JOURNAL OF NEUROLOGY AND PSYCHOLOGY RESEARCH

CLINICAL STUDY Open Access

Prion-like Mechanisms in Neurodegenerative diseases: II. Parkinson's disease

Dr. Alain L. Fymat*

Professor, International Institute of Medicine & Science, California, USA.

Received date: December 03, 2025, **Accepted date:** December 09, 2025, **Published date:** December 13, 2025.

***Corresponding Author:** Dr. Alain L. Professor, International Institute of Medicine & Science, California, USA.

Abstract

After a review of Parkinson's disease and other movement disorders, this article describes the prion-like mechanisms therein, including the: 1) evidence that α-synucleinopathies are prion-like disorders; 2) mechanisms that underlie the intercellular transfer of misfolded α-synuclein; and 3) relevance to future diagnostics and therapies. It will further be shown that Parkinson's similarities to a prion disease include protein misfolding, self-propagation, spreading, and neurodegeneration whereas its dissimilarities include infectivity and the root cause of the disease. In sum, Parkinson's may not strictly be a prion disease but a prion-like disease.

Abbreviations

AD: Alzheimer's disease; ANS: Autonomic nervous system; ALS: Amyotrophic lateral sclerosis; BBB: Blood-Brain Barrier; CJD: Creutzfeldt-Jakob disease; CNS: Central Nervous System; DBS: Deep-Brain Stimulation; DLB: Dementia with Lewy Bodies; HD: Huntington's disease; HYS: Hoehn and Yahr Scale; iCJD: iatrogenic CJD; IPMDS: International Parkinson and Movements Disorder Society; LB: Lewy bodies; LN: Lewy neurites; LSVT: Lee Silverman Voice Treatment; MAO: Monoamine Oxidase; MDS-UPDRS: Movement Disorders Society-Unified Parkinson's Disease Rating Scale; MRI: Magnetic Resonance Imaging; MSA: Multiple system atrophy; NDD: Neurodegenerative disorder; NIH: (U.S.) National Institutes of Health; NINDS: (U.S.) National Institute of Neurological Disorders and Stroke; NSAID: nonsteroidal anti-inflammatory drugs; OH: Orthostatic hypotension; OS: Oxidative Stress; OT: Occupational therapy; PC: Palliative care; PD: Parkinson's disease; PDD: Parkinson's disease dementia; PSP: Progressive supranuclear palsy; QSBBND: (U.K.) Queen Square Brain Bank for Neurological Disorders; TRBG: Tremor, Rigidity, Bradykinesia, Gait and posture.

Keywords

Alzheimer's disease; Creutzfeldt-Jakob disease; Huntington's disease; Lewy body dementia; neurodegenerative diseases; multiple system atrophy; Parkinson's disease; prion diseases; prion-mimic diseases; prionopathies; progressive supranuclear palsy.

-oOo-

Nearly two centuries after the description of the cardinal motor symptoms of Parkinson's disease (PD) and more than a century after the identification of its two neuropathological hallmarks, two advances have changed the field. The first was the discovery that a mutation in the gene for the protein alpha-synuclein causes a rare form of autosomal-dominant PD, thereby identifying the genetic component of PD and explaining the presence of pathological alpha-synuclein-aggregations in the Lewy bodies (LB) in the substantia nigra. The second was the confluence of the Braak's staging and the "dual hit theory", positing that PD is a late-stage phenotype preceded by years, if not decades, by three prodromal stages. While testable in the clinic, it faced conflicting results; furthermore, the longtime lag required militates against its general acceptance. A recent striking theory by Prusiner and collaborators links several neurodegenerative proteinopathies, referring to the conformational change of a protein as a common disease-causing mechanism. While not generally accepted, this last theory emphasizes the "prion-like" activity of α-synuclein, which shows the ability of self-aggregation and self-cell-to-cell propagation.

In this article, after a review of Parkinson's disease and other movement disorders, I will describe: 1) the evidence that α-synucleinopathies are prion-like disorders; 2) the mechanisms that underlie the intercellular transfer of misfolded α-synuclein; and 3) the relevance to future therapies and diagnostics. (I refer to my book titled "Creutzfeldt-Jakob disease" and related articles, and article I in this series for complete information on prions, prion diseases and prion-mimic diseases.)

Parkinson's disease and other movement disorders

Introduction

Parkinson's disease (PD) is a degenerative disorder of the central nervous system (CNS) that belongs to a group of conditions called motor system (or movement) disorders (Figure 1). It is both chronic (meaning, it persists over a long period of time) and progressive (that is, its symptoms grow worse over time). The disorders are the result of the loss of dopamine-producing brain cells. As nerve cells (neurons) in parts of the brain become impaired or die, four primary symptoms appear: (1) tremor, or trembling in hands, arms, legs, jaw, and face; (2) rigidity, or stiffness of the limbs or trunk of the body; (3) bradykinesia, or slowness of movement; and (4) postural instability, or impaired balance and coordination (my acronym: TRBG, where T stands for Tremor, R for Rigidity, B for Bradykinesia, and G for Gait). As these symptoms become more pronounced, patients may have difficulty walking, talking, or completing other simple tasks. Other symptoms may include: (5) depression and other emotional changes; (6) difficulty in swallowing, chewing, and speaking; (7) urinary problems or constipation; (8) skin problems; and (9) sleep disruptions. The symptoms may begin to interfere with daily activities. However, these symptoms appear in other diseases as well so that not everyone with one or more of these symptoms has PD. Early symptoms are subtle and occur gradually. In some people, the disease progresses more quickly than in others.

Nature of the disease

PD is a long-term degenerative disorder of the CNS that mainly affects the motor system. It is a common,

disabling and currently incurable neurodegenerative condition that affects over 2% of people over the age of 75. Tremendous progress has been made in recent years in understanding better its possible causes. This has been principally driven by genetic discoveries of the genes/molecules that determine a higher risk factor for developing the disease. We now can harness these discoveries into a more complete understanding of neurodegeneration (cell death) and dysfunction in this disease and to fully characterize the common clinical traits so that PD treatment could be realized.

