PARKINSON'S DISEASE : THE PSYCHOSIS SPECTRUM

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Parkinson's Disease : The Psychosis Spectrum

ANCC Accredited NCPD Hours: 2.2hrs

Target Audience: RN/APRN

Need Assessment

Parkinson's Disease is increasingly recognized as a heterogeneous multisystem disorder involving other neurotransmitter systems, such as the serotonergic, noradrenergic and cholinergic circuits. Thus, a wide variety of nonmotor symptoms (Nonmotor symptoms) linked with these neurotransmitters are commonly observed in patients with Parkinson's Disease. In light of this variability, subtyping of Parkinson's Disease has been proposed, including a system based on time of onset and ongoing rate of cognitive decline.

In light of the different aspects related to Parkinson's disease, ***the present article has the following aims:***

The timing, profile and rate of cognitive decline vary widely among individuals with Parkinson's Disease. Therefore, identifying and predicting future cognitive decline in this population is crucial for researchers and clinicians alike. Identification of clinical and biological markers that can predict which patients are at increased risk of early and rapid cognitive decline is important for communicating the prognosis and managing patients clinically. Established demographic and clinical risk factors include increasing age and more severe parkinsonism, in particular, non-tremor features. Here, we focus on cognitive and biomarker features as potential predictors of cognitive decline in Parkinson's Disease. [1, Rank 5]

Objectives

- Discuss the landscape of psychosis in Parkinson's disease
- Describe the psychosis spectrum in Parkinson's disease
- Identify the early psychosis Parkinson's Disease symptoms
- Describe the psychosis spectrum progression in Parkinson's disease
- Discuss the mechanisms and risk factors in Parkinson's disease

Goal

The goal of this article is to discuss clinical and biological markers that can predict patients who are at increased risk of Parkinson's disease (PD) along with prognosis and clinical management of these patients. The article also discusses key research findings and directions in Parkinson's Disease psychosis, and their implications for clinical practice and the neuroscience of Parkinson's Disease.

Introduction

Recently, the clinical and research profile of illusions, hallucinations, delusions and related symptoms in Parkinson disease (PD) was raised with the publication of a consensus definition of Parkinson's Disease psychosis. ***Symptoms that were previously deemed benign and clinically insignificant were incorporated into a continuum of severity, leading to the rapid expansion of literature focusing on clinical aspects, mechanisms and treatment.*** Major research topics include

- The prospective risk of dementia in individuals with Parkinson's Disease psychosis, causal and modifying effects of Parkinson's Disease medication along with recent developments
- Recognition of an increase in the prevalence of psychosis with disease duration
- Addition of new visual symptoms to the psychosis continuum
- Identification of frontal executive, visual perceptual and memory dysfunction at different disease stages.

In addition, there are several novel risk factors — for example, autonomic dysfunction — that have emerged from prospective studies, ***structural MRI evidence of frontal, parietal, occipital and hippocampal involvement, for the treatment of Parkinson's Disease psychosis.*** The accumulating evidence raises novel questions and directions for future research to explore the clinical management and biomarker potential of Parkinson's Disease psychosis. [2, Rank 4]

> **"Symptoms of psychosis, such as illusions, hallucinations and delusions, are collectively referred to as 'positive'"**

Landscape of Psychosis in Parkinson's disease

In a study, Researchers redefined the landscape of psychosis in Parkinson disease (Parkinson's Disease). Symptoms of psychosis, such as illusions, hallucinations and delusions, are collectively referred to as 'positive', carrying the implication of an excess of function or brain activity, in contrast with 'negative' symptoms of deficit. Though all long recognized as nonmotor manifestations of Parkinson's Disease, positive symptoms (as shown in fig.1)such as illusions, hallucinations and delusions were traditionally considered to be distinct from one another, with different clinical implications. In particular, hallucinations of a person, animal or indefinite object passing through

the peripheral visual field (passage hallucinations), misperception of actual stimuli (illusions) and a distinct class of perceptual experiences without visual content but a 'feeling' of someone present (presence hallucinations) were not thought to carry the same clinical significance as formed visual hallucinations of animals, objects or figures. This distinction was reflected in the terminology, whereby illusions and passage and presence hallucinations were described as 'benign' or 'minor' hallucinations. [3, Rank 3]

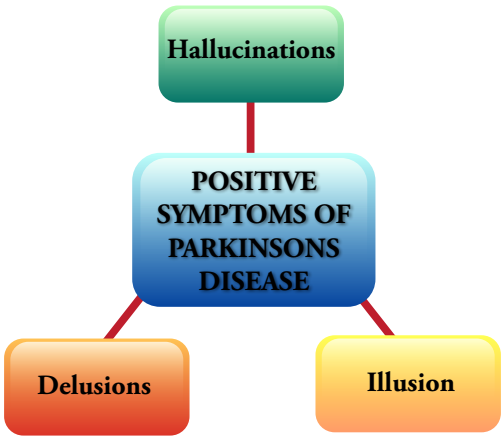

Figure 1 : Positive symptoms of Parkinson's disease

The Psychosis Spectrum in Parkinson's disease

Positive symptoms in Parkinson disease (Parkinson's Disease) vary across its course. Early in the disease, symptoms experienced include passage hallucinations (where a person, animal or indefinite object is seen briefly passing in the peripheral visual field), illusions (for example, seeing the branch of a tree as a cat), and presence hallucinations (a feeling that someone is nearby).

Pareidolia refers to a specific class of illusion where faces and objects are seen in formless visual stimuli, such as clouds, flames or tree bark, or in geometric visual patterns, such as carpets or wallpaper. ***This type of illusion can occur as a normal perceptual experience, but is increased in frequency in Parkinson's Disease and related disorders such as dementia with Lewy bodies.***

Later in Parkinson's Disease, formed visual hallucinations, typically of animals or people, occur. Insight — that is, recognition that the experiences are hallucinations — is preserved at this stage, but becomes lost as Parkinson's Disease progresses, with the onset of false beliefs (delusions) and hallucinations in other sensory modalities (multimodality hallucinations). Cognitive decline and loss of insight follows symptom progression.

The terms pseudo hallucination and hallucinosis are used as synonyms for hallucinations with insight in some psychiatric and neurological traditions. [4, Rank 3]

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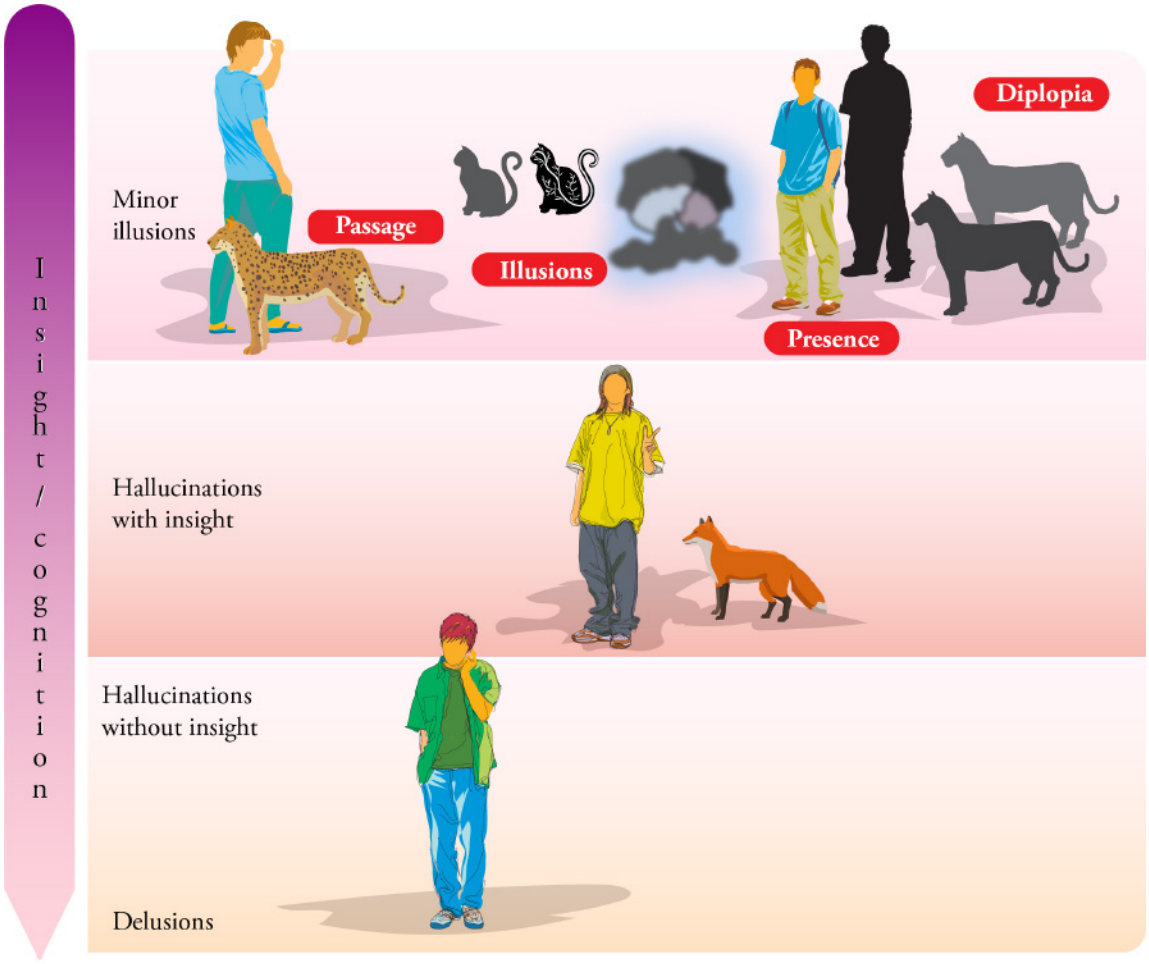

Figure 2 : Insight and Parkinson's disease

Early Parkinson's Disease Psychosis Symptoms

Symptoms of the psychosis spectrum in early stages of Parkinson's Disease include minor experiences, such as passage and presence hallucinations, illusions, and formed hallucinations — most commonly, recurring visual hallucinations of people, animals or inanimate objects — with insight preserved. In later Parkinson's Disease stages, delusions and hallucinations occur in other modalities.

