents in the 1980s in the study of rare fatal neurodegenerative diseases known as the transmissible spongiform encephalopathies (TSEs) [2]. These include Creutzfeldt–Jakob disease (CJD), kuru, scrapie (affecting sheep and goats), and bovine spongiform encephalopathy (BSE, affecting cattle) [2]. Prions were originally thought to be a part of an abnormal class of 'slow viruses', until it was found that they were resistant to heat and treatment with formaldehyde, which are both known to inactivate most viruses [3,4]. Further research indicated that treatment with both ionising radiation and UV light irradiation (nucleic acid damaging agents) also had little effect, prompting the proposal that TSEs such as scrapie were mediated by a self-replicating protein [5,6]. The term 'prion' was coined by Stanley Prusiner in 1982 as a part of his work studying the proteinaceous scrapie agent; work for which he later received a Nobel prize [7,8].

The prion protein (PrP) is a membrane-bound surface receptor implicated in cell survival and is the protein agent involved in the transmission of TSEs (see **Figure 1**) [1,9]. PrP is thought to mediate this survival function via the

interaction with a ligand on the cell surface (LPrP) which transduces anti-apoptotic signals [9]. PrP can exist in both normal and pathogenic conformations, both of which are thermodynamically stable [1]. Prions are initially formed via random cellular events, such as the mutation of the DNA encoding PrP, or less commonly, through contact with an infectious inoculum [10]. The normal, cellular conformation of PrP (PrP^{C}) has a secondary structure rich in α-helices, while the secondary structure of the pathogenic, scrapie conformation of PrP (PrP^{Sc}) is rich in β-sheets [11]. Thus, both conformations have vastly different properties, with the β-sheets found in PrP^{Sc} conferring the protein with unique properties classic to prions, such as decreased solubility in detergents, and resistance to digestion by proteases [1]. It is important to note that prions such as PrP^{Sc} can exist in many different strains, differing by as little as a single amino acid substitution, yet yielding distinctive conformations, phenotypes, nervous distributions, and clinical manifestations [2,12]. Newly introduced PrP^{Sc} exists as small soluble oligomers, which are able to incorporate both PrP^{Sc}, and PrP^{C}, causing a template-directed conformational change in the latter, leading to the formation of new PrP^{Sc} isoforms [2]. PrP^{Sc} oligomers further recombine to form large, insoluble, amyloid-like protein fibrils known as scrapie associated fibrils (SAFs) [13]. PrP^{Sc} may also be N-terminally truncated via proteinase K (PK), to form PrP 27-30, a β-sheet rich derivative that retains infectivity, and whose oligomers are able to self-assemble into distinct amyloid-like fibrils known as prion rods [11,13,14]. SAFs and prion rods can then fragment back into oligomers leading to further prion propagation in the cell ('seeding') [1,2,14]. Infective prion 'seeds' are then able to propagate between cells via the random partitioning of parent cellular proteins between daughter cells during mitosis in previously affected cells, and/or extracellular secretion and uptake (e.g. in cells that are unable to divide) [2]. PrP^{Sc} oligomers are thought to be secreted for uptake by neighbouring cells via exosomes, which are the secreted intraluminal contents of multivesicular bodies (MVBs) originally bound for lysosomal degradation [15]. This is mediated by a calcium-dependent, endoplasmic reticulum (ER)/Golgi-independent pathway [15]. Due to the ability of prions to self-replicate and partition into daughter cells, prion propagation can be considered a unique type of genetic inheritance modulated by the tertiary and quaternary structures of implicated proteins [2].