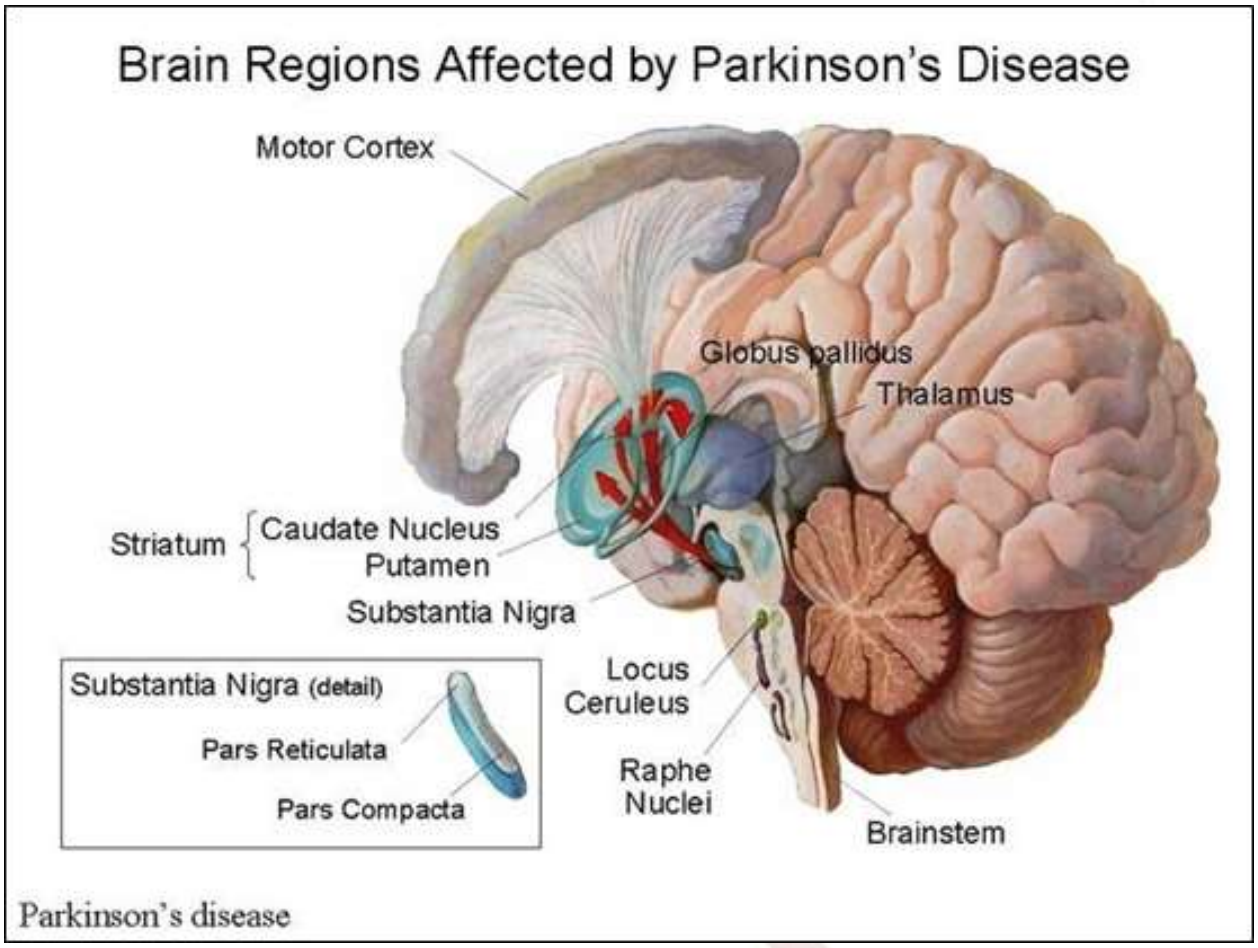

Figure 1: Illustrating the brain regions affected by Parkinson's disease

Signs and symptoms

The most recognizable symptoms in PD are movement ("motor") related. Non-motor symptoms, which include autonomic dysfunction, neuropsychiatric problems (mood, cognition, behavior or thought alterations), and sensory (especially altered sense of smell) and sleep difficulties, are also common. Some of these non-motor symptoms may be present at the time of diagnosis.

A. Motor symptoms

The motor symptoms of PD are the result of reduced dopamine production in the brain's basal ganglia. Four primary motor symptoms are considered cardinal in PD: tremor, rigidity, slowness of movement (bradykinesia, and postural instability (gait).

• **Tremor:** The most common presenting sign is a coarse slow tremor of the hand at rest, which disappears during voluntary movement of the affected arm and in the deeper stages of sleep. It typically appears in only one hand, eventually affecting both hands as the disease progresses. A feature of tremor is pill-rolling, the tendency of the index finger and thumb to touch and perform together a circular movement.

• **Bradykinesia (slowness of movement):** Found in every case of PD, it is due to disturbances in motor planning of movement initiation and associated with difficulties along the whole course of the movement process, from planning to initiation to execution of a movement. Performance of sequential and simultaneous movement is impaired.

• **Rigidity:** This is stiffness and resistance to limb movements caused by increased muscle tone, an excessive and continuous contraction of muscles. The rigidity can be uniform (“lead-pipe rigidity”) or ratchety (“cogwell rigidity”). With the progression of the disease, rigidity typically affects the whole body and reduces the ability to move.

• **Gait and postural instability:** It is typical in the later stages of the disease, leading to impaired balance and frequent falls, and secondarily to bone fractures, loss of confidence, and reduced mobility. Instability is often absent in the initial stages, especially in younger people, especially prior to the development of bilateral symptoms. Other recognized motor signs and symptoms including festination (rapid shuffling steps and a forward-flexed posture when walking with no flexed arm swing). Freezing of gait (brief arrests when the feet seem to get stuck to the floor, especially on turning or changing direction), a slurred monotonous quiet voice, mask-like facial expression, and handwriting that gets smaller are other common signs.

PD does not affect everyone the same way, and the rate of progression and the symptoms differ among individuals. Early symptoms of PD may be subtle and occur gradually. As the disease progresses, the symptoms may begin to interfere with daily activities. People with PD often develop a so-called parkinsonian gait that includes a tendency to lean forward, taking small quick steps as if hurrying (or festination), and reduced swinging in one or both arms. They may have trouble initiating movement (start hesitation), and they may stop suddenly as they walk (freezing).

Several other symptoms may accompany PD; some can be treated with medication or physical therapy. These include depression, emotional changes, difficulty with swallowing and chewing, speech changes, urinary problems or constipation, sleep problems, orthostatic hypotension, muscle cramps and dystonia, pain, fatigue and loss of energy, sexual dysfunction, hallucinations, delusions, and other psychotic symptoms.

B. Neuropsychiatric symptoms

PD can also cause neuropsychiatric disturbances, which can range from mild to severe. These include disorders of cognition, mood, behavior, and thought.

• **Cognitive disturbances:** They can occur in the early stages of the disease (sometimes prior to diagnosis) and increase in prevalence with the duration of the disease. The most common cognitive deficit in PD is executive dysfunction (which can include problems with planning), cognitive flexibility, abstract thinking, rule acquisition, inhibiting inappropriate actions, initiating appropriate actions, working memory, and control of attention. Other cognitive difficulties include slowed cognitive processing speed, impaired recall and impaired perception and estimation of time.

• **Dementia or other cognitive problems:** Some people with PD may develop memory problems and slow thinking. Cognitive problems become more severe in late stages of PD, and a diagnosis of Parkinson's disease dementia (PDD) may be given.

• **Impulse control disorders:** These include pathological gambling, compulsive sexual behavior, binge eating, compulsive shopping and reckless generosity that can be caused by medication, particularly orally active dopamine agonists.

• **Behavior and mood alterations:** The most frequent mood difficulties are depression, apathy, and anxiety

• **Punding:** Here, complicated, repetitive, aimless stereotyped behaviors occurring for many hours is another disturbance caused by anti-Parkinson medication.

• **Hallucinations or delusions:** These range from minor hallucinations – "sense of passage" (something quickly passing beside the person) or "sense of presence" (the perception of something/someone standing just to the side or behind the person) – to full blown vivid, formed visual hallucinations and paranoid ideation. Auditory hallucinations are uncommon in PD and are rarely described as voices. It is now believed that psychosis is an integral part of the disease.

In addition to neuropsychiatric and motor symptoms, PD can impair other functions:

• **Alterations in the autonomous nervous system:** They can lead to orthostatic hypotension (OH or low blood pressure upon standing), oily skin and excessive sweating, urinary incontinence, and altered sexual function. Constipation and impaired stomach emptying (gastric dysmotility) can be severe enough to cause discomfort and even endanger health. Changes in perception may include an impaired sense of smell, disturbed vision, pain, and paresthesia (tingling and numbness). All these symptoms can occur years before diagnosis of the disease.

Staging of the disease

The 1967 "Hoehn and Yahr Scale" (HYS) for the staging of PD (Table 1) and its modified version is commonly employed by neurologists:

Stage	Symptoms
1	Symptoms on one side of the body only
2	Symptoms on both sides of the body. No impairment of balance
3	Balance impairment. Mild to moderate disease. Physically independent
4	Severe disability, but still able to walk or stand unassisted
5	Wheelchair-bound or bedridden unless assisted

Table 1: The Hoehn and Yahr scale for staging Parkinson's disease

Another commonly used scale is the "Movement Disorders Society-Unified Parkinson's Disease Rating Scale" (MDS-UPDRS), which measures motor movement in PD (Table 2):

Stage	Symptoms
1	Non-motor experiences of daily living
2	Motor experiences of daily living
3	Motor examination
4	Motor complications

Table 2: The Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) for staging Parkinson's disease

Both the HYS and the MDS-UPDRS scales are used to describe how individuals are faring, and to help assess treatment response.