For example, auditory hallucinations consisting of a voice that may not be comprehensible, or non-verbal sounds, such as steps or music. The hallucinations tend to occur in conditions of low ambient stimulation, typically when the individual is alone in a quiet environment. The person may experience symptoms, several times a day, and last for seconds to minutes in the early stages of Parkinson's Disease psychosis. Evidence that has emerged since the publication of the consensus work group recommendations has helped to further

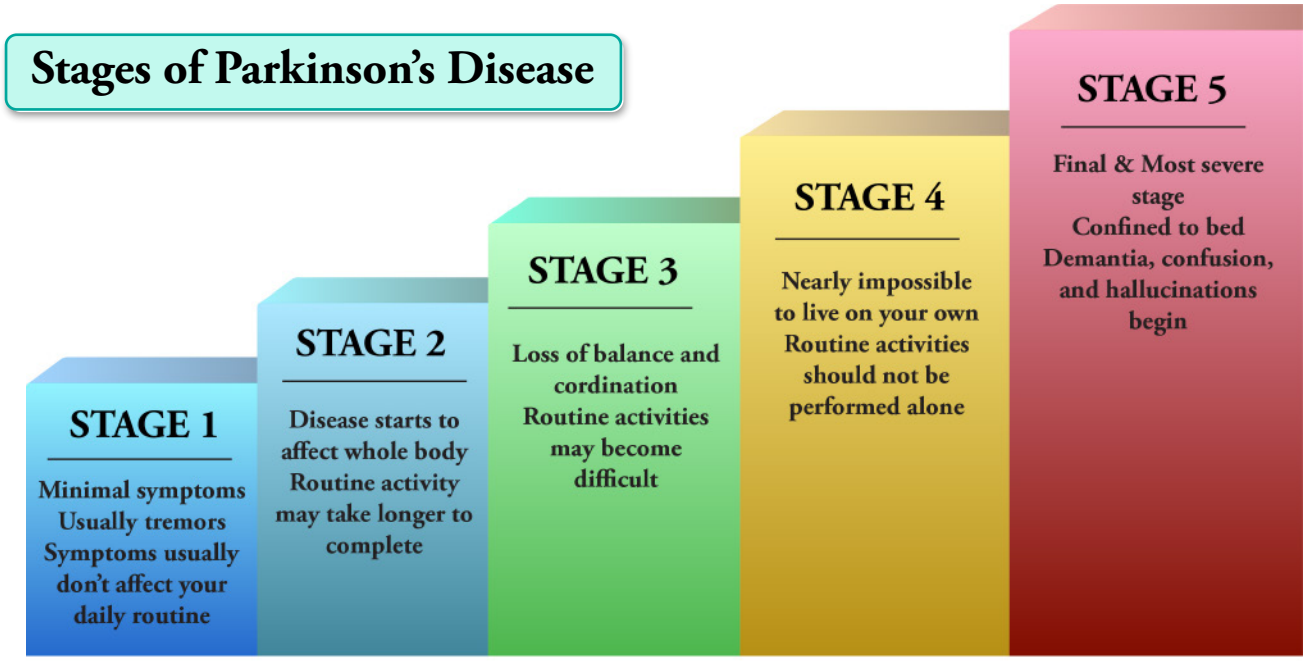

Figure 3: Psychosis symptoms in different stages of parkinson's disease

characterize the phenomenology of different Parkinson's Disease psychosis stages, and their relationship with the progression of Lewy body pathology. [6, Rank 3]

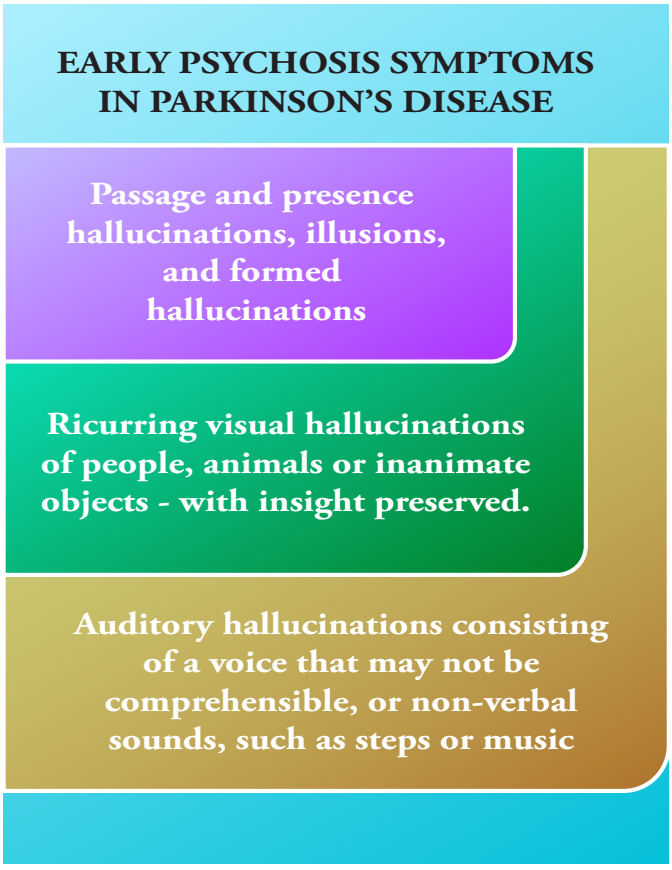

Figure 4 : Early psychosis symptoms in parkinson's disease

Psychosis Spectrum Progression in Parkinson's Disease

The fact that illusions, passage and presence hallucinations progress to formed visual hallucinations in Parkinson disease (Parkinson's Disease) do not imply that they all have the same underlying mechanism. Evidence showed minor hallucinations and formed ***visual hallucinations are associated with different sets of risk factors.*** For example, presence hallucinations have been linked to sleep regulation and somnolence scores whereas, illusions are related to somnolence. Neurobiological explanations of passage hallucinations implicate dysfunctional brainstem eye movement control mechanisms and subcortical and cortical motion pathways, including dorsal stream areas in the visual

parietal lobe are responsible for the symptoms.

Previous studies of visual hallucinations have linked visual parietal areas to hallucinations in the peripheral visual field (as described for passage hallucinations). ***By contrast, formed visual hallucinations are associated with changes in cognition, visual function and affect, probably reflecting cortical involvement in ventral occipitotemporal lobe regions. The onset of minor hallucinations might even precede the development of motor symptoms.***

As Parkinson's Disease progresses, hallucinations in non-visual (auditory, tactile and olfactory) modalities occur alongside visual hallucinations (as shown in fig.5). In one cohort of Parkinson's Disease patients without hallucinations at baseline,

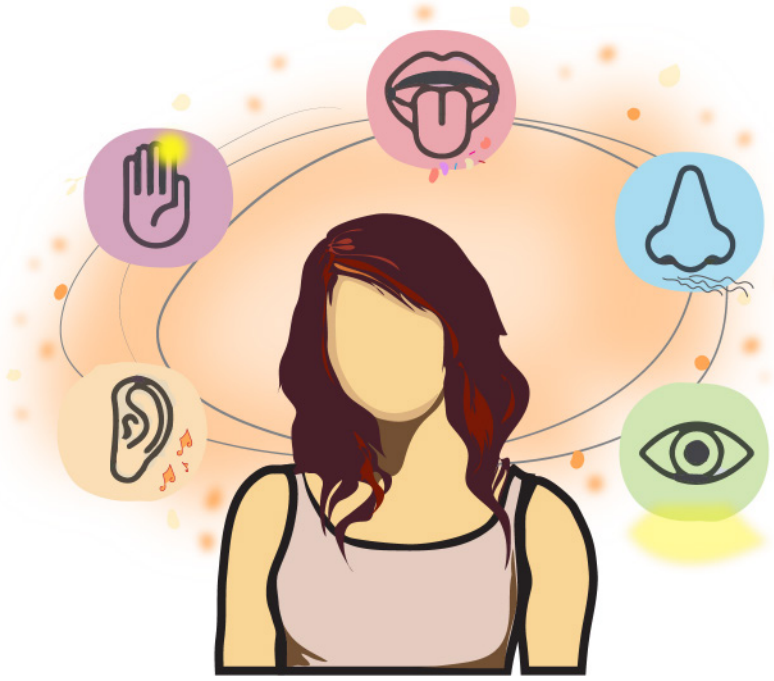

Figure 5: Hallusinations and Parkinson's disease

majority were experiencing hallucinations in multiple sensory modalities by 10 years of follow-up. These non-visual hallucinations are not confined to end-stage Parkinson's Disease dementia; they are also found in patients whose cognition is relatively intact (Mini-Mental State Examination (MMSE) score 24 or 25).