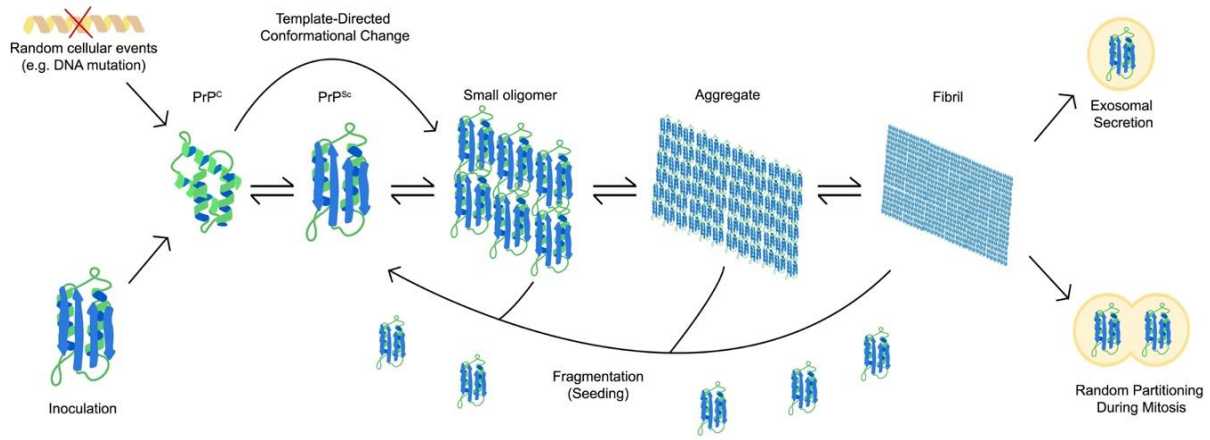

Figure 1. Mechanisms of prion formation, aggregation, and spread. Random cellular events (such as DNA mutation) and/or inoculation with pathogenic PrP^{Sc} can induce normal cellular PrP^{C} to adopt a pathogenic conformation. Pathogenic PrP^{Sc} can then form oligomers which can aggregate with other PrP, inducing template-directed conformational changes to generate further PrP^{Sc} and fragment creating new 'seeds' for further pathogenic PrP^{Sc} formation. Once formed, pathogenic PrP^{Sc} can reach other cells through exosomal secretion, and/or random partitioning of proteins between daughter cells during mitosis (in cells that divide) (illustrated using Adobe Illustrator).

PrP^{Sc} accumulation can be highly neurotoxic, leading to the neurodegeneration characteristic of the TSEs [9,16]. The neurotoxicity of PrP^{Sc} has been found to be a result of the confluence of several factors [9]. Neurotoxicity primarily results from subfibrillar PrP^{Sc} oligomers, with large amyloid-like fibrils likely serving as neuroprotective reservoirs for toxic subfibrillar oligomeric species as they accumulate in neurons [9,16]. PrP^{Sc} oligomers are also able to bind and saturate LPrP but are unable to mediate the normal survival function resulting in cell lethality through the loss of function of this pathway [9]. Additionally, once higher oligomer concentrations are reached, apoptotic signals result from the saturation of proteasomal, and other degradative pathways [9,17]. The hydrophobic region of PrP 106-126 (an internal peptide of PrP from residues 106-126 that serves as a model for pathogenic PrP^{Sc} oligomers) oligomers also interacts abnormally with the mitochondria, leading to the release of

cytochrome *c* (cyt *c*) and induction of apoptotic signalling [18,19].

Since the characterisation of the replicative and neurotoxic mechanisms used by PrP^{Sc} in causing the TSEs, there has been growing evidence that many other neurodegenerative conditions, collectively termed prionopathies, follow similar prion-like mechanisms [20,21]. A variety of proteins implicated in a diverse cluster of neurodegenerative diseases are thought to propagate in this way (see **Table 1**).

Table 1. Some neurodegenerative diseases thought to be prionopathies [1,13,20,21]

Neurodegenerative Disease	Implicated Protein	Amyloid-like Fibrils Formed	Location of Deposition
Transmissible spongiform encephalopathies (TSEs)	Prion protein (PrP)	Scrapie associated fibrils (SAFs), prion rods	Extracellular
Alzheimer's disease (AD)	β-Amyloid peptide (Aβ)	Amyloid plaques	Extracellular
Parkinson's disease (PD)	α-Synuclein (α-Syn)	Lewy bodies (LBs), Lewy neurites (LNs)	Intracellular
Frontotemporal lobar degeneration (FTLD)	Tau (τ)	Neurofibrillary tangles (NFTs)	Intracellular
Amyotrophic lateral sclerosis (ALS)	Superoxide dismutase 1 (SOD1)	Inclusion bodies	Intracellular
Huntington's disease (HD)	Huntingtin (Htt)	Inclusion bodies	Intracellular