Classification

Disorder type	Features	Region(s) affected	Characteristics
Parkinsonism (Parkinson syndrome) or bradykinesia	Causes: • Toxins • Infections • Drugs' side effects • Metabolic derangements • Brain lesions (stroke)	Main motor systems	• Slowness in initiating movements • Progressive reduction in speed and range of repetitive actions • Muscular rigidity • Tremor at rest • Postural instability
Idiopathic parkinsonism	Most common form of parkinsonism Cause: None identifiable		
Atypical parkinsonism (Parkinson-plus syndromes)		• Multiple system atrophy • Progressive supranuclear palsy • Corticobasal degeneration • Dementia with Lewy bodies	
Parkinson	Long term degenerative disorder of the central nervous system Causes: • Genetic & environmental factors • Exposure to pesticides • History of head injury • Tobacco smoking (?) • Coffee/tea drinking (?)	Motor system: cells death in the *substantia nigra*	• Come on slowly over time • Early stage: shaking, rigidity, slowness of movement, difficulty walking. Also: thinking and behavioral problems • Advanced stage: dementia, depression, anxiety. Also: sensory, sleep and emotional problems
Synucleinopathy	Example: Dementia with Lewy bodies		Abnormal accumulation of alpha-synuclein protein in the brain

Table 3: Features, region(s) affected and symptoms of Parkinson's disease and its variations

Scientists sometimes refer to PD as a “synucleiopathy” (due to an abnormal accumulation of alpha-synuclein protein in the brain) to distinguish it from other neurodegenerative diseases, such as “tauopathy” where the brain accumulates the tau protein. Considerable clinical and pathological overlap exists between tauopathies and synucleinopathies. DLB is another synucleinopathy and it has close pathological similarities with PD, especially with the subset of PD cases with dementia. The relationship between PD and DLB is complex and incompletely understood. They may represent parts of a continuum with variable distinguishing clinical and pathological features, or they may prove to be separate diseases.

Causes of the disease

The cause of PD is generally unknown, but research indicates that PD is the product of a complex interaction of genetic and environmental factors:

A. Genetic causes

Scientists have identified several genetic mutations associated with PD, including the alpha-synuclein gene, and many other genes. Studying the genes responsible for inherited cases of PD can help understand both inherited and sporadic cases. The same genes and proteins that are altered in inherited cases may also be altered in sporadic cases by environmental toxins or other factors. Discovering genes will help identify new ways of treating PD. The first to be identified was alpha-synuclein followed by parkin, DJ-1, PINK1, and LRRK2.

In addition, several Parkinson-related genes are involved in the function of lysosomes, which are organelles that digest cellular waste products. It has been suggested that some cases of PD may be caused by lysosome dysfunctions that reduce the ability of cells to break down alpha-synuclein.

B. Environmental causes

Exposure to certain toxins has caused parkinsonian symptoms in rare circumstances Other still-unidentified environmental factors may also cause PD in genetically susceptible individuals. Main environmental causes are:

• **Postencephalitic parkinsonism:** Just after the first World War, the viral disease encephalitis lethargica affected almost 5 million people throughout the world and, then, suddenly disappeared in the 1920s. Known as ‘sleeping sickness’ in the United States, this disease killed one-third of its victims and led to post-encephalitic parkinsonism in many others. This resulted in a movement disorder that appeared sometimes years after the initial illness. In rare cases, other viral infections, including equine encephalomyelitis (western, easter, and Japanese B encephalitis) have caused parkinsonian symptoms.

• **Drug-induced parkinsonism:** A reversible form of parkinsonism sometimes results from use of certain drugs (such as Chlorpromazine and Haloperidol), which are typically prescribed for patients with psychiatric disorders. Some drugs used for stomach disorders (Metoclopramide), high blood pressure (Reserpine), and others such as Valproate can cause tremor and bradykinesia. Stopping the medication or lowering the dosage of these medications usually causes the symptoms to go away.

• **Toxin-induced parkinsonism:** Some toxins can cause parkinsonism by various mechanisms. For example, the chemical MPTP causes a permanent form of parkinsonism that closely resembles PD. Investigators discovered this reaction in the 1980s when heroin addicts in California who had taken an illicit street drug contaminated with MPTP began to develop severe parkinsonism. This discovery showed that a toxic substance could damage the brain and produce parkinsonian symptoms, leading to a dramatic breakthrough in Parkinson's research.

• **Parkinsonism-dementia complex of Guam:** This disease occurs among the Chamorro populations of

Guam and the Mariana Islands and may be accompanied by a motor neuron disease resembling amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease). The course of the disease is rapid, with death typically occurring within 5 years.

Diagnosis

There are currently no blood or laboratory tests to diagnose sporadic PD. There are four approaches to diagnosis:

• **Initial clinico-medical:** It is based on a careful medical history, neurological examination, and a Levodopa test which, if resulting in any improvement in motor impairment, helps confirm the diagnosis. This is followed by periodical reviews to confirm the accuracy of the diagnosis.

• **The (U.K.) Queen Square Brain Bank for Neurological Disorders (QSBBND) at the UCL Institute of Neurology:** The bank holds a unique archive of brains donated by individuals with neurodegenerative diseases and neurologically normal controls. It specializes in parkinsonian movement disorders, including PD and multiple system atrophy. It also holds the national collection of brains donated by individuals with progressive supranuclear palsy (PSP).

• **The (U.S.) National Institute of Neurological Disorders and Stroke (NINDS):** This Institute within the National Institutes of Health (NIH) aims to seek fundamental knowledge about the brain and nervous system and to use that knowledge to reduce the burden of neurological disease.

• **The International Parkinson and Movements Disorder Society (IPMDS)' s task force:** It has proposed diagnostic criteria for PD as well as research criteria for the diagnosis of prodromal disease, but these will require validation against the more established criteria.

Treatment

At present, there is no cure for PD, but medications or surgery can often provide improvement in the motor symptoms. Initial treatment is typically with the anti-Parkinson medication *Levodopa* (L-dopa) with dopamine agonists being used once *Levodopa* becomes less effective. As the disease progresses and neurons continue to be lost, these medications become less effective while at the same time they produce a complication marked by involuntary writhing movements. Diet and some forms of rehabilitation have shown some effectiveness at improving symptoms. Surgery to place microelectrodes for deep brain stimulation (DBS) has been used to reduce motor symptoms in severe cases where drugs are ineffective. Evidence for treatments for the non-movement-related symptoms of PD, such as sleep disturbances and emotional problems, is less strong.

A. Drug therapy

A variety of medications provide dramatic relief from the symptoms. Anticholinergics (category 5 in Table 4 below) and surgery (lesioning of the corticospinal pathway or some of the basal ganglia structures) were the only treatments until the arrival of Levodopa, which reduced their use dramatically. The motor symptoms of PD are the result of reduced dopamine production in the brain's basal ganglia. Dopamine does not cross the blood-brain barrier (BBB), so it cannot be taken as a medicine to boost the brain's depleted levels of dopamine. However, a precursor of dopamine, Levodopa, can pass through the BBB to the brain where it is readily converted to Dopamine, and administration of Levodopa temporarily diminishes the motor symptoms of PD. Levodopa has been the most widely used PD treatment for over 40 years. However, only 5–10% of Levodopa crosses the BBB. Much of the remainder is metabolized to Dopamine elsewhere in the body, causing a variety of side effects including nausea, vomiting and orthostatic hypotension (OH).

Carbidopa and Benserazide are dopa decarboxylase inhibitors, which do not cross the BBB and inhibit the

conversion of Levodopa to Dopamine outside the brain, reducing side effects and improving the availability of Levodopa for passage into the brain. One of these drugs is usually taken along with Levodopa, often combined with Levodopa in the same pill. Levodopa use leads in the long term to the development of complications: involuntary movements called dyskinesias and fluctuations in the effectiveness of the medication. Although Levodopa/Carbidopa helps most people with PD, not all symptoms respond equally to the drug. Levodopa usually helps most with bradykinesia and rigidity. Problems with balance may not respond.

Medications for PD fall into six categories (see Table 4):

• **Drugs that increase the level of Dopamine in the brain:** The most common drugs for PD are Dopamine precursors-substances such as Levodopa that cross the BBB and are then changed into dopamine. Usually, affected individuals are given Levodopa combined with Carbidopa. Carbidopa delays the conversion of Levodopa into Dopamine until it reaches the brain.