The delusional themes (as shown in fig.6) identified depends on the assessment instruments used. They typically include sin or guilt, grandiosity, reference, religion, persecution, jealousy, and theft, without prominence of any specific theme. ***Delusional mis-identification syndromes are a specific subset of delusions characterized by pathological familiarity. This include the Capgras delusion (the belief that someone familiar has been replaced by an imposter), reduplicative paramnesia (the belief that a room or place has been duplicated and is present at two locations simultaneously) and the mirror sign (failure to recognize oneself in the mirror).*** In patients who have dementia with Lewy bodies (DLB), the prevalence of misidentification syndromes was found to increase with greater cognitive decline. A similar trend was observed in individuals with Alzheimer's disease, although the prevalence was lower overall. A smaller-scale study of patients with Parkinson's Disease dementia found a 16.7% prevalence of mis-

identification symptoms, and also noted an association between these symptoms and a specific profile of memory and language deficits. [5, Rank 1]

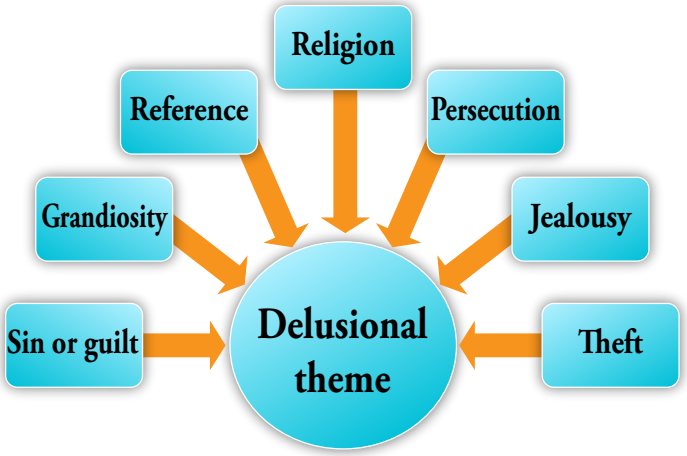

Figure 6: Delusional theme in Parkinson's disease

Frequency and Clinical Consequences of Parkinson's disease

Psychosis spectrum symptoms are common in Parkinson's Disease and have important clinical consequences, in particular, an increased risk of dementia, nursing home placement and mortality. Quality of life is also impaired, both overall and in subdomains of emotional well-being, daily living, cognition and bodily discomfort. Recent studies have provided revised prevalence estimates for Parkinson's Disease psychosis based on longitudinal study data, and have better characterized the link to poor cognitive outcome. [9, Rank 3]

> **"Previous studies of visual hallucinations have linked visual parietal areas to hallucinations in the peripheral visual field (as described for passage hallucinations) and palinopsia (helping to account for palinparousia — recently described palinopsia-like presence hallucinations), and subregions of the intraparietal sulcus are linked to eye movement control."**

Mechanisms and Risk Factors for Parkinson's disease

A range of possible mechanisms to explain the psychosis spectrum, including changes in visual function, sleep, medication effects and cognition, were identified by researchers.

The eye and low-level vision

The predominantly visual nature of Parkinson's Disease psychosis spectrum symptoms points to dysfunction in the visual system. Early studies focused on low-level deficits in colour vision, contrast sensitivity and acuity. More recently, evidence has emerged of retinal changes in Parkinson's Disease, as measured by techniques such as ocular coherence tomogra-

phy (OCT) and electroretinography. However, to date, only one study using such techniques has investigated the retinal associations of the Parkinson's Disease psychosis spectrum. ***In patients with visual hallucinations, OCT revealed thinning of the retinal ganglion cell layer in the dominant eye at both nasal and temporal retinal locations.*** Such thinning could be the result of a primary process within the eye, or could be secondary to retrograde trans-synaptic degeneration caused by changes in the brain. Thinning was more pronounced in Parkinson's Disease psychosis patients without dementia, pointing to a primary process within the eye.

Visual perception and cognition

Early studies of the psychosis spectrum focused on visual hallucinations, and included patients with a range of severity of what might now be termed Parkinson's Disease-Mild Cognitive Impairment (PD-MCI). There are a range of cognitive tests that have been repeated in different studies, although the same version of a given test is rarely used by different groups. Most studies investigating visual perception, irrespective of the selection criteria (for example, unselected Parkinson's Disease-MCI cohorts versus participants selected for higher cognitive function) have shown deficits in the perception of objects, including faces. Similarly, most studies investigating executive function, as measured by the Stroop task, response inhibition and verbal fluency, have found deficits in patients with visual hallucinations. [10, Rank 2]

Deficits in memory and related hippocampal function tests are found in Parkinson's Disease patients with visual hallucinations, in both unselected Parkinson's Disease-MCI and higher-function groups. Some studies have reported deficits that are specific to visual — as opposed to verbal — memory. Greater memory deficits have also been found for black-and-white visual stimuli than for coloured visual stimuli. A transitive inference test thought to measure hippocampal function has uncovered impairments in patients with Parkinson's Disease psychosis. [7, Rank 2]

> **" The clinical and research profile of illusions, hallucinations, delusions and related symptoms in Parkinson disease (PD) was raised with the publication of a consensus definition of Parkinson 's disease psychosis "**

Minor hallucinations

Only few studies focused on the cognitive profile associated with minor hallucinations in Parkinson's Disease. Compared with patients without psychosis spectrum symptoms, patients with minor hallucinations had no significant differences in verbal memory, verbal fluency or sustained attention. Progressive decreases in cognitive performance were seen across the spectrum from no hallucinations, through minor hallucinations and hallucinations with insight, to hallucinations without insight. The lack of cognitive deficits in patients with minor hallucinations raises the issue of whether the onset of psychosis spectrum symptoms predates measurable cognitive decline.

Multimodal hallucinations

One might expect patients with non-visual hallucinations in the later stages of Parkinson's Disease to exhibit greater cognitive deficits or a different cognitive profile compared with Parkinson's Disease patients with visual hallucinations alone. However, one study compared patients with visual only and visual plus non-visual hallucinations found no evidence of significant additional decline in the latter group for any of the cognitive domains tested (including verbal memory and verbal fluency). The number of patients with hallucinations in multiple modalities were small, as the study might have been underpowered to detect such changes.

Delusions

Only one study has compared cognitive profiles between Parkinson's Disease psychosis spectrum patients with hallucinations but not delusions and those with delusions but not hallucinations. Cognitive profiles did not differ significantly between the two groups. Cognitive scores in a range of domains were found to correlate with the severity and number of hallucination modalities (for example, auditory, olfactory somatic and/or visual), but not with the severity and number of delusion modalities (for example, jealousy, grandiosity and/or religious delusions). These findings suggest that cognitive risk factors for hallucinations and delusions might differ. This view is supported by evidence from a study investigating risk factors for a specific delusion (delusional jealousy), where an association was found with dopamine agonist treatment but not dementia, in contrast to hallucinations, where an association was found with dementia but not dopamine agonist treatment

" Compared with patients without psychosis spectrum symptoms, patients with minor hallucinations had no significant differences in verbal memory, verbal fluency or sustained attention "

Neuropathology of Parkinson's disease

Neuropathological studies provide important insights into the distribution of Lewy body (DLB) pathology at different stages of the Parkinson's Disease psychosis spectrum. ***The first study to report on this issue found significantly higher Lewy body load in the amygdala and parahippocampal gyrus in patients with visual hallucinations, half of whom met the clinicopathological criteria for Parkinson's Disease and half of whom met the criteria for DLB.*** Subsequent studies have replicated the finding of limbic pathology associated with visual hallucinations. Increased pathology also found in other regions, including the superior and lateral frontal cortex (Brodmann area), inferior and lateral temporal cortex, inferior parietal cortex, and cingulate cortex. Visual hallucinations are also linked to higher levels of amyloid and tau pathology in frontal, parietal and hippocampal areas. Only one study has investigated the occipital lobe in patients with visual hallucinations: Lewy body and tau pathologies were found to be absent, and amyloid burden was rated as mild.

Unlike patients with Parkinson's Disease psychosis who have dementia, those without dementia do not have cortical Lewy body involvement. An early study of Parkinson's Disease patients with visual hallucinations and MMSE scores >25 found increased Lewy body load in the basolateral nucleus of the amygdala, but only sparse Lewy bodies in the cortex and hippocampus. Consistent with the lack of cortical involvement, a recent study has found no association between Lewy body, tau or amyloid pathology in frontal, parietal and temporal regions and visual hallucinations after controlling for dementia, but found strong associations with dementia after controlling for visual hallucinations. Such findings suggest that the neuropathological changes underlying visual hallucinations are distinct from those underlying dementia.