Parkinson's disease (PD) is the fastest growing globally prevalent neurodegenerative disorder [22]. PD affects many different parts of the central nervous system (CNS) and is thus marked by a variety of motor and non-motor symptoms, most notably bradykinesia, rigidity, and resting tremor, resulting from a pronounced loss of dopaminergic neurons from the pars compacta of the substantia nigra (snPC) in the midbrain [23]. PD is thought to be a prionopathy, characterised by intracellular inclusions known as Lewy bodies (LBs), and Lewy neurites (LNs), made up primarily of the protein α-synuclein (α-Syn) [23,24]. This review aims to analyse and synthesise current and past research surrounding the mechanism of prion-like propagation of α-Syn in the formation of LBs/LNs in PD, and the resulting cytotoxic effects of these inclusions. LBs/LNs may propagate in a predictable pattern, leading to an observed spatiotemporal pattern of disease progression [25]. The affected regions of the CNS and resulting symptomatologies as the disease progresses will thus also be reviewed and linked to the prion-like nature of α-Syn in PD.

Methods

Preliminary research was conducted to identify important topics related to prions, PD and its prion-like propagation mechanism, determine the state of current literature, and identify gaps in knowledge. Relevant sources were identified through academic databases, including PubMed and Google Scholar, using keywords such as 'prions', 'α-synuclein', 'prionopathies', and 'Parkinson's disease' to identify research in these preliminary areas and previously conducted literature reviews. English language papers were selected using the following criteria:

1. *Title must be relevant to topic*- The title of the identified sources must appear relevant to the search performed and the topics being explored.
2. *Abstract and main body text must contain content that is relevant to the review*- Once some relevant sources were selected via examination of the title, the contents of the abstract and main body text were used to determine if the source was relevant and useful to this review.

Using these criteria, relevant literature was identified, allowing for deeper exploration of the topic. Other sources were drawn directly from citations in previously identified literature, using the same selection criteria described above, as needed. Further research was conducted in a similar manner, so as to examine the specific cellular pathology, and pathophysiology of PD as it relates to the prion-like mechanism of the disorder. Specific questions that arose during the research process were addressed via additional searches, where no information was available in previously identified literature. Results were critically analysed, and implications were determined.

Results

α-Syn is a 140-amino acid protein encoded by the *SNCA* gene, that was first identified in 1988 in the nervous tissues of the pacific electric ray (*Torpedo californica*) [26,27]. In this study, α-Syn was found to be localised to neuronal presynaptic terminals and specific regions of the nuclear envelope, via immunohistochemistry, hence the name of the protein [26]. However, this is a misnomer, as nuclear localisation of α-Syn was likely a result of antibody contamination in the study in which it was first identified and was not demonstrated in the majority of future research studies [28]. Homologues β-synuclein (formerly phosphoneuroprotein 14) and γ-synuclein (formerly BCSGC1/persyn) were characterised soon after, however α-Syn soon returned to the forefront of investigation following a genetic study implicating it in neurodegenerative diseases such as PD [27,29–33].

All synucleins possess a conserved, amphipathic N-terminal domain (residues 1–67), containing one of two amino acid sequences characteristic of fatty acid binding proteins (FABPs), and an 11-amino acid consensus sequence (XKTKEGVXXXX) repeated seven times in α- and γ-synuclein, and six times in β-synuclein [34–36]. α-Syn also possesses a middle hydrophobic region identified in amyloid plaques in AD, and highly involved in fibril formation, known as the non-Aβ component of plaque (NACP) domain (residues 61–95) [34,37,38]. Finally, α-Syn possesses a C-terminal domain (residues 96–140) rich in Pro, Glu and Asp, involved in the chaperone-like activity of the protein, and containing another FABP-like region [34,35,39]. α-Syn is natively unfolded and exists as a random monomeric coil in solution but can adopt stable α-helical conformations upon membrane phospholipid binding [40,41]. Membrane-bound α-Syn can then form stable native α-helical oligomers which may be essential for physiological function [42].