• **Drugs that mimic Dopamine (Dopamine agonists):** These drugs, which include Apomorphine, Pramipexole, Ropinirole, and Rotigotine, mimic the role of Dopamine in the brain. They can be given alone or with Levodopa. They are somewhat less effective than Levodopa in treating PD symptoms but work for longer periods of time.

• **Drugs that inhibit Dopamine breakdown (MAO-B inhibitors):** These drugs inhibit the enzyme monoamine oxidase B (MAO-B), which breaks down Dopamine in the brain.

• **Drugs that inhibit Dopamine breakdown (COMT inhibitors):** Catechol-O-methyltransferase (COMT) is another enzyme that breaks down Dopamine. The drugs Entacapone and Tolcapone prolong the effects of Levodopa by preventing the breakdown of dopamine. COMT inhibitors can decrease the duration of "off periods" of one's dose of Levodopa.

• **Drugs that decrease the action of acetylcholine (anticholinergics):** These drugs, which include Trihexyphenidyl, Benztropine, and Ethopropazine, decrease the activity of the neurotransmitter acetylcholine (production or uptake) and can be particularly effective in reducing tremors.

• **Drugs with an unknown mechanism of action for PD:** Dyskinesias, or involuntary movements such as twisting and writhing, commonly develop in people who take Levodopa over an extended period. These movements may be either mild or severe. Some doctors start younger individuals with PD on drugs that act directly like Dopamine itself and add Levodopa later in the course of the disease. The dosage of Levodopa is sometimes reduced in order to lessen these drug-induced movements.

• **Drugs that help control the non-motor symptoms of the disease:** The non-motor symptoms are the symptoms that do not affect movement. For example, people with PD-related depression may be prescribed antidepressants.

Category	Generic	Brand name
1. Drugs that increase brain levels of dopamine	Levodopa/Carbidopa	Parcopa, Sinemet
2. Drugs that mimic dopamine (dopamine agonists)	Apomorphine Pramipexole Ropinirole Rotigotine	Apokyn Mirapex Requip Neupro
3. Drugs that inhibit dopamine breakdown (MAO-B inhibitors)	Rasagiline Selegiline (deprenyl)	Azilect Eldepryl, Zelapar
4. Drugs that inhibit dopamine breakdown (COMT inhibitors)	Entacapone Tolcapone	Comtan Tasmar
5. Drugs that decrease the action of acetylcholine (anticholinergics)	Benztropine Ethopropazine Trihexyphenidyl	Cogentin Parsidol Artane
6. Drugs with an unknown mechanism of action for PD	Amantadine	Symmetrek
7. Drugs that help control the non-motor symptoms of PD	Antidepressants	
8. Other drugs	Quetiapine (for psychosis) Cholinisterase inhibitors for dementia Modafinil for daytime sleepiness	

Table 4: Medications to treat the motor symptoms of Parkinson's disease

B. Surgery

Treating motor symptoms with surgery was once a common practice, but since the discovery of Levodopa, the number of operations has declined. Studies in the past few decades have led to great improvements in surgical techniques, so that surgery is again being used in people with advanced PD for whom drug therapy is no longer sufficient.

Surgery for PD can be divided into three main groups:

- Lesional (Pallidotomy and Thalamotomy): The earliest types of surgery for PD involved selectively destroying specific parts of the brain that contribute to PD symptoms. The most common lesion surgery is called pallidotomy in which a portion of the brain (called the globus pallidus) is destroyed. Pallidotomy can improve symptoms of tremor, rigidity, and bradykinesia, possibly by interrupting the connections between the globus pallidus and the striatum or thalamus. Some studies have also found that pallidotomy can improve gait and balance and reduce the amount of Levodopa people require, thus reducing drug-induced dyskinesias. Another procedure, called thalamotomy, involves surgically destroying part of the thalamus; this approach is useful primarily to reduce tremors. Because these procedures cause permanent destruction of small amounts of brain tissue, they have largely been replaced by deep brain stimulation for treatment of PD.
- Deep brain stimulation (DBS): Target areas for DBS or lesions include the thalamus, the globus pallidus, and the subthalamic nucleus. DBS is the most used surgical treatment. It can reduce the need for

Levodopa and related drugs. It is recommended for people who have PD with motor fluctuations and tremor inadequately controlled by medication, or to those who are intolerant to medication, if they do not have severe neuropsychiatric problems.

C. Complementary and supportive therapies

A wide variety of complementary and supportive therapies may be used for PD. Among these therapies are:

• **Therapeutic approach:** It involves speech-and-swallowing evaluation and therapy. Certain techniques can help with the low voice volume that individuals with Parkinson's often experience.

• **Standard physical, occupational, and speech therapy techniques:** These can help with such problems as gait and voice disorders, tremors and rigidity, and cognitive decline.

• **Diet:** Currently, there are no specific vitamins, minerals, or other nutrients that have any proven therapeutic value in PD.

• **Exercise:** Exercise can help people with PD improve their mobility and flexibility.

• **Others:** Other complementary and supportive therapies that are used by some individuals with PD include massage therapy, yoga, hypnosis, acupuncture, and the Alexander technique, which optimizes posture and muscle activity.

Rehabilitation

Exercise programs are recommended in people with PD. There is some evidence that speech or mobility problems can improve with rehabilitation, although studies are scarce and of low quality. Regular physical exercise with or without physical therapy can be beneficial to maintain and improve mobility, flexibility, strength, gait speed, and quality of life. In terms of improving flexibility and range of motion for people experiencing rigidity, generalized relaxation techniques such as gentle rocking have been found to decrease excessive muscle tension. Other effective techniques to promote relaxation include slow rotational movements of the extremities and trunk, rhythmic initiation, diaphragmatic breathing, and meditation techniques. As for gait and addressing the challenges associated with the disease such as hypokinesia (slowness of movement), shuffling and decreased arm swing, physiotherapists have a variety of strategies to improve functional mobility and safety.

One of the most widely practiced treatments for speech disorders associated with PD is the Lee Silverman Voice Treatment (LSVT). Speech therapy and specifically LSVT may improve speech. Occupational therapy (OT) aims to promote health and quality of life by helping people with the disease to participate in as many of their daily activities as possible. There have been few studies on the effectiveness of OT and their quality is poor, although there is some indication that it may improve motor skills and quality of life for the duration of the therapy.

Palliative care

Palliative care (PC) is specialized medical care for people with serious illnesses, including PD. The goal of this specialty is to improve quality of life for both the person suffering from PD and the family by providing relief from the symptoms, pain, and stress of illnesses. As PD is not a curable disease, all treatments are focused on slowing the decline and improving the quality of life and are therefore palliative in nature.

• **Prognosis:**

PD is a slowly progressive disorder. It is not possible to predict what course the disease will take for an

individual person. The average life expectancy of a person with PD is generally the same as for people who do not have the disease. Fortunately, there are many treatment options available for people with PD. However, in the late stages, PD may no longer respond to medications and can become associated with serious complications such as choking, pneumonia, and falls.

The life expectancy of people with PD is reduced. Mortality ratios are around twice those of unaffected people. Cognitive decline and dementia, old age at onset, a more advanced disease state and the presence of swallowing problems are all mortality risk factors. On the other hand, a disease pattern mainly characterized by tremor (as opposed to rigidity) predicts an improved survival. Death from aspiration pneumonia is twice as common in individuals with PD as in the healthy population.