Involvement of the cholinergic system in visual hallucinations is suggested by brainstem atrophy in the pedunculopontine nucleus and atrophy of the substantia innominata, which contains the nucleus basalis of Meynert. The cause of the atrophy is unclear, as no association has been found between visual hallucinations and Lewy body, tau or amyloid load in the nucleus basalis of Meynert. [8, Rank 3]

Patients with visual hallucinations exhibit abnormalities on a range of autonomic tests, including the tilt-table test, the Valsalva manoeuvre. In addition, autonomic dysfunction was found to be an independent risk factor for hallucinations (all modalities included) in, a large-scale 5-year

prospective study. The same study also reported female sex as an independent risk factor. REM sleep behaviour disorder (REM Sleep behavior disorder) is also associated with visual hallucinations, although the association is weak. Proportions of patients with visual hallucinations who do and do not have REM Sleep behavior disorder are similar. Vivid dreams are associated with visual hallucinations after controlling for factors including Parkinson's Disease duration, depression, anxiety and scores. ***Depression has been associated with hallucinations in Parkinson's Disease.*** The urinary concentration of the oxidative stress marker 8-hydroxydeoxyguanosine was found to correlate with the hallucination score (modality unspecified) after controlling for MMSE score, age, duration and part 3 score. [12, Rank 4]

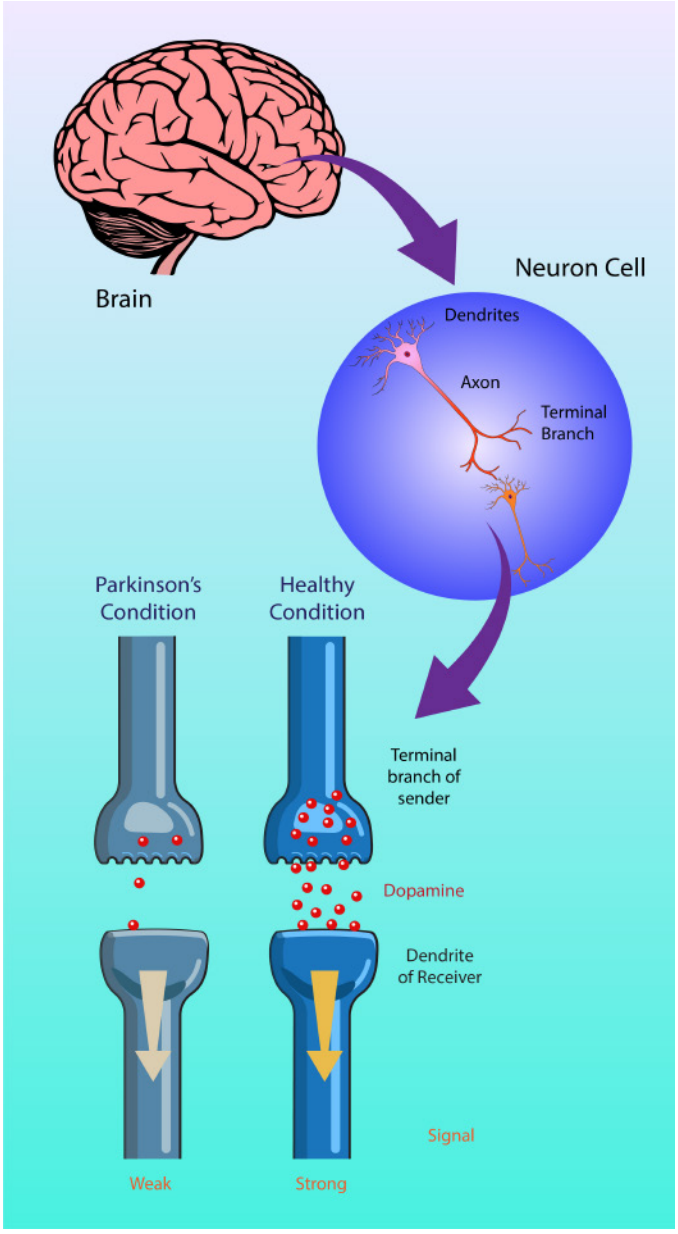

Figure 7: Neuronal activity in Parkinson's disease

Genetic Aetiology of Psychosis in Parkinson's disease

The genetic aetiology of psychosis in Parkinson's Disease is complex, and is likely to involve many genes each with a small effect size. In the broader literature, recent advances in the analysis of genome-wide data sets have uncovered genetic pleiotropy between clinically distinct diseases. Moreover, analyses whereby biological pathways (for example, molecular, cellular, organ/sys-

> **"Neuropathological studies have replicated the finding of limbic pathology associated with visual hallucinations, with increased pathology also found in other regions, including the superior and lateral frontal cortex, inferior and lateral temporal cortex, inferior parietal cortex, and cingulate cortex"**

tem or disease) are constructed on the basis of genomic data have shown promise in late-life depression. These types of emerging techniques have clear applications in heterogeneous conditions such as Parkinson's Disease, where questions surrounding the overlapping etiology of psychosis across neurodegenerative diseases and psychiatric disorders remain unanswered. The increasing availability of larger, better-characterized data sets will provide greater potential to conduct these more-sophisticated genetic analyses. [14, Rank 4]

Developments in Imaging Methodology in Parkinson's disease

The raised profile of Parkinson's Disease psychosis, combined with developments in imaging methodology, has resulted in a rapidly advancing evidence base that helps to inform the risk factor and mechanistic accounts of the symptom spectrum

Structural MRI

Despite methodological differences, structural imaging studies of visual hallucinations have yielded a number of consistent findings. Several studies have reported atrophy in the visual cortex — broadly defined as extending into lateral and ventral occipitotemporal regions including the fusiform gyrus and visual parietal cortex (corresponding to dorsal and ventral visual streams) — although this finding is not universal. A study focusing on minor hallucinations found atrophy in the midbrain, cerebellar vermis and visual parietal cortex, as well as areas of increased cortical volume in the limbic cortex and the posterior lobe of the cerebellum, which might be linked to compensatory mechanisms..

The distribution of atrophy described in the various studies is consistent with the profile of cognitive deficits found in Parkinson's Disease psychosis. At 30-month follow-up, patients who report visual hallucinations at baseline have greater progression of cortical atrophy within limbic, frontal and thalamic regions, and are more likely to have developed dementia. The greater rate of atrophy and hypothesized progression from hippocampal head involvement to diffuse hippocampal atrophy in patients with visual hallucinations might account for the association between visual hallucinations and poor cognitive outcome. [13, Rank 3]

Few studies have investigated white matter changes in Parkinson's Disease psychosis. An early study found no differences with regard to a range of clinically defined white matter lesion indices in patients with and without visual hallucinations. A more recent volumetric study described decreased

white matter volume in occipital and parahippocampal regions. Another study showed that the microstructural integrity of deep white matter, as measured by fractional anisotropy, was affected in Parkinson's Disease psychosis (defined as the presence of perceptual errors, hallucinations in any modality, or delusions).

> **"Reduced occipital low frequency fluctuations have been found in the resting state in Parkinson's Disease patients with a history of visual hallucinations. These fluctuations are thought to be an indirect measure of cerebral glucose metabolism and local field potentials, supporting the idea of occipital hypometabolism in patients with Parkinson's Disease who are susceptible to visual hallucinations"**

Neurotransmitter Imaging

Reduced dopamine transporter binding in the striatum in early Parkinson's Disease is associated with an increased prospective risk of Parkinson's Disease psychosis at 5 years. It is unclear whether this binding reduction represents the underlying mechanism of the psychosis spectrum or is an indirect association, for example, reflecting more-extensive neurodegenerative involvement in Parkinson's Disease psychosis.In a serotonergic imaging study [16, Rank 2]

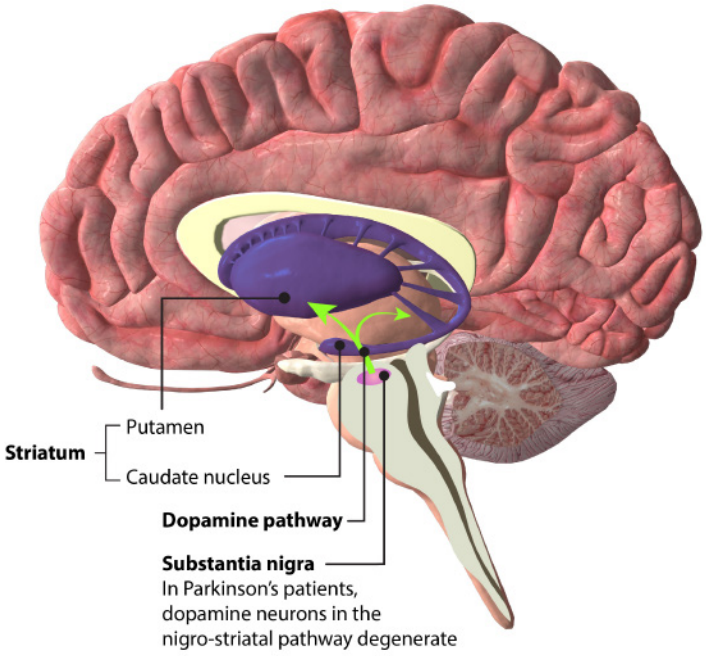

Figure 8 : Dopamine activity in Parkinson's disease

Functional MRI

There is a paucity of data on brain changes occurring in Parkinson's Disease at the time of a hallucination. ***One functional MRI (fMRI) case study found a decrease in activity in visual areas coincident with visual hallucinations. This decrease in occipital activity contrasts with evidence from eye disease, schizophrenia and induced visual hallucinations, which indicates that activity in visual areas increases at the time of visual hallucinations.*** The Parkinson's Disease case study also reported increased activity in the frontal lobe during the hallucinations. Frontal activations are not found in eye disease and schizophrenia during hallucinations.