Under normal conditions, α-Syn has a variety of functions in the presynaptic terminal [28,34]. α-Syn is able to associate with and bind membrane phospholipids, with a preference for binding vesicles of higher curvature and smaller diameter, such as the synaptic vesicles found in the terminal [26,35,41,43]. It is thus implicated in several roles related to vesicular trafficking and neurotransmission [28,34]. Phospholipases D1 and D2 are responsible for catalysis of the hydrolysis of phosphatidylcholine to produce diacylglycerol and phosphatidic acid (an important mediator in control of vesicular trafficking) [44]. α-Syn is a specific inhibitor of phospholipases D1 and D2 *in vitro* and *in vivo*, and thus may be involved in regulation of vesicular trafficking via this mechanism [44,45]. Native α-Syn oligomers also act as a molecular chaperone and are able to bind to the soluble N-ethylmaleimide-sensitive factor attachment receptor (SNARE) protein, vesicle-associated membrane protein 2 (VAMP2) and promote SNARE-complex assembly, along with the cochaperone, cysteine string protein α (CSPα) [42,46,47]. However, native α-Syn oligomers predominantly hinder neurotransmission by regulating neurotransmitter pools via direct (phospholipid) and indirect (VAMP2) binding to synaptic vesicles, clustering the vesicles and inhibiting motility and docking [48,49]. Upon nervous stimulation, α-Syn oligomer clusters disperse from synaptic vesicles, allowing vesicles to dock and exocytose into the synaptic cleft [49,50]. α-Syn has also been shown to associate and interact with other organelles such as the nucleus, mitochondria, ER, and Golgi apparatus, however the physiological significance of these interactions is unclear considering the localisation of α-Syn to the presynaptic terminals [28,51–53].

α-Syn also plays important roles in dopamine-specific pathways [28,34]. α-Syn has been shown to block dopamine biosynthesis through inhibition of tyrosine hydroxylase (TH) expression and activity [54,55]. α-Syn also modulates vesicular monoamine transporter 2 (VMAT2), a transport protein found on synaptic vesicles responsible for dopamine storage and homeostasis, with α-Syn knockouts leading to decreased number of vesicles, but increased vesicular density of VMAT2, and overexpression inhibiting VMAT2 activity [56,57]. α-Syn has furthermore been shown to modulate the dopamine transporter (DAT), responsible for dopamine reuptake in the synapse, increasing DAT insertion into the presynaptic membrane, but also modifying its activity [56,58,59].

In PD, α-Syn monomers take on a β-sheet rich secondary structure and aggregate in amyloid-like fibrils making up intracellular LBs (in somas) and LNs (in axons) [23,60]. It is thought that β-sheet rich α-Syn isoforms represent pathogenic protein conformations which follow a mechanism of prion-like propagation [61]. In accordance with a prion-like model, in PD pathogenic α-Syn may be introduced via contact with an external source of the misfolded isoform (inoculation), or as a result of random cellular events such as gene mutation, protein overexpression, and post- translational modification (PTM) [2]. Inoculation with pathogenic α-Syn (synthetic or from aggregate-containing brain lysates) has been shown to lead to similar PD-like patterns of LB/LN aggregation and neurotoxicity *in vitro* and *in vivo* (in animal models) [62,63].

Random cellular events can also lead to increased α-Syn aggregation. In fact, shifting the structure of α-Syn to an unfolded/partially folded state may be sufficient to induce a pathogenic conformation and seed aggregate formation [64]. Given that α-Syn is natively unfolded, this may proceed through several distinct mechanisms [40]. It has been shown that membrane binding (mediated by the FAPB-like regions of the C- and N-termini) is important in preventing α-Syn aggregation [35,60]. Interactions between the C-terminal and the N-terminal or the NACP region are also important in maintaining the natively unfolded structure of α-Syn, and consequently these regions may be further involved in pathogenicity [65]. Thus, various mutations in the *SNCA* gene leading to single amino acid substitutions in α-Syn have been shown to stabilise the pathogenic, β-sheet rich

conformation of the protein, leading to increased LB/LN aggregation [66]. Mutations in genes for other proteins apart from α-Syn have also been linked to PD, likely enhancing α-Syn aggregation or neurotoxicity via modulation of downstream protein interactions [67]. Proteolytically modified, C-and N-terminally truncated versions of α-Syn are also present in the brains of healthy individuals and PD patients and are shown to have increased propensities for aggregation [68]. Overexpression of α-Syn through gene duplication and triplication, or polymorphism in the regulatory REP1-SNCA microsatellite also induces increased LB/LN aggregation [69–71]. This likely occurs because an increase in concentration of α-Syn modulates the equilibrium between native and pathogenic protein conformations [64]. Post-translational modification of α-Syn, including phosphorylation, ubiquitination, acetylation, *O*-glycosylation, and nitration, have also been demonstrated and shown to modify levels of LB/LN aggregation as well, however many of these PTM likely represent rare events, and as such their physiological significance remains unclear [28,72–76]. Exogenous compounds such as the pesticides rotenone, dieldrin, and paraquat can also lead to α-Syn aggregation, likely by modulating the above pathways [77].