Prediction and prevention

• **Prediction:** In most cases, there is no way to predict or prevent sporadic PD. However, researchers are looking for a biomarker (a biological abnormality that all people with PD might share) that could be detected by screening techniques or by a simple chemical test given to people who do not yet have any parkinsonian symptoms. One important area of research in this domain involves imaging techniques, such as special MRI techniques or nuclear imaging techniques currently under study at the NIH and elsewhere. In rare cases, where people have a clearly inherited form of PD, researchers can test for known gene mutations as a way of determining an individual's risk of developing the disease

• **Prevention:** Exercise in middle age may reduce the risk of PD later in life. Caffeine also appears protective with a greater decrease in risk occurring with a larger intake of caffeinated beverages such as coffee. People who smoke cigarettes or use smokeless tobacco are less likely than non-smokers to develop PD, and the more they have used tobacco, the less likely they are to develop PD. It is not known what underlies this effect. Antioxidants such as vitamins C and E have been proposed to protect against the disease, but results of studies have been contradictory, and no positive effect has been proven. The results regarding fat and fatty acids have been contradictory, with various studies reporting protective effects, risk-increasing effects or no effects. There have been preliminary indications that the use of anti-inflammatory drugs and calcium channel blockers may be protective. A 2010 meta-analysis found that nonsteroidal anti-inflammatory drugs (NSAID) apart from aspirin have been associated with a reduction of incidence of the development of PD (by at least 15% or higher in long-term and regular users).

After this long but necessary foray into PD, it is now time to dwell with the subject at hand, i.e., whether PD is a prion or a prion-like disease. To begin with, does the disease's basic protein behave like a prion?

Does α-synuclein behave like a prion?

Pathologically, PD is characterized by a loss of dopamine neurons in the *substantia nigra* pars compacta coupled with proteinaceous inclusions in nerve cells and terminals, known as Lewy bodies (LB) and Lewy neurites (LN), respectively. PD pathology is also known to affect non-dopamine neurons in the upper and lower brainstem, the olfactory system, the cerebral hemisphere, the spinal cord, and the autonomic nervous system (ANS). The cause of cell death in PD is not known, but proteolytic stress with the accumulation of misfolded proteins has been implicated.

The notion that prion-like spreading of misfolded α-synuclein (α-syn) causes PD has received a great deal of attention. Although attractive in its simplicity, the hypothesis is difficult to reconcile with *post-mortem*

analysis of human brains and connectome-mapping studies. An alternative hypothesis is that PD pathology is governed by regional or cell-autonomous factors. Although these factors provide an explanation for the pattern of neuronal loss in PD, they do not readily explain the apparently staged distribution of Lewy pathology in many PD brains - the feature of the disease that initially motivated the spreading hypothesis by Braak and colleagues. While each hypothesis alone has its shortcomings, a synthesis of the two can explain much of what we know about the etiopathology of PD.

Aberrant protein accumulation and PD pathogenesis

That the aberrant accumulation of proteins might feature in the pathogenesis of PD is a reasonable posit, given that Lewy bodies, the hallmark of the disease, are composed of a variety of aggregated proteins. Among these, α-synuclein has attracted particular attention. α-synuclein is a 140-aa synaptic protein that is unstructured in aqueous buffers but adopts an α-helical-rich conformation when bound to membranes and can acquire a β-sheet-rich structure that readily polymerizes into fibrils when present in high concentration or in a mutant form.

Mutations in α-synuclein have been reported in association with familial PD. More interestingly, cases of familial PD have also been described with duplication and triplication of the wild-type protein. These findings suggest that increased production of mutant or wild-type α-synuclein can by itself lead to the development of PD. Indeed, gene delivery of α-synuclein to the *substantia nigra* induces degeneration of dopamine neurons with inclusions that stain for α-synuclein and mirrors the pathology of PD. Most cases of PD, however, do not appear to be inherited, but rather occur sporadically. In these cases, as well, α-synuclein has been implicated because it is a major component of Lewy bodies and neurites. There, increased levels of α-synuclein might derive from impaired clearance of the protein by the lysosome and proteasome, as alterations in these systems have been observed in patients with sporadic PD. Further, inhibition of protein clearance produces dopamine neuronal degeneration with the formation of inclusions that stain for α-synuclein.

Increased levels of α-synuclein, regardless of cause, can promote self-aggregation and interfere with proteasomal and lysosomal functions, leading to further accumulation of the protein. Thus, increased production or impaired clearance of α-synuclein could initiate a vicious cycle with continued accumulation and misfolding of the protein and the subsequent formation of potentially toxic oligomers and amyloid fibrils.

The role of α-synuclein misfolding in the pathogenesis of cell death in PD and its potential to spread from one nerve cell to another has been highlighted by the recent discovery that embryonic dopamine neurons that had been transplanted into PD patients 11–14 years earlier developed PD pathology with classic Lewy bodies that stained for α-synuclein and thioflavin-S (a marker for β-sheet-rich protein polymers). The likelihood that these embryonic neurons had been adversely affected by the accumulation and misfolding of α-synuclein is supported by evidence of reduced staining for the dopamine transporter and tyrosine hydroxylase (in some nerve cells). Because α-synuclein-positive inclusions have not previously been seen in such young nerve cells, and because the transplants were derived from multiple, genetically unrelated donors, it seems likely that the inclusions arose because of factors inherent to the PD brain. One possible explanation is that misfolded α-synuclein was transmitted from pathologically affected neurons to healthy grafted embryonic dopamine neurons and there, recruited nascently, produced α-synuclein to misfold.

α-synuclein can transfer from nerve cells to embryonic stem cells

Desplat *et al.* (2009) demonstrated that nerve cells that

overexpress tagged α-synuclein can transmit the protein to neural stem cells in both in vitro and in vivo models. It demonstrates that α-synuclein can be directly transferred from nerve cells that overexpress the protein to neighboring healthy embryonic stem cells both in tissue culture and in transgenic animals. This important study could explain the remarkable finding that human embryonic dopamine nerve cells implanted into the striatum of patients with PD develop PD pathology with loss of dopamine markers and classic Lewy bodies. It also provides insight into how α-synuclein pathology might sequentially spread throughout the nervous system in PD.

This, in turn, was associated with pathological changes in acceptor cells as evidenced by the development of inclusion bodies and neuronal degeneration with markers of apoptosis. This same mechanism might account for the accumulation of misfolded α-synuclein and the development of PD pathology in the implanted dopamine neurons. It could also account for the pathologic findings of Braak *et al.* in the PD brain, which suggest that α-synuclein spreads in a sequential and predictable manner, beginning in the dorsal motor nucleus in the lower brainstem and extending to involve upper brainstem nuclei (including the substantia nigra) and cerebral hemispheres. Indeed, it is possible that aggregated α-synuclein, frequently detected in autonomic plexi of the gastrointestinal tract of neurologically intact individuals who are suspected of having preclinical PD might be the initial site of α-synuclein misfolding.

α-synuclein behaves like a prion

Based on the available evidence, there is much to suggest that α-synuclein behaves like a prion, and that PD might be a prion (or prion-like) disorder. Both α-synuclein and the cellular form of the prion protein (PrPC) adopt an α-helical-rich conformation under physiological conditions, and both can refold into a β-sheet-rich conformation that readily aggregates into oligomers and amyloid fibrils. Both misfolded proteins (especially the oligomers) are thought to be toxic and capable of inducing neurodegeneration. Furthermore, protein aggregates formed from each of these misfolded proteins can promote the misfolding of additional wild-type proteins, and in this way, act as prion conformers. One can envision that the continued accumulation of misfolded proteins challenges the capacity of the lysosomal and proteasomal systems to clear these unwanted proteins, thus promoting their further accumulation and the development of a self-propagating cycle that eventually leads to cell death. As in the prion diseases, there is now also evidence that α-synuclein can be directly transmitted from pathologically affected to healthy, unaffected cells, thereby potentially extending the disease process throughout the nervous system.

Figure 2 illustrates the similarities in the relationships between the PrPC protein and prion diseases, and the α-synuclein protein and PD. In Figure 2(A), the cellular prion protein (PrPC) comprises ≈210 aa. The function of PrPC is unknown. It has a largely α-helical conformation and resides on the surface of cell membranes. When PrPC misfolds, it acquires a high β-sheet content and assembles into rods that coalesce to form amyloid plaques. PrPSc is the sole component of the infectious prion and can lead to disease in animals and humans. In Figure 2(B), α-synuclein is a protein of ≈140 aa. The function of α-synuclein is unknown. It acquires a largely α-helical conformation when it binds to cell membranes. When it misfolds, it acquires a high β-sheet content and polymerizes into fibrils that are associated with the formation of Lewy bodies. Overexpression of α-synuclein alone can induce a PD syndrome in animals and humans.