Studies in which visual stimulation was used to probe cerebral activity have reported decreased activation in the parietal lobe, lateral occipitotemporal cortex and occipital cortex in Parkinson's Disease patients with a history of visual hallucinations. [16, Rank 5]

Treatment Options for Parkinson's disease Psychosis

Treatment of Parkinson's Disease psychosis includes psychological therapies, dose reduction of Parkinson's Disease medication, and medication to treat psychosis symptoms. For patients without prominent cognitive impairment, clozapine and pimavanserin have the best evidence of efficacy in Parkinson's Disease psychosis. In patients with cognitive impairment and visual hallucinations, rivastigmine was found to reduce the Neuropsychiatric Inventory score (predominantly the agitation component) in a secondary analysis. Unpublished evidence suggests efficacy of pimavanserin in Parkinson's Disease psychosis with cognitive impairment. The clozapine and pimavanserin trials have indicated a therapeutic effect specific to hallucinations as a whole but, to date, no studies have reported a specific effect on visual hallucinations. No treatment trials targeting minor symptoms have yet been reported. [23, Rank 4]

Atypical Antipsychotics

Evidence for the efficacy of clozapine in Parkinson's Disease psychosis sparked interest in the potential efficacy of quetiapine, a structurally related compound. Although early studies suggested a beneficial effect of quetiapine, several subsequent studies failed to replicate the findings in Parkinson's Disease and across the spectrum of dementia with parkinsonian symptoms. Similarly, open-label studies suggested that olanzapine was efficacious for Parkinson's Disease psychosis, but placebo-controlled and comparative trials found a worsening of motor symptoms without significant improvement of hallucinations. The Movement Disorder Society evidence-based medicine review of treatments for nonmotor symptoms concluded that there was insufficient evidence on the efficacy of quetiapine, and that olanzapine carried unacceptable risk.

Despite the lack of an evidence base, atypical and typical antipsychotics continue to be used in clinical practice, but are associated with increased mortality in the context of clinical trials and a retrospective database analysis, which ranked haloperidol as carrying the highest risk, followed by olanzapine, risperidone and

quetiapine. Such evidence cautions against the use of antipsychotics in Parkinson's Disease, and highlights the need for further studies in this area, as well as the development of new therapeutic approaches for Parkinson's Disease psychosis. [25, Rank 2]

> "Exploratory and confirmatory cluster analysis of a large Parkinson's Disease data set revealed associations between non-tremor-dominant Parkinson's Disease and psychopathology, including hallucinations and cognitive impairment"

Pimavanserin

A large double-blind, placebo-controlled study of pimavanserin found a significant improvement on the brain, with greater improvement in a subgroup with more-pronounced cognitive impairment. In an earlier study, a global measure of hallucinations assessed as a secondary end point improved in patients treated with pimavanserin, but the reduction in visual hallucinations was not significant when considered separately. Pimavanserin received FDA approval for the treatment of Parkinson's Disease psychosis. Its adverse event profile to date suggests advantages over other anti-psychotics in terms of risk of stroke, falls, fatigue, blood dyscrasia, neuroleptic malignant syndrome, orthostatic hypotension, and worsening of motor symptoms. [29, Rank 3]

Apomorphine

Unlike other dopamine agonists, this drug exerts intrinsic antagonist effects at the 5-HT2A receptor and agonist affects at both D1-like and D2-like receptors. This unique profile might account for case report and open-label study evidence that apomorphine does not exacerbate psychosis symptoms and, in some studies, may ameliorate these symptoms or improve visual contrast sensitivity. The mode of apomorphine administration may influence its impact on psychotic symptoms. An open-label study found improvements in perceptual and hallucination symptoms in patients treated with either apomorphine or intrajejunal levodopa. The effect size for apomorphine was larger than for intrajejunal levodopa, although the difference was not significant. Apomophine might have a place in the treatment of Parkinson's Disease psychosis; however, a better evidence base is needed to guide future recommendations. [33, Rank 3]

Electroconvulsive therapy

No sham-controlled studies of electroconvulsive therapy (ECT) for Parkinson's Disease psychosis have been undertaken, but two case series have reported improvements in Parkinson's Disease psychosis spectrum symptoms. In one study, Brief Psychiatric Rating Scale scores improved after five to 12 ECT sessions, and the effects persisted for 5–30 weeks. [36, Rank 2]

Systemic illness

Psychosis is part of a range of acute events in Parkinson's Disease, and is often seen in hospitalized patients with systemic infection, dopamine agonist withdrawal syndrome or parkinsonism– hyperpyrexia syndrome, as well as in postsurgical states. Management of the underlying precipitant, along with rehydration, cautious use of antipsychotic agents and — in suitable cases — gentle introduction of low-dose dopamine agonists, may be required. [41, Rank 3]

> **" As Parkinson's Disease progresses, hallucinations in non-visual (auditory, tactile and olfactory) modalities occur alongside visual hallucinations. "**

Cognitive Decline in Parkinson's disease

Parkinson disease (Parkinson's Disease) is one of the most common age-related brain disorders. Parkinson's Disease is defined primarily as a movement disorder, with the ***typical symptoms being resting tremor, rigidity, bradykinesia and postural instability,*** and is pathologically characterized by degeneration of nigrostriatal dopaminergic neurons and the presence of Lewy bodies in the surviving neurons.

In addition to the defining dopamine-related motor symptoms, Parkinson's Disease is increasingly recognized as a heterogeneous multisystem disorder involving other neurotransmitter systems, such as the serotonergic, noradrenergic and cholinergic circuits. Thus, a wide variety of nonmotor symptoms (Nonmotor symptoms) linked with these neurotransmitters are commonly observed in patients with Parkinson's Dis-

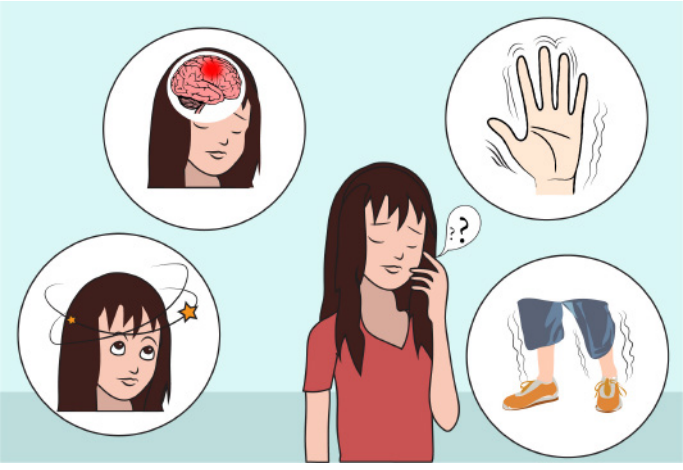

Figure 9: Typical symptoms of Parkinson's disease

ease. In light of this variability, subtyping of Parkinson's Disease has been proposed, including a system based on time of onset and ongoing rate of cognitive decline.

Cognitive decline is among the most common and important Nonmotor symptoms, and in this article we review the current status of knowledge regarding cognitive impairment in Parkinson's Disease. Robust evidence indicates that in comparison with age-matched groups without Parkinson's Disease, people with exhibit more rapid decline in a number of cognitive domains — in particular, executive, attentional and visuospatial domains, but also memory. The full spectrum of cognitive abilities can be observed in Parkinson's Disease, from normal cognition, through early mild subjective and objective decline (mild cognitive impairment (MCI)), to mild, moderate and even severe Parkinson's Disease dementia (Parkinson's Disease). Studies convincingly demonstrated a much higher cumulative risk of dementia in people with Parkinson's Disease than in the general population. Systematic reviews showed that the point prevalence of dementia was 25–30%. Several long-term longitudinal studies have indicated that the majority of patients with Parkinson's Disease will develop dementia if they survive for more than 10 years after diagnosis. On the basis of numerous, varied studies, we now know that dementia in Parkinson's Disease has important adverse implications for functioning, quality of life, caregiver burden, and health-related costs.

The timing, profile and rate of cognitive decline vary widely among individuals with Parkinson's Disease. Therefore, identifying and predicting future cognitive decline in this population is crucial for researchers and clinicians alike. Identification of clinical and biological markers that can predict which patients are at increased risk of early and rapid cognitive decline is important for communicating the prognosis and managing patients clinically. Established demographic and clinical risk factors include increasing age and more severe parkinsonism, in particular, non-tremor features. [44, Rank 4]

Clinical Challenges in Parkinson's disease

Cognitive decline in Parkinson's Disease is a continuous process affecting nearly all patients over time. ***A clinical challenge is the distinction between Parkinson's Disease with Dementia (PDD) and dementia with Lewy bodies (DLB), owing to their clinical and pathological overlap.*** The '1-year rule', in which PDD is defined as dementia that occurs at least 1 year after onset of Parkinson's Disease motor symptoms, whereas dementia occurring before, simultaneously with, or

within the first year of onset of parkinsonism is classified as DLB. A substantial proportion of patients lie within the grey zone, and categorization is usually performed retrospectively. In addition, prodromal Parkinson's Disease and DLB symptoms overlap; for example, REM sleep behaviour disorder (REM Sleep behavior disorder) can evolve into either Parkinson's Disease or DLB.