Pathogenic α-Syn is thought to seed and spread between neurons via secretion using unconventional ER/Golgi-independent exocytosis pathways, and uptake by neighbouring neurons and microglia [78,79]. Initially thought to be an exclusively intracellular protein, pathogenic α-Syn has since been identified in extracellular fluids such as plasma and cerebrospinal fluid (CSF), and constitutive secretion and uptake of α-Syn has been demonstrated in several cell lines [78,80,81]. α-Syn secretion has also been found to be calcium-dependent, and is thought to be mediated by exosomes, similarly to PrP^{Sc} [15,78]. Following secretion, α-Syn is degraded in the extracellular space by matrix metalloproteases, and/or taken up into neighbouring cells via endocytosis, and/or cellular translocation, leading to the prion-like spread of α-Syn between neighbouring cells [82–84]. In fact, the prion-like propagation of PD was first hypothesised as a result of post-mortem studies of patients who had received fetal mesencephalic intrastriatal transplants to treat PD, which showed that the grafted neurons developed LBs/LNs that were virtually identical to those in the PD-afflicted brain [28,85].

Once formed, LBs/LNs cause neurotoxicity via disruption of normal α-Syn function combined with activation of other prion-like apoptotic pathways (See **Figure 2**) [59]. It is thought that subfibrillar pathogenic α-Syn oligomers are the most neurotoxic species, while LBs/LNs act as neuroprotective reservoirs for toxic subfibrillar oligomeric species as they accumulate [34,86]. α-Syn aggregation leads to loss of function resulting in increased cytosolic dopamine levels via disinhibition of TH, reduction of number of dopamine-containing vesicles, increased levels/activity of VMAT and DAT, and dysregulation of vesicular trafficking [49,54,55,57–59]. Cytosolic dopamine auto-oxidises to produce reactive oxygen species (ROS) as well as the highly reactive and neurotoxic dopamine quinone, contributing significantly to α-Syn aggregate-mediated neurotoxicity [87]. Dopamine-associated neurotoxicity resulting from α-Syn aggregation could even go so far as to explain the differential susceptibility to PD of neurons which use dissimilar neurotransmitters [59]. Once higher oligomer concentrations are reached, further apoptotic signals result from the saturation of proteasomal, and other degradative pathways [88]. α-Syn oligomers also interact abnormally with the mitochondria, leading to the release of cyt *c* and induction of apoptotic signalling [89].

α-Syn aggregation in LBs/LNs and associated neurotoxicity are also hallmarks of many other neurodegenerative disorders also thought to spread via prion-like propagation, collectively termed the α-synucleinopathies, including dementia with Lewy bodies (DLB), and multiple system atrophy (MSA) [61]. While the α-synucleinopathies share some symptomatology, they are distinct conditions marked by unique deficits and patterns of progression [90]. The prion strain of α-Syn found in LBs/LNs is thought to determine which α-synucleinopathy presents, and it's resulting clinical manifestation [61].

Due to the prion-like propagation of pathogenic α-Syn strains between neighbouring cells, and differential susceptibility to pathogenic α-Syn-mediated neurotoxicity, LBs/LNs move along predominantly unmyelinated axons, and may follow a distinct spatiotemporal pattern of disease progression (See **Figure 3**) [25]. The *Braak et al.* staging scheme describes α-Syn pathology initially developing in the peripheral mucosa, allowing simultaneous spread to the olfactory bulb and enteric nervous system (ENS)- the 'dual-hit' hypothesis [25,91,9]. From the olfactory bulb pathology spreads to the anterior olfactory nucleus (AON) into the olfactory structures of the temporal lobe, leading to loss of smell characteristic of early-stage PD [25,92,93]. Simultaneously, pathology spreads from the ENS to the dorsal motor nucleus of the vagal nerve (dmX) [25,92]. Pathology in the ENS likely leads to gastrointestinal problems, which have been observed prior to motor dysfunction in PD [94]. From dmX, lesions progress through the level-setting nuclei of the lower brainstem, and other regional nuclei including the coeruleus–subcoeruleus complex, leading to sleep-wake disturbances, movement problems, lowered blood pressure, constipation, and/or emotional disorders [25,93]. From here pathology progresses to the midbrain, including the snPC and the central subnucleus of the amygdala, triggering thermoregulation disorder, and/or cognitive impairment [25,93]. As lesions continue to invade the amygdala and cerebral cortex, traditional symptoms such as bradykinesia, resting tremor, rigidity, and postural instability, begin to manifest [25,93].