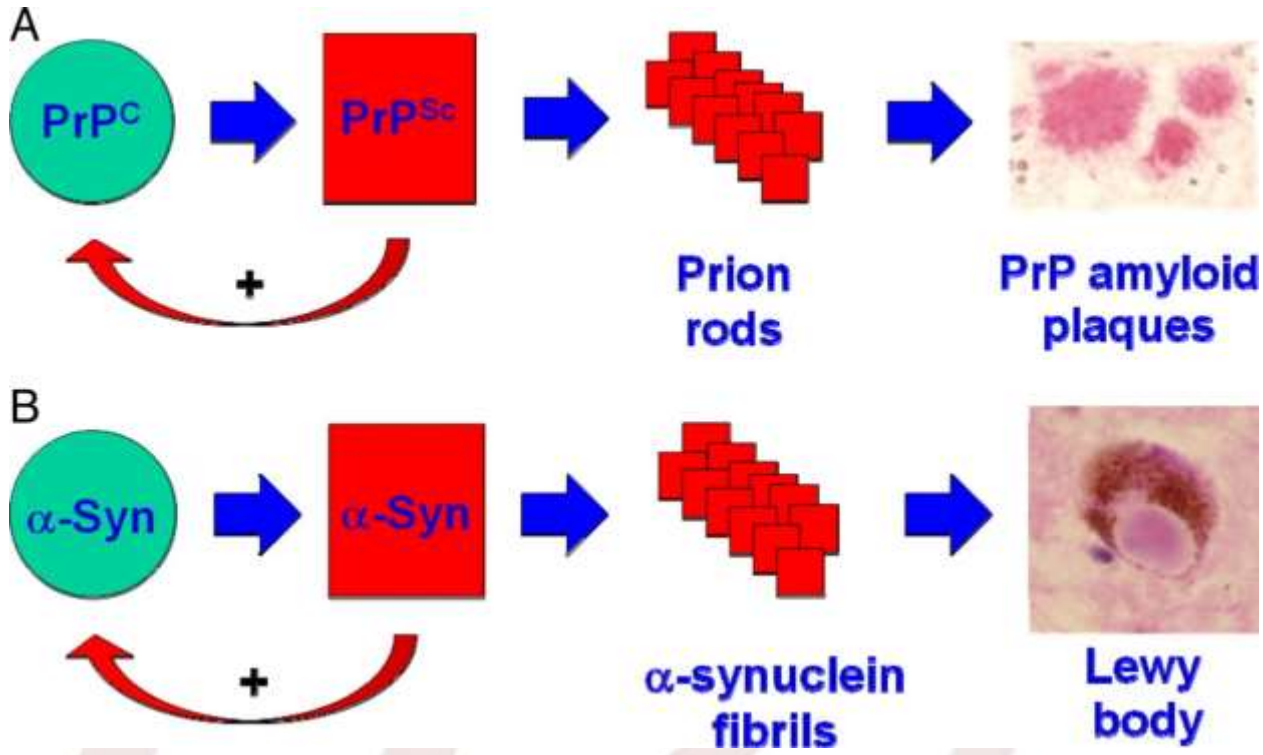

Figure 2: There is much to suggest that α-synuclein behaves like a prion

Reference: Olanow and Prusiner (2009)

It is, thus, possible that PD is a prion disorder resulting from increased production and/or impaired clearance of proteins such as α-synuclein, leading to misfolding and the formation of toxic oligomers, aggregates, and cell death. Further, it is possible that α-synuclein is a prion protein that can self-aggregate and be transmitted to unaffected cells, thus extending the disease process. While genetic causes represent an obvious source of increased levels of aberrantly folded α-synuclein in familial PD cases, a combination of aging, oxidative stress (OS), inflammation, environmental toxins, hereditary factors, and impaired clearance may all feature in varying ways in causing altered metabolism of α-synuclein, resulting in the pathogenesis of sporadic PD. This concept suggests that drugs directed toward reducing the formation, and/or facilitating the clearance of misfolded α-synuclein, to arrest or reverse the self-propagation process, might represent a novel therapeutic intervention for the treatment of PD.

α-synucleinopathy is not communicable

The experimental transmission of α-synuclein leads to the question: Is PD (and/or related α-synucleinopathies) a communicable disease? The epidemiology studies conducted so far do not support that PD is a communicable disease. Thus, a retrospective analysis of patients who received cadaveric human growth hormone (c-hGH), the same cohort that hosted an outbreak of more than 200 cases of iatrogenic Creutzfeldt-Jakob disease (iCJD), revealed no cases of PD. A caveat of the study is that the follow-up period might not have been long enough. The incubation time for iCJD can be as long as 42 years and it might take several decades for misfolded α-synuclein to cause a widespread aggregation. Another caveat is the reliance on death certificates, but not neuropathological analyses, to ascertain if the subjects had PD or not. Finally, we do not know if the protocol used to extract

growth hormone affects the stability of the putatively pathogenic α-synuclein conformers. While currently available evidence does not support that PD is a communicable disease; the limited observation period and lack of neuropathology data in this key study means that we cannot be certain.

Experiments support the idea that misfolded α-synuclein behaves in a protein-like fashion

Both in vitro and animal experiments provide support to the idea that misfolded α-synuclein behaves in a protein-like fashion:

A. In vitro experiments

Numerous *in vitro* studies have convincingly shown that cultured neurons can both secrete α-synuclein and take it up from the extracellular space. In other experiments, recombinant α-synuclein protein added to the culture medium was found to be taken up by cultured neurons. Once inside a "new" neuron, "exogenous" α-synuclein (both when cell-derived and when added as recombinant protein) can oligomerize with endogenous α-synuclein and seed the formation of aggregates.

B. Animal experiments

Similarly, animal experiments have shown that α-synuclein can be released and taken up by neurons. Moreover, using strategies involving the intracerebral, intramuscular or intraperitoneal injections of oligomeric or fibrillar α-synuclein derived either from recombinant protein of from post-mortem brain samples obtained at autopsies of patients with α-synucleinopathies (e.g. PD, MSA and DLB), the injected material triggers accumulation of α-synucleinin in the host rodent or non-human primate brain. However, while the demonstration of induced α-synucleinopathy in experimental animals is undeniably fascinating, critics have argued that the models are not relevant to the human diseases.

The Braak's two-stage process supports propagation of α-synuclein aggregates

Braak's two-stage process for the disease process, namely the olfactory system and the enteric nervous system support the idea of propagation of α-synuclein aggregates. This "dual-hit hypothesis", states that an unknown toxic agent or pathogen was inhaled, affecting the olfactory bulb and the gut wall, after being swallowed. This hypothesis is also consistent with clinical observations that hyposmia and constipation are prevalent at the time of PD diagnosis and often precede the development of overt motor symptoms by several years.

Cellular and molecular mechanisms of α-synuclein intercellular transfer and interregional transport

Several studies, mostly on cultured neurons, have defined molecular mechanisms of α-synuclein release, uptake and axonal transport. It is important to emphasize that the underlying mechanisms differ depending on whether the α-synuclein is present as a monomer, oligomer, or fibril.

The uptake of extracellular α-synuclein, whether it is oligomeric or fibrillar, is believed to be mediated via endocytosis. Several pharmacologic and genetic experiments have demonstrated that endocytosis is a major mechanism for the uptake of extracellular α-synuclein. However, how α-synuclein binds the outer cellular membrane is not fully understood.

While transfer from neuron-to-neuron has been primarily considered, astrocytes, microglia and oligodendrocytes can also all take up extracellular α-synuclein. Uptake of α-synuclein has been suggested to activate astrocytes, which can explain the astrocytosis sometimes observed in α-synucleinopathies. Uptake of α-synuclein by microglia is enhanced by immunoglobulins binding to α-synuclein, which is relevant to ongoing immunotherapy trials in PD and

MS. Further, uptake of α-synuclein by oligodendrocytes might explain why these cells exhibit α-synuclein aggregates in multiple system atrophy (MSA), although they also can synthesize α-synuclein endogenously.

Evidence will now be described to support the hypothesis that α-synuclein has a prion-like role in PD and related α-synucleinopathies. How this novel thinking impacts the development of diagnostics and disease-modifying therapies is also discussed.