Recent evidence indicates that cognitive impairment can be present in prodromal Parkinson's Disease, further blurring the distinction between Parkinson's Disease and DLB. The recently revised clinical diagnostic criteria for Parkinson's Disease propose that Parkinson's Disease can be diagnosed regardless of when dementia occurs in relation to parkinsonism onset. In cases where parkinsonism subsequently develops in a patient with dementia, the diagnosis 'Parkinson's Disease (DLB subtype)' is recommended. The relationship between Parkinson's Disease and DLB requires further exploration. For example, recent findings indicate several nonmotor subtypes of Parkinson's Disease, including cognitive and non-cognitive forms, which can occur in early untreated motor disease in late-onset Parkinson's Disease and in early-onset Parkinson's Disease [55, Rank 5]

Visual hallucinations and dementia risk

Several longitudinal studies have identified visual hallucinations and illusions as risk factors for cognitive decline and dementia in Parkinson's Disease, with the time frame depending on the study design. In one study, a history of visual hallucinations at baseline was found to increase the risk of dementia at 8 years, and another group found that baseline visual hallucinations or illusions increased the risk of dementia at 4–5 years. The association between visual hallucinations and dementia that has been observed in prospective studies might reflect progression of cognitive dysfunction, which seems to be present before or coincident with hallucination onset. [51, Rank 4]

Mechanisms of Cognitive Decline

A variety of mechanisms, in addition to the classic nigrostriatal α-synuclein misfolding and dopaminergic neuronal loss, contribute to the brain changes associated with Parkinson's Disease. Parkinson's Disease is now recognized to involve multisystem, multipeptide neurodegeneration, with non-dopaminergic degeneration having a crucial role.

Compared with the motor symptoms, little is known about the mechanisms underlying cognitive decline in Parkinson's Dis-

ease. Information on the mechanisms underlying cognitive decline in Parkinson's Disease has come from a variety of sources. In addition to post-mortem studies, in vivo studies, including clinicopathological studies and biomarker studies involving ***electrophysiological, imaging, electrophysiology and biofluid analyses, and genetic studies, have all contributed to an increased understanding.*** [34, Rank 4]

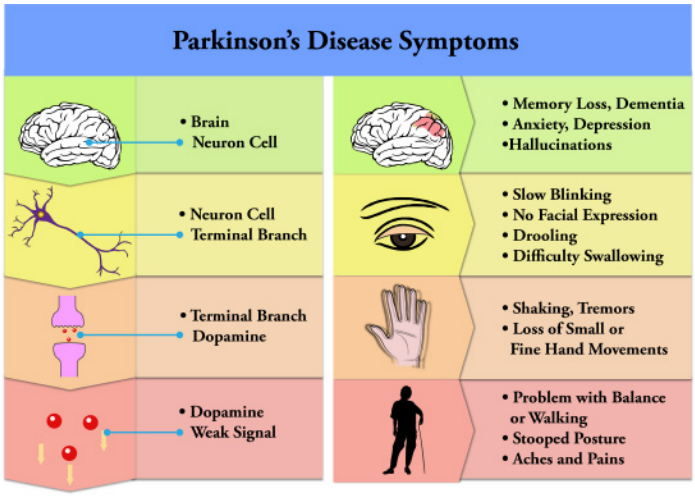

Figure 10: Parkinson's symptoms based on the affected area

Synaptic pathology and cognition

The structural pathologies described above are relevant, but only partially explain the variance in cognitive decline in patients with Parkinson's Disease. A better understanding of the disease substrate is needed for targeted drug discovery and to enable better monitoring of disease progression. Changes in synaptic function followed by synaptic loss are likely to be early and key events in neurodegenerative diseases. In Alzheimer's dimentia, loss of synapses was found to be more robustly correlated with cognitive decline than was morphological pathology [39, Rank 5].

Neurotransmitters

Convincing evidence is available that mesolimbic and mesocortical dopaminergic activity is associated with cognitive functioning. The association between dopaminergic drugs and cognition is complex, however, and antiparkinson drugs can improve, worsen or have no influence on cognition. For example, good evidence from postmortem and imaging studies indicates that the cholinergic system is affected relatively early in Parkinson's Disease and contributes to the cognitive decline. Interestingly, Lewy body and amyloid plaque pathologies were associated with earlier onset of dementia. Cholinergic deficits were more pronounced in individuals with dementia occurring later in the disease course. These observations provide a rationale for the positive effects of cholinesterase inhibitors in Parkinson's Disease, and worsening cognition associated with the use of medications with anticholinergic activity. [43, Rank 4]

Striatal GABAergic neurons express adenosine A2A receptors, which have become a drug target to improve motor functioning in Parkinson's Disease. These

receptors are also located in the thalamus and neocortex, and some evidence indicates that increased receptor activity is associated with worsening cognition. Adenosine A2A antagonists may increase dopamine activity in the prefrontal cortex, and preliminary evidence suggests that they can improve cognition — in particular, working memory — in Parkinson's Disease.

Mitochondrial activity

Mitochondrial dysfunction occurs in Parkinson's Disease, but little is known regarding its potential role in cognitive decline. However, mitochondrial pathology seems to contribute to cognitive decline in Alzheimer's disease. Mitochondrial activity is particularly high at the synapse, and is crucial to synaptic activity. A relationship between α-synuclein and mitochondrial activities at the level of synapses has been demonstrated, but their causal relationship needs to be further explored. Therapeutic approaches targeting mitochondrial activity are being developed. The role of mitochondrial dysfunction in cognitive decline in Parkinson's Disease needs to be further explored. [29, Rank 3]

Inflammation and neurotrophic factors

Neuroinflammation is relevant for both Alzheimer's Disease and Parkinson's Disease, and might have important implications for cognitive decline in Parkinson's Disease, with a potential for novel treatment targets. Increased microglial activation is thought to lead to cell death in Alzheimer's Disease and Parkinson's Disease with dementia, and inflammation markers represent possible prognostic biomarkers. Interestingly, CSF levels of cytokines are found to be associated with cognitive impairment in Parkinson's Disease and, thus, represent possible biomarkers.

Findings from many different sources convincingly demonstrate a link between diabetes, insulin resistance and Parkinson's Disease, possibly via mechanisms involving neuro-inflammation and mitochondrial dysfunction. A recent imaging study in a cohort of 36 patients, 12 of whom had diabetes, reported an association between diabetes, grey matter loss and cognitive impairment in Parkinson's Disease, indicating a possible role for antidiabetic drugs in the treatment or prevention of cognitive decline in Parkinson's Disease, as has been suggested in Alzheimer's disease.

Neurotrophic factors are crucial for neuronal plasticity and, thus, learning and other cognitive functions. A longitudinal study showed that cognitive impairment in Parkinson's Disease was associated with reduced levels of growth factors, such as brain-derived neurotrophic factor and epidermal growth factor, in CSF and plasma [54, Rank 4]

Genetic Effects on the Clinical Presentation of Parkinson's Disease

Genetic variants that cause monogenic forms of Parkinson's Disease have been extensively investigated with respect to their effects on the clinical presentation of Parkinson's Disease, including cognition and susceptibility to dementia. Most other research in sporadic Parkinson's Disease has largely focused on four candidate genes: glucosylceramidase (GBA), microtubule-associated protein tau (MAPT), apolipoprotein E (APOE) and catechol-O-methyltransferase (COMT).

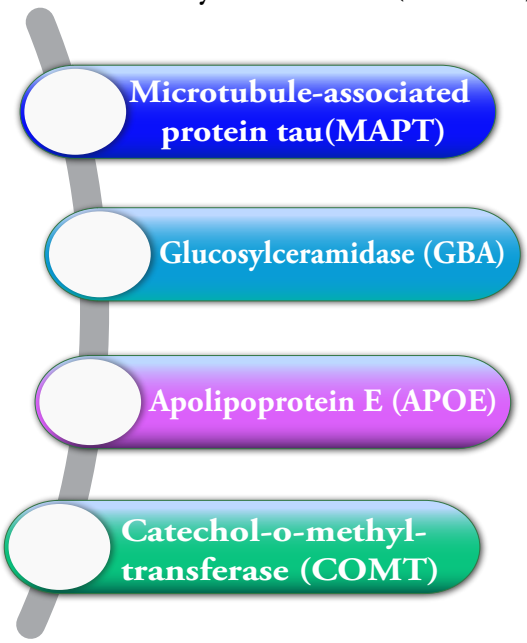

Figure 11: Genes associated in Parkinson's disease

Of these, GBA has the strongest evidence base for association with cognitive measures. GBA is a highly polymorphic gene, and two large independent studies found that the type of mutation modulates the relationship with cognitive decline, furthering the possibility of disease subtyping on the basis of genetic status.

Despite some compelling findings, experiments designed to examine the effects of single genes can only capture a small proportion of the variance of complex traits such as cognition. Genome-wide association studies go some way towards addressing this issue by simultaneously genotyping markers across the genome. One such study conducted in Parkinson's Disease cognition found no genome-wide significant hits but, with only some cases, was underpowered. The application of genome-wide methods in other diseases across neurology and psychiatry has generated promising findings, but much larger data sets are needed in Parkinson's Disease. The availability of such samples — and, consequently, the potential to conduct more powerful genetic analyses — is increasing. [56, Rank 3]

Management of Patients with REM Sleep Behaviour disorder and Parkinson's Disease

Adequately powered, randomized studies for treatment of REM Sleep behavior disorder in Parkinson's Disease have not been conducted. Clonazepam and melatonin are commonly used based on guidelines established for idiopathic REM Sleep behavior disorder, but there are limited data on the efficacy of these drugs in individuals with REM Sleep behavior disorder and a diagnosed neurodegenerative disorder.