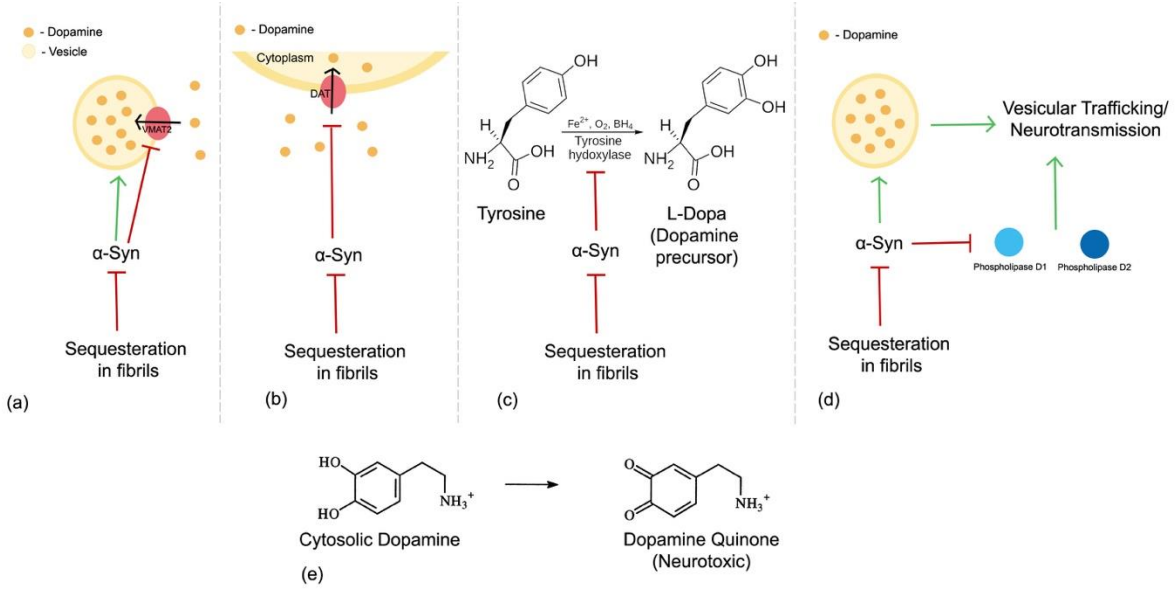

Figure 2. Loss-of-function mechanisms of pathogenic α-Syn mediated neurotoxicity. In PD, pathogenic α-Syn is no longer able to perform its normal cellular functions leading to increased cytosolic dopamine via (a) changes in interactions with dopamine transport vesicles and VMAT2, (b) changes in interactions with DAT in the presynaptic membrane, (c) disinhibition of TH leading to increased dopamine biosynthesis, and (d) issues with vesicular trafficking/neurotransmission both directly (via excitation decoupling) and indirectly (via disinhibition of phospholipases D1 and D2). Increases in cytosolic dopamine promote dopamine autoxidation to neurotoxic dopamine quinone (e). Note that other mechanisms of neurotoxicity associated with prions themselves also occur, but are not shown (e.g., proteasomal saturation) (illustrated using Adobe Illustrator).

As the deep layers of the neocortex are affected in the late stages of the disease, motion fluctuations, frequent fatigue, visual hallucination, dementia, and psychiatric symptoms present [25,93].

This staging scheme has had several criticisms, as it fails to account for conflicting reports of PD spread and relies on the 'dual-hit' hypothesis which incorrectly assumes PD is exclusively caused by some neurotropic pathogen [91,95,96]. In fact, as many as 43% of cases may fail to align with the ascending *Braak et al.* model [97]. This model fails to account for cases demonstrating considerable Lewy pathology and cell death, yet few reported neuropsychiatric cognitive deficits, and cases in which LB/LN progression is limited to the olfactory bulb or bypasses the brainstem (at least initially) [96,97], The functional threshold theory may resolve inconsistencies with this staging scheme, stating that symptom presentation occurs once a brain region reaches its functional threshold of inclusions, which is distinct depending on the region [98]. This model better accounts for different sources of pathological α-Syn (mutation, inoculation, etc.), and explains both anterograde and retrograde spread of pathology, which has been suggested by past work [98,99].