Evidence supporting Parkinson's disease as a prion disorder

The realization that α-synuclein pathology can propagate between brain regions in neurodegenerative diseases (NDD) has deepened and expanded our understanding of potential pathogenic processes which can lead to the development of novel diagnostic tools as well as the identification of new therapeutic targets.

The neuropathology of PD is characterized, in part, by the severe loss of dopaminergic neurons in the *substantia nigra* and the development of intraneuronal α-synuclein aggregates called Lewy bodies and Lewy neurites (collectively Lewy pathology) in widespread brain regions. Patients with dementia with Lewy bodies (DLB) also develop intraneuronal α-synuclein aggregates while, in multiple system atrophy (MSA), most of the α-synuclein aggregates are in oligodendrocytes. Due to the shared pathological feature of α-synuclein aggregates, PD, DLB and MSA are known as α-synucleinopathies. Recently, several proteins that are prone to misfold and form aggregates in the brain, each defining specific neurodegenerative disorders have been shown to transmit from one cell to another in experimental disease models. This applies to α-synuclein in models of PD, DLB and MSA, as well as tau in models of Alzheimer's disease (AD); mutant huntingtin in Huntington's disease (HD) models, and mutant SOD in amyotrophic lateral sclerosis (ALS) models. The behavior of these disease-related proteins has been called "prion-like". However, PD may not be simply a prion disorder, as will next be discussed.

Parkinson's disease may not be simply a prion disorder

The notion that prion-like spreading of misfolded α-synuclein (α-syn) causes (PD) has received a great deal of attention. Although attractive in its simplicity and in its promise for future diagnostic and therapeutic approaches, the hypothesis is difficult to reconcile with postmortem analysis of human brains and connectome-mapping studies. An alternative hypothesis is that PD pathology is governed by regional or cell-autonomous factors. Although these factors provide an explanation for the pattern of neuronal loss in PD, they do not readily explain the apparently staged distribution of Lewy pathology in many PD brains, the feature of the disease that initially motivated the spreading hypothesis by Braak and colleagues. While each hypothesis alone has its shortcomings, a synthesis of the two could explain much of what we know about the etiopathology of PD.

In sum, PD is not a prion disease, but it is considered a prion-like disease because its pathology involves the misfolding and spreading of the alpha-synuclein protein in a way that is similar to prions. While classic prion diseases are infectious, there is no evidence that PD is transmissible from person to person, making the term "prion-like" more accurate.

How Parkinson's is similar to a prion disease

- **Prion misfolding:** In both PD and prion diseases, a protein misfolds into a harmful shape.
- **Self-propagation:** The misfolded protein can then "seed" its misfolding onto other normal proteins, causing a chain reaction.
- **Spreading:** The misfolded proteins can spread from cell to cell and through neural connections.
- **Neurodegeneration:** This process leads to a build-up

of protein aggregates and the death of nerve cells.

How Parkinson's differs from a prion disease

• **Infectivity:** Classic prion diseases, such as Creutzfeldt-Jakob disease (CJD), can be transmitted between individuals, whereas PD is not considered infectious.

• **Cause:** The root cause of Parkinson's is multifactorial, involving a combination of genetic and environmental factors that trigger alpha-synuclein misfolding. In contrast, prion diseases are caused by the misfolding of a specific prion protein.

The lack of such evidence emphasizes the main difference between the pathologies, ultimately suggesting that PD is not a classic prion disease.

New diagnostic and treatment strategies based on α-synuclein acting like a prion

If the cell-to-cell propagation of α-synuclein aggregates is linked to clinical progression of α-synucleinopathies, then preventing its spread may be a powerful clinical target. At least two principally different strategies are evident:

A. Inhibition of α-synuclein release/uptake

Inhibition of α-synuclein or its uptake by neurons (for PD and DLB) or oligodendroglia (for MSA).

B. Prevention of α-synuclein seeding/clearance

Prevention of α-synuclein seeding and promotion of α-synuclein clearance from the extracellular space. It is conceivable that α-synuclein can be reduced by promoting its intracellular clearance by enhancing the lysosomal-autophagy system through inhibition of the mammalian target of rapamycin, using, e.g., drugs such as Rapamycin or Metformin. Immunotherapy is currently being pursued both in the laboratory and clinically in attempts to clear α-synuclein from the extracellular space.

The therapeutic potential of any of these approaches will be maximized once diagnostic and progression biomarkers would have been established. Such biomarkers would potentially allow for the identification of PD prior to the onset of the motor symptoms. Related to the prion hypothesis for α-synucleinopathies, extensive efforts are being made to identify the pathological expression of α-synuclein in peripheral tissues, although the field remains controversial with contradicting results.

Conclusions and take-aways

• The discovery of a mutation in the gene for the protein alpha-synuclein has simultaneously provided an element of the cause of Parkinson's disease, that is its genetic component (in both its motor and neuropsychiatric manifestations), and the explanation of the presence of pathological alpha-synuclein-aggregations in the Lewy bodies in the substantia nigra.

• Most Parkinson patients, even at the very early stage of neurological diagnosis, present a late-stage phenotype of an alpha-synucleinopathy.

• The field has steadily shifted away from developments of symptomatic therapy to preventive therapy, with several different options: active immunization, passive immunization, development of small molecules that function as alpha-synuclein aggregation modulators and, most recently, an autophagy enhancer with a known adverse profile.

• For the very first time, the possibility of a disease-modifying therapy appears to be testable. However, disease-modifying therapy is not cure!

• Taking together the discoveries on the genetic background and the Braak staging hypothesis and considering the interactions of our two brains (brain-under-the-skull, brain-in-the-gut), new avenues for drug

development and clinical testing have opened-up. In the next few years of clinical testing, we predict that potential disease-modifying compounds will be tested in the early stages of motor PD. However, the diagnostic methodology should identify a primary endpoint for clinical neuroprotective trials, not only in early motor PD but also in the prodromal stages of PD.

• For "true" neuroprevention, parameters and biomarkers which reflect the progression of the alpha-synucleinopathy in the prodromal stage have yet to be discovered. Such a parameter must be responsive to therapy even in the prodromal stage to qualify as a primary endpoint for pivotal registration trials. At present, this parameter has not been identified.

• Deep brain stimulation and high-intensity focused ultrasound guided by magnetic resonance imaging still have their place in the therapeutic armamentorium.

• Experimental studies demonstrating cell-to-cell transfer of α-synuclein pathology firmly establish that, in addition to its normal conformation, α-synuclein can exist in altered, self-propagating conformation(s).

• Emerging evidence suggests that α-synuclein pathology can propagate from cell-to-cell in a prion-like manner, progressively engaging additional brain regions, and that this spreading might contribute to the symptomatic progression.

• The molecular mechanisms underpinning cell-to-cell spreading of α-synuclein pathology are currently being elucidated and are leading to the identification of new therapeutic targets.

• Intraneuronal α-synuclein aggregates are a key feature of Parkinson's disease neuropathology.

• Although attractive in its simplicity and promise for future diagnostic and therapeutic approaches, the hypothesis that Parkinson's disease may be a prion disease is difficult to reconcile with post mortem analyses of human brains and connectome-mapping studies.

• Despite several similarities at the cellular level, current evidence does not support that PD or other α-synucleinopathies are communicable diseases like several other prion diseases.

• Animal models of Parkinson's disease that are based on α-synuclein acting in a prion-like fashion offer a powerful test bed for novel therapeutic interventions.