While data are limited, it is probable that this group of patients are more susceptible to side effects of benzodiazepines. In regards to other drug classes examined in studies including more than 30 patients, open-label data suggest that memantine may reduce the frequency of dream enactment.

An integral part of the management of REM Sleep behavior disorder is intervention aimed at reducing injury to both the patient and the bed-partner. This includes not only pharmacologic management but also institution of environmental modifications, such as removing sharp objects on which the patient can injure themselves, placing the mattress on the floor, and securing windows.

Nocturnal hallucinations are common in Parkinson's Disease, particularly advanced Parkinson's Disease, and are more common in Parkinson's Disease patients with REM Sleep behavior disorder compared to those without. Anecdotally, individuals with Parkinson's Disease, particularly those with vivid dreams as occurs in REM Sleep behavior disorder, often have difficulty distinguishing nocturnal hallucinations from dreams. In such individuals, particularly when hallucinations are frightening and contribute to insomnia, consideration for treatment with anti-psychotics such quetiapine is warranted. Of course, the risks of worsening parkinsonism and other side effects need to be weighed against potential benefits in such cases. [34, Rank 5]

The majority of RCTs investigating treatment of insomnia in Parkinson's Disease in the past decade have included <30 patients and were excluded from this review. The available evidence to support treatment of insomnia in Parkinson's Disease was considered insufficient in the Movement Disorders Society Taskforce Guidelines. Controlled release carbidopa-levodopa, eszopiclone, and melatonin 3-5 mg were considered to have an acceptable risk without need for specialized monitoring. Since that time, some additional randomized trial data has become available for eszopicilone and melatonin, though the quality of evidence for these and other agents continues to be suboptimal.

While insomnia can be a side effect of anti-depressants, placebo-controlled studies of nortriptyline, paroxetine, and venlafaxine provide evidence that treating depression in Parkinson's Disease improves symptoms of insomnia. Though evidence supporting treatment of other psychiatric disorders that may be contributing to insomnia are limited, targeting specific psychiatric symptoms such as anxiety, nocturnal panic attacks, and nocturnal hallucinations in the management of insomnia are worthy of consideration and investigation in clinical trials. [55, Rank 5]

Restless Leg Syndrome in Patients with Parkinson's disease

Restless legs syndrome (RLS) or Willis Ekbom disease belongs to the group of Sleep-Related Movement Disorders. ***According to ICSD III criteria, RLS diagnosis requires "an urge to move the legs, usually accompanied by uncomfortable and unpleasant sensations in the legs".*** These symptoms must begin or worsen during periods of relative inactivity and must be partially or totally relieved by movement. The symptoms must cause significant distress or impairment in function. The interface of RLS and Parkinson's Disease has been of increasing interest over the past decade.

Compared to RLS, Periodic limb movement disorder (PLMD) has drawn less attention in Parkinson's Disease research. PLMD is a sleep-related movement disorder characterized by periodic limb movements during sleep (PLMS) (>5/hr in children and >15/hr in adults) that result in clinically significant sleep disturbance or impairment of functioning. [27, Rank 4]

RLS in Parkinson's Disease negatively impacts quality of life. One study found associations between RLS and younger age of Parkinson's Disease onset, male gender and higher Mini-Mental State Examination score. RLS has also been associated with non-motor Parkinson's Disease symptoms, which suggests the role of a non-dopaminergic system in the link between RLS and Parkinson's Disease. However, domperidone treatment has been linked with higher rates of RLS in Parkinson's Disease, suggesting a role for dopaminergic neurons outside of the blood-brain barrier in the pathophysiology of RLS. The main obstacle in interpreting these studies is that most enrolled Parkinson's Disease patients are already treated with dopaminergic agents, which may mask co-existent RLS. Associations between RLS and neuropathy have been well recognized, but not systematically studied. In one study, no correlations were found between RLS and neuropathy, levodopa exposure, and vitamin B12 levels in patients with Parkinson's Disease. Although not systematically studied in the Parkinson's Disease population, it is likely that RLS contributes not only to sleep onset insomnia but also sleep maintenance insomnia in Parkinson's Disease. This aspect is even more significant considering that RLS frequently mimics many symptoms intrinsic to Parkinson's Disease, making timely diagnosis challenging. [47, Rank 4]

While ***many of the dopaminergic agents used to treat Parkinson's Disease (levodopa, ropinirole, pramipexole, and rotigotine) also have been independently demonstrated in randomized trials to be***

effective in treating RLS, there are no randomized trials examining the treatment of RLS specifically in the Parkinson's Disease population. In addition, the occurrence and management of augmentation of RLS symptoms in Parkinson's Disease patients being treated with dopaminergic medications for their motor symptoms is poorly described. ***Two mainstays of evidence-based treatment of RLS in the non-Parkinson's Disease literature are applicable to Parkinson's Disease as well:*** (i) assessment for and correction of any iron deficiency, and (ii) consideration of reduction of and/or discontinuation of contributing agents such as anti-depressants.

Deep brain stimulation (DBS) is an important treatment modality for patients with Parkinson's Disease. Several groups reported positive postoperative effects of subthalamic nucleus(STN) DBS on RLS. However, emergence of RLS subsequent to STN DBS may occur as well, emphasizing the need to screen for RLS postoperatively as the reduction in anti-parkinsonian medications may lead to unmasking of RLS. [59, Rank 4]

Central sleep apnea in Parkinson's Disease patients has been associated with higher doses of dopamine agonists. Interestingly, control subjects with OSA have higher levels of sympathetic activity during sleep than Parkinson's Disease patients with OSA, suggesting that sympathetic dysfunction in Parkinson's Disease leads to a blunted response to apnea. These findings support the argument that sleep apnea in Parkinson's Disease may have fewer cardiovascular consequences. In addressing cardiovascular health among Parkinson's Disease patients with and without SDB, one study showed a trend toward more history of cardiovascular events in Parkinson's Disease patients with sleep apnea, but this did not reach significance. Another study found no difference in presence of cardiovascular disease between Parkinson's Disease participants with and without SDB or between controls and Parkinson's Disease subjects with OSA. [56, Rank 2]

The association between daytime sleepiness and sleep apnea has not been definitively established in Parkinson's Disease. Among Parkinson's Disease patients not selected for any sleep complaint, patients with objective sleepiness by MSLT had higher apnea hypopnea index (AHI), with no correlation between subjective sleepiness and AHI. Similar findings of absence of correlation between ESS and AHI have been reported in other studies as well, and one study found no correlation between self-reported snoring and subjective sleepiness.

In contrast, other studies have demonstrated a relationship between subjective sleepiness and sleep apnea, including

one showing significant correlation between both subjective and objective sleepiness and AHI. Available data indicate that objective sleepiness is consistently influenced by the presence of sleep-disordered breathing, but its effect on subjective sleepiness is less well established. This suggests that some Parkinson's Disease patients may underestimate their degree of sleepiness. [42, Rank 3]

Dopaminergic medications may also affect levels of somnolence, and studies of dopamine agonists frequently note somnolence as an adverse effect. However, some investigations have shown no correlation between medications and subjective sleepiness. To summarize, dopaminergic medications, particularly dopamine agonists, influence subjective sleepiness in some patients, but do not appear to cause changes in objective measures of sleepiness. This is another example of the disconnect between patient perception and objective outcomes.

Conclusion

The paradigmatic shift in perspective that followed the consensus definition of Parkinson's Disease psychosis, revitalized research interest and led to a rapidly expanding literature. The impact of these studies is still evolving, but there have already been important clinical consequences, such as a change in our understanding of the prevalence of Parkinson's Disease psychosis, given that it increases with Parkinson's Disease duration. These research evidence also helped in expansion of the range of symptoms considered part of the psychosis spectrum and recognition of new prospective risk factors for Parkinson's Disease psychosis. The largest expansion of literature has been in the mechanism domain, particularly in studies of cognitive profile, structural brain imaging and genetics. Evidence from studies of minor hallucinations, formed hallucinations and delusions, for example, suggest that the mechanisms are not the same for all symptoms. This information has significant implications for the assessment of Parkinson's Disease psychosis in research studies. [60, Rank 5]

Dopaminergic medications may also affect levels of somnolence, and studies of dopamine agonists frequently note somnolence as an adverse effect. However, some investigations have shown no correlation between medications and subjective sleepiness. To summarize, dopaminergic medications, particularly dopamine agonists, influence subjective sleepiness in some patients, but do not appear to cause changes in objective measures of sleepiness. This is another example of the disconnect between patient perception and objective outcomes.