Discussion

There are clearly many similarities between prion propagation in the TSEs, and propagation of α-Syn in PD. Both PrP and α-Syn are able to adopt pathogenic β-sheet rich conformations, which mediate template-directed conformational changes in healthy proteins, and thus may be introduced via random cellular events, or through inoculation. PrP^{Sc} and pathogenic α-Syn are also both seeded and propagated between cells via exosomal secretion followed by uptake into neighbouring cells. Even elements of neurotoxicity are similar between proteins, with toxicity mediated by pathogenic oligomers, resulting in loss of protein function, and proteasomal saturation and inhibition, with formation of aggregates that likely act as neuroprotective reservoirs for subfibrillar oligomeric species. These similarities are striking, and exploring them further, along with the other prionopathies, may be of immense value in developing broad-spectrum anti-prion agents.

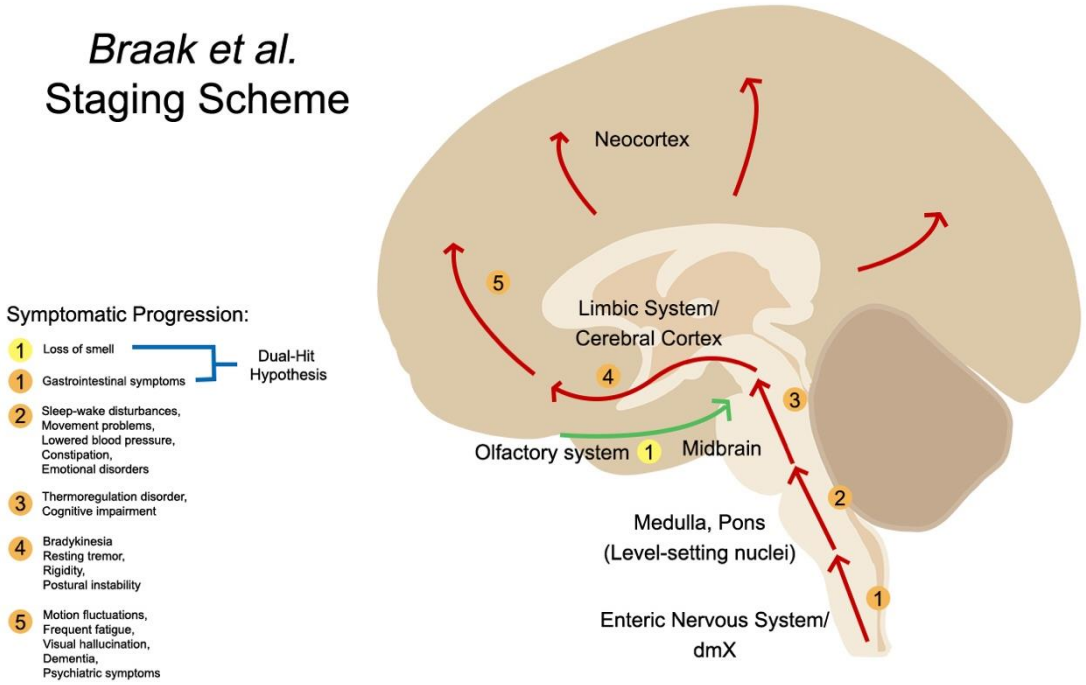

Figure 3. Overview of *Braak et al.* staging scheme for LB/LN spatiotemporal disease progression in PD, and associated symptoms (illustrated using Adobe Illustrator).

However, despite these similarities, α-Syn propagation does have several distinct differences, relating to the structure and function of the protein. One unique element of α-Syn propagation relative to PrP is it's increased conformational flexibility. Given that the protein is natively unfolded, and secondary structure is heavily dependent on small fluctuations in its cellular environment, α-Syn may be induced into a pathogenic conformation much more easily than PrP. This may be why so many distinct random cellular events can lead to α-Syn aggregation, over PrP^{Sc}, potentially even explaining the epidemiology of the diseases on a global scale. Another significant difference is in the loss-of-function mechanism of neurotoxicity mediated by pathogenic α-Syn aggregates. Since a major component of pathogenic α-Syn-mediated neurotoxicity lies in an increase in cytosolic dopamine resulting from dysregulation of dopamine biosynthesis and transport, several entirely separate pathways that may be influenced by unrelated cellular events are suddenly implicated. This adds an additional layer of complexity to the pathway and may be a potential target for PD-specific therapeutics.