References

1. Ahlskog JE (2011) "Does vigorous exercise have a neuroprotective effect in Parkinson;'s disease", Neurology 77.3:288-94.
2. Barranco Quintana JL., et al. (2009). "Parkinson's disease and tea: a quantitative review". Journal of the American College of Nutrition 28.1: 1-6.
3. Bertrand C., et al. (1973). "Stereotactic surgery for Parkinsonism". Progress in Neurological Surgery 5:79-112.
4. Braak H., et al. (2003). "Staging of brain pathology related to sporadic Parkinson's disease" Neurobiology of Aging 24.2:197-211.
5. Bronstein M., et al. (2011). "Deep brain stimulation for Parkinson disease: an expert consensus and review of key issues". Archives of neurology 68.2:165.
6. Caallol N, et al. (2007). "Cognitive dysfunction and dementia in Parkinson's disease". Movement Disorders 22 Suppl 17: S358-66.
7. Coffey RJ. (2009). "Deep brain stimulation devices: a brief technical history and review". Artificial Organs 33.3:208-20.
8. Cooper G., et al. "Parkinson's disease". In Conn PM. Neuroscience in Medicine. Totowa, NJ: Humana Press. (2008): pp. 508–12. ISBN 978-1-60327-454-8.
9. Dafsari HS., et al. (2016). "Beneficial Effects of Bilateral Subthalamic Stimulation on Non-Motor Symptoms in Parkinson's Disease", Brain Stimulation. 9.1:78-85.
10. Donaghy PC., et al. (2015). "Prodromal dementia with Lewy bodies". Psychological Medicine 45.2:259-68.
11. Feng LR and Maguire-Zeiss KA.

"Gene therapy in Parkinson's disease: rationale and current status". CNS Drugs 24.3:177-92.

12. Fishman PS and Frenkel V. (2017). “Treatment of movement disorders with focused ultrasound”. Journal of Central Nervous System Disease 9.

13. Friedman JH (2010). “Parkinson’s disease psychosis: A review article”.

14. Fymat AL (2020). “Parkinson’s Disease and other Movement Disorders: A Review”. Current Opinions in Neurological Science 2.1:316-443.

15. Fymat AL (2018). “Neurological Disorders and the Blood Brain Barrier: 2. Parkinson and Other Movement Disorders”. Current Opinions on Neurological Science 2.1: 362-83.

16. Fymat AL (2018). “Blood Brain Barrier Permeability and Neurodegenerative Diseases”. Current Opinions in Neurological Science 2.2:411-4.

17. Fymat AL (2018). “Regulating the Brain Autoimmune System: The End of All Neurodegenerative Diseases?” Current Opinions in Neurological Science 2.3:475-9.

18. Fymat AL (2018). “Neutrophils-mediated treatment of neurodegenerative and other inflammatory diseases”. Clinical Research in Neurology 1.1:1-5.

19. Fymat AL (2018). “Harnessing the immune system to treat cancers and neurodegenerative diseases”. Clinical Research in Neurology 1.1:1-14.

20. Fymat AL (2019). “On the pathogenic hypothesis of neurodegenerative diseases”. Clinical Research in Neurology 2.1\:1-7.

21. Fymat AL (2019). “Our Two Interacting Brains – Etiologic Modulations of Neurodegenerative and Gastroenteric Diseases”. Current Opinions in Neurological Science 4.2: 50-4.

22. Fymat AL. “Parkin... ss..oo..nn: Elucidating the Disease... and What You Can Do About it”, Tellwell Talent Publishers, pp 258, 6 April 2020. ISBN: 978-0-2288-2874-7 (Hardcover); 978-0-2228-2875-4 (Paperback).

23. Fymat AL. “Creutzfeldt-Jakob Disease: The Enchanted Loom’s Spongiform Disease in Search of a Cure”, Tellwell Talent Publishers, pp xxx, 2025, ISBN-xxxxx; ISBN-xxxxx. (in press, to appear in November 2025).

24. Fymat AL (2025). “Creutzfeldt-Jakob as an example of prion disease: I. Prions, Journal of Neurology & Psychology Research 6(3):1-27.

25. Fymat AL (2025). “Creutzfeldt-Jakob as an example of prion disease: II. Prion diseases”, Journal of Neurology & Psychology Research 6(3):1-19.

26. Fymat AL (2025). “Creutzfeldt-Jakob as an example of prion disease: III. Prion mimic diseases”, Journal of Neurology &Psychology Research 6(3):1-27.

27. Fymat AL (2025). “Creutzfeldt-Jakob as an example of prion disease: IV. Understanding Creutzfeldt-Jakob disease, Journal of Neurology & Psychology Research 6(3):1-27.

28. Fymat AL (2025). “Prion-like mechanisms in neurodegenerative diseases: I. Alzheimer’s disease, Journal of Neurology & Psychology Research 6(4):1-22.

29. Garcia-Ptacek S and Kramberger MG (2016). "Parkinson's disease and dementia". Journal of Geriatric Psychiatry and Neurology 29.5: 261-70.

30. Goedert M., et al. (2017). “The Synucleinopathies: Twenty Years On". Journal of Parkinson's Disease 71:S51–S69.

31. Hawkes CH., et al. (2007). “Parkinson's disease: a dual-hit hypothesis”, Neuropathology and Applied Neurobiology 33.6:599-614.

32. Hernandez DG., et al. (2016).

"Genetics in Parkinson disease: Mendelian versus non-Mendelian inheritance". Journal of Neurochemistry 139.1:59-74.

33. Jankovic J (2008). "Parkinson's disease: Clinical features and diagnosis", Journal of Neurology, Neurosurgery, and Psychiatry 79.4:36876.79.4.

34. Jeanmonod D., et al. (2012). "Transcranial magnetic resonance imaging-guided focused ultrasound: noninvasive central lateral thalamotomy for chronic neuropathic pain". Neurosurgical Focus 32.1: E1.

35. Kalia LV and Lang AE (2015). "Parkinson's disease". Lancet 9996:896-912.

36. Lesage S and Brice A (2009). "Parkinson's disease: from monogenic forms to genetic susceptibility factors". Human Molecular Genetics 18.R1:R48–59.

37. Lewitt PA., et al. (2011). "AAV2-GAD gene therapy for advanced Parkinson's disease: a double-blind, sham-surgery controlled, randomized trial". Lancet Neurology 10: 309-19.

38. Moser D., et al. (2013). "MR-guided focused ultrasound technique in functional neurosurgery: targeting accuracy". Journal of Therapeutic Ultrasound :1-3.

39. Mosley AD (2010). "The encyclopedia of Parkinson's disease". (2nd Edition.). New York: Facts on File: p89.

40. Nalls MA., et al. (2014). "Large-scale meta-analysis of genome-wide association data identifies six new risk loci for Parkinson's disease". Nature Genetics 46.9:989-93.

41. National Parkinson Foundation (2017). "Parkinson's Disease vs. Parkinsonism".

42. Parker KL, et al. (2013). "Executive dysfunction ion Parkinson's disease and timing deficits", Frontiers in Integrative Neuroscience 7:785.

43. Redmond DE (2002). "Cellular replacement therapy for Parkinson's disease--where we are today?". The Neuroscientist 8.5:457-88.

44. Rodriguez-Oroz M., et al. (2005). "Bilateral deep brain stimulation in Parkinson's disease: a multicenter study with 4 years follow-up". Brain 128.10:2240–9.

45. Samii A., et al. "Parkinson's disease". Lancet 363.9423:1183-93.

46. Shergill SS. et al. (1989). "A preliminary investigation of laterality in Parkinson's disease ans susceptibility to psychosis". Journal of Neurology, Neurosurgery, and Psychiatry 65.4 :610–1.

47. Shulman JM., et al. (2011). "Parkinson's disease: genetics and pathogenesis". Annual Review of Pathology 6:193–222.

48. St Louis EK., et al. (2017). "REM sleep behavior disorder in Parkinson's disease and other synucleinopathies". Journal of Movement Disorders 32.5:645-8.

49. St Louis EK and Boeve BF. (2017). "REM sleep behavior disorder: diagnosis, clinical implications, and future directions". Mayo Clinic Proceedings 92.11:1723-36.

50. The National Collaborating Centre for Chronic Conditions, ed. (2006). "Surgery for Parkinson's disease". Parkinson's Disease. London: Royal College of Physicians. pp. 101–11. ISBN 1-86016-283-5.

51. Tse W., et al. (2004). "Movement disorders and AIDS: a review". Parkinsonism & Related Disorders 10.6:323-34.

52. Zlokovic BV (2008). "The blood-brain barrier in health and chronic neurodegenerative disorders", Neuron. 57.2:178-201.