***Important information for post-test are highlighted in red letters, boxes and diagrams.**

References

1. Ravina B, et al. Diagnostic criteria for psychosis in Parkinson's disease: report of an NINDS, NIMH work group. Mov Disord. 2017

2. Diederich NJ, Fénelon G, Stebbins G, Goetz CG. Hallucinations in Parkinson disease. Nat Rev Neurol. 2019

3. Fénelon G, Alves G. Epidemiology of psychosis in Parkinson's disease. J Neurol Sci. 2015

4. Rabey JM. Hallucinations and psychosis in Parkinson's disease. Parkinsonism Relat Disord. 2018

5. Friedman JH. Parkinson's disease psychosis 2010: a review article. Parkinsonism Relat Disord. 2019

6. Friedman JH. Parkinson disease psychosis: update. Behav Neurol. 2015

7. Goetz CG. New developments in depression, anxiety, compulsiveness, and hallucinations in Parkinson's disease. Mov Disord. 2016

8. Fénelon G. Psychosis in Parkinson's disease: phenomenology, frequency, risk factors, and current understanding of pathophysiologic mechanisms. CNS Spectr. 2018

9. Inzelberg R, Kipervasser S, Korczyn Alzheimer's disease. Auditory hallucinations in Parkinson's disease. J Neurol Neurosurg Psychiatry. 2018

10. Fénelon G, Mahieux F, Huon R, Ziegler M. Hallucinations in Parkinson's disease: prevalence, phenomenology and risk factors. Brain. 2016

11. Fénelon G, Soulas T, Cleret de Langavant L, Trinkler I, Bachoud-Levi AC. Feeling of presence in Parkinson's disease. J Neurol Neurosurg Psychiatry. 2016

12. Wood RA, Hopkins SA, Moodley KK, Chan D. Fifty percent prevalence of extracampine hallucinations in Parkinson's disease patients. Front Neurol. 2015

13. Boubert L, Barnes J. Phenomenology of visual hallucinations and their relationship to cognitive profile in Parkinson's disease patients: preliminary observations. 2016

14. Goetz CG, Stebbins GT, Ouyang B. Visual plus nonvisual hallucinations in Parkinson's disease: development and evolution over 10 years. Mov Disord. 2013

15. Goetz CG, Fan W, Leurgans S, Bernard B, Stebbins GT. The malignant course of "benign hallucinations" in Parkinson disease. Arch Neurol. 2017

16. Chou KL, et al. Drug-induced psychosis in Parkinson disease: phenomenology and correlations among psychosis rating instruments. Clin Neuropharmacol. 2015

17. Papapetropoulos S, et al. A questionnaire-based (UM-Parkinson's DiseaseHQ) study of hallucinations in Parkinson's disease. BMC Neurol. 2018

18. Factor SA, et al. Cognitive correlates of hallucinations and delusions in Parkinson's disease. J Neurol Sci. 2015

19. Moro A, Munhoz RP, Moscovich M, Arruda WO, Teive HA. Delusional misidentification syndrome and other unusual delusions in advanced Parkinson's disease. Parkinsonism Relat Disord. 2017

20. Pagonabarraga J, et al. A prospective study of delusional misidentification syndromes in Parkinson's disease with dementia. Mov Disord. 2018

21. Ballard C, et al. Psychiatric morbidity in dementia with Lewy bodies: a prospective clinical and neuropathological comparative study with Alzheimer's disease. Am J Psychiatry. 2019

22. Fernandez HH, et al. Scales to assess psychosis in Parkinson's disease: critique and recommendations. Mov Disord. 2018

23. Mosimann UP, et al. A semi-structured interview to assess visual hallucinations in older people. Int J Geriatr Psychiatry. 2018

24. Voss T, et al. Performance of a shortened Scale for Assessment of Positive Symptoms for Parkinson's disease psychosis. Parkinsonism Relat Disord. 2017

25. Yokoi K, et al. Hallucinators find meaning in noises: pareidolic illusions in dementia with Lewy bodies. Neuropsychologia. 2016

26. McKinlay A, et al. A profile of neuropsychiatric problems and their relationship to quality of life for Parkinson's disease patients without dementia. Parkinsonism Relat Disord. 2017

27. Fénelon G, Soulas T, Zenasni F, Cleret de Langavant L. The changing face of Parkinson's disease-associated psychosis: a cross-sectional study based on the new NINDS–NIMH criteria. Mov Disord. 2015

28. Pagonabarraga J, et al. Minor hallucinations occur in drug-naive Parkinson's disease patients, even from the premotor phase. Mov Disord. 2016

29. Friedman JH. Editorial on: Pagonabarraga, J et al Minor hallucinations occur in drug-naive Parkinson's disease patients even from the premotor phase Movement Disorders 2015; available from: 10.1002/mds.26432. Mov Disord. 2016

30. Mack J, et al. Prevalence of psychotic symptoms in a community-based Parkinson disease sample. Am J Geriatr Psychiatry. 2015

31. Gibson G, et al. Frequency, prevalence, incidence and risk factors associated with visual hallucinations in a sample of patients with Parkinson's disease: a longitudinal 4-year study. Int J Geriatr Psychiatry. 2017

32. De la Riva P, Smith K, Xie SX, Weintraub D. Course of psychiatric symptoms and global cognition in early Parkinson disease. Neurology. 2015

33. Forsaa EB, et al. A 12-year population-based study of psychosis in Parkinson disease. Arch Neurol. 2016

34. Aarsland D, Andersen K, Larsen JP, Lolk A, Kragh-Sorensen P. Prevalence and characteristics of dementia in

Parkinson disease: an 8-year prospective study. Arch Neurol. 2017

35. Anang JB, et al. Predictors of dementia in Parkinson disease: a prospective cohort study. Neurology. 2018

36. Uc EY, et al. Incidence of and risk factors for cognitive impairment in an early Parkinson disease clinical trial cohort. Neurology. 2019

37. Morgante L, et al. Psychosis associated to Parkinson's disease in the early stages: relevance of cognitive decline and depression. J Neurol Neurosurg Psychiatry. 2018

38. Ibarretxe-Bilbao N, et al. Differential progression of brain atrophy in Parkinson's disease with and without visual hallucinations. J Neurol Neurosurg Psychiatry. 2015

39. Ramirez-Ruiz B, Junque C, Marti MJ, Valldeoriola F, Tolosa E. Cognitive changes in Parkinson's disease patients with visual hallucinations. Dement Geriatr Cogn Disord. 2017

40. Gasca-Salas C, Clavero P, Garcia-Garcia D, Obeso JA, Rodriguez-Oroz MC. Significance of visual hallucinations and cerebral hypometabolism in the risk of dementia in Parkinson's disease patients with mild cognitive impairment. Hum Brain Mapp. 2016

41. Reijnders JS, Ehrt U, Lousberg R, Aarsland D, Leentjens AF. The association between motor subtypes and psychopathology in Parkinson's disease. Parkinsonism Relat Disord. 2019

42. Rana AQ, Vaid HM, Edun A, Dogu O, Rana MA. Relationship of dementia and visual hallucinations in tremor and non-tremor dominant Parkinson's disease. J Neurol Sci. 2018

43. Bodis-Wollner I. Foveal vision is impaired in Parkinson's disease. Parkinsonism Relat Disord. 2017

44. Lee JY, et al. Retinal nerve fiber layer thickness and visual hallucinations in Parkinson's disease. Mov Disord. 2018

45. Ramirez-Ruiz B, Junque C, Marti MJ, Valldeoriola F, Tolosa E. Neuropsychological deficits in Parkinson's disease patients with visual hallucinations. Mov Disord. 2016

46. Shin S, et al. Neuroanatomical substrates of visual hallucinations in patients with non-demented Parkinson's disease. J Neurol Neurosurg Psychiatry. 2015

47. Barnes J, Boubert L. Visual memory errors in Parkinson's disease patient with visual hallucinations. Int J Neurosci. 2015

48. Moustafa AA, Krishna R, Frank MJ, Eissa AM, Hewedi DH. Cognitive correlates of psychosis in patients with Parkinson's disease. Cogn Neuropsychiatry. 2014

49. Ozer F, et al. Cognitive impairment patterns in Parkinson's disease with visual hallucinations. J Clin Neurosci. 2017

50. Katzen H, et al. Multi-modal hallucinations and cognitive function in Parkinson's disease. Dement Geriatr Cogn Disord. 2015

51. Koerts J, et al. Attentional and perceptual impairments in Parkinson's disease with visual hallucinations. Parkinsonism Relat Disord. 2016

52. Llebaria G, et al. Neuropsychological correlates of mild to severe hallucinations in Parkinson's disease. Mov Disord. 2015

53. Poletti M, et al. Dopamine agonists and delusional jealousy in Parkinson's disease: a cross-sectional prevalence study. Mov Disord. 2017

54. Harding AJ, Broe GA, Halliday GM. Visual hallucinations in Lewy body disease relate to Lewy bodies in the temporal lobe. Brain. 2017

55. Gallagher DA, et al. Testing an aetiological model of visual hallucinations in Parkinson's disease. Brain. 2018

56. Papapetropoulos S, McCorquodale DS, Gonzalez J, Jean-Gilles L, Mash DC. Cortical and amygdalar Lewy body burden in Parkinson's disease patients with visual hallucinations. Parkinsonism Relat Disord. 2016

57. Jacobson SA, et al. Plaques and tangles as well as Lewy-type alpha synucleinopathy are associated with formed visual hallucinations. Parkinsonism Relat Disord. 2016

58. Kalaitzakis ME, et al. Dementia and visual hallucinations associated with limbic pathology in Parkinson's disease. Parkinsonism Relat Disord. 2019

59. Harding AJ, Stimson E, Henderson JM, Halliday GM. Clinical correlates of selective pathology in the amygdala of patients with Parkinson's disease. Brain. 2018

60. Janzen J, et al. The pedunculopontine nucleus is related to visual hallucinations in Parkinson's disease: preliminary results of a voxel-based morphometry study. J Neurol. 2017