Since such tiny fluctuations can drastically influence pathogenicity and so many pathways are implicated in neurotoxicity, there is an increased need for the mapping of α-Syn's true cellular fate *in vivo*. Many past lines of research implicate specific events and modifications in α-Syn pathogenicity and neurotoxicity, however without knowledge of α-Syn's true fate *in vivo*, there may be little significance to such research.

Connecting cellular pathology to pathophysiology has also been challenges in PD research. While *Braak et al.*'s staging scheme has had some success at describing PD progression and symptomatology based on the presupposition that pathology spreads in a predictable (prion-like) manner, it may not be entirely accurate, as it fails to explain various clinical observations previously mentioned and does not account for differential susceptibility to neurotoxicity mediated by pathogenic α-Syn lesions. The functional threshold theory does resolve some of these criticisms, but it could also be expanded on by further inquiry into how α-Syn cellular pathology influences specific neural circuits affected in PD.

Conclusions

α-Syn is a conformationally mobile protein that is involved in synaptic regulation and dopamine homeostasis. In PD, α-Syn adopts a pathogenic conformation as a result of random cellular events or inoculation, leading to β-sheet rich aggregates comprising LBs/LNs. Pathogenic α-Syn spreads intra- and extracellularly via mechanism of prion-like propagation, similar to the propagation of PrP^{Sc} in the TSEs, and leads to neurotoxicity via loss-of-function causing cytosolic dopamine accumulation, combined with proteasomal saturation and inhibition. Due to its prion-like propagation, and differential susceptibility to pathogenic α-Syn-mediated neurotoxicity, LBs/LNs may follow a distinct spatiotemporal pattern of disease progression, which has

been modelled. This information may be used to better understand PD cellular pathology and pathophysiology, and implicated pathways may be valuable targets for new broad-spectrum anti-prion, or PD-specific therapeutics. Future work should focus on mapping α-Syn's true cellular fate *in vivo*, and better connecting cellular pathology to pathophysiology via closer examination of prion-like pathways, prion strains, differential susceptibility in neurons, and specific neural circuits affected in PD. The specific mechanisms behind prion-like template-directed conformational change should also be further analysed and connected to the β-sheet rich structures required for this process.

List of Abbreviations Used
Prions: proteinaceous infectious only particles
TSE: transmissible spongiform encephalopathy
CJD: Creutzfeldt–Jakob disease
BSE: bovine spongiform encephalopathy
PrP: prion protein
LPrP: ligand bound by PrP
PrP^{C}: cellular isoform of PrP (normal)
PrP^{Sc}: scrapie isoform of PrP (pathogenic)
SAF: scrapie associated fibril
MVB: multivesicular body
ER: endoplasmic reticulum
cyt *c*: cytochrome *c*
PK: proteinase K
AD: Alzheimer's disease
Aβ: β-amyloid peptide
PD: Parkinson's disease
α-Syn: α-synuclein
LB: Lewy body
LN: Lewy neurite
FTLD: frontotemporal lobar degeneration
T: tau
NFT: neurofibrillary tangle
ALS: amyotrophic lateral sclerosis
SOD1: superoxide dismutase 1
HD: Huntington's disease
Htt: Huntingtin
CNS: central nervous system
snPC: pars compacta of the substantia nigra
FABP: fatty acid binding protein
NACP: non-Aβ component of plaque
SNARE: soluble N-ethylmaleimide-sensitive factor attachment receptor
VAMP2: vesicle-associated membrane protein 2
CSPα: cysteine string protein α
TH: tyrosine hydroxylase
VMAT2: vesicular monoamine transporter 2
DAT: dopamine dransporter
CSF: cerebrospinal fluid
ROS: reactive oxygen species
DLB: dementia with Lewy bodies
MSA: multiple systems atrophy
ENS: enteric nervous system
AON: anterior olfactory nucleus
dmX: dorsal motor nucleus of the vagal nerve

Conflicts of Interest
The author declares that he has no conflicts of interest.

Ethics Approval and/or Participant Consent
This study did not require ethics approval and/or participant consent as no experiments were performed, and no participants were recruited for this literature review.

Authors' Contributions
RI: designed the study, drafted the manuscript, critically appraised, and revised the manuscript and gave approval of the final version to be published.

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