

Advances in Biological Psychiatry

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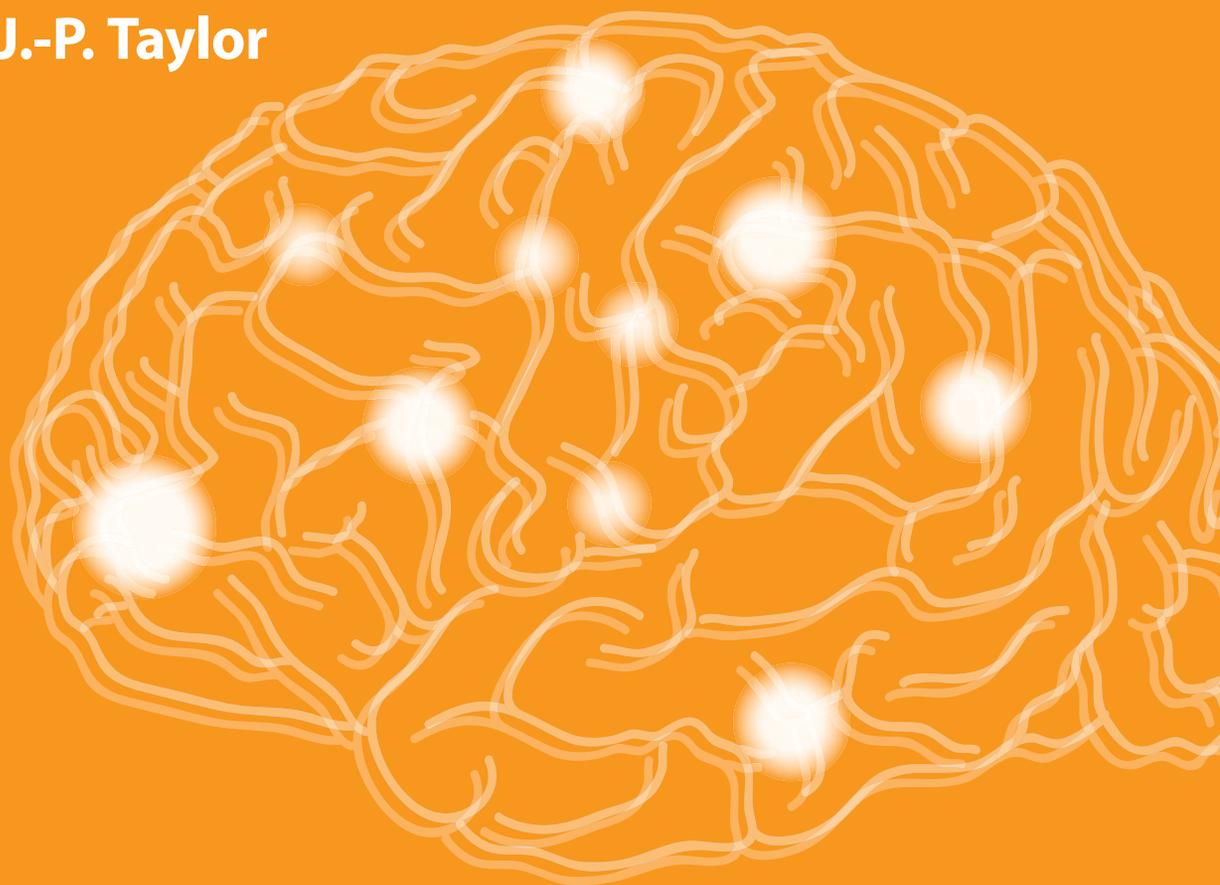
Psychiatry of Parkinson's Disease

Editors

K.P. Ebmeier

J.T. O'Brien

J.-P. Taylor



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Psychiatry of Parkinson's Disease

Advances in Biological Psychiatry

Vol. 27

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Psychiatry of Parkinson's Disease

Volume Editors

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Preface

Working in old age psychiatry, the clinician will frequently come across patients with Parkinson's disease (PD). In fact, the dual training in neurology and psychiatry, as it is practised in some continental European countries, seems particularly desirable here: the neurologist is well advised to know about the psychopathology and various psychiatric presentations of organic brain disease, while the psychiatrist needs to be well informed about the neurology and neuropharmacology of the same patients. For this reason, we assembled a number of chapters that present the state of the art knowledge about the various psychiatric syndromes found in PD, covering epidemiology, psychopathology, potential mechanisms, as well as treatments and general management of these disorders. As some psychiatric presentations of PD have not been described systematically until quite recently, we have not removed redundancy too energetically: the treatment of certain topics, such as apathy actually benefits from a multifaceted presentation. Some disorders, such as depression and dementia in PD will have been well described many times, while others, such as the relationship between somatoform disorders and parkinsonism are relatively new and hypothetical, and require further confirmation. Moreover, the pathophysiology of parkinsonism, rather transparent compared with most psychiatric disorders, supplies ready-made models for psychiatric syndromes and aetiological hypotheses, even when these are occurring outside parkinsonism proper.

Some syndromes, such as the psychotic disorders of parkinsonism are a genuine conundrum for the clinician: anti-psychotic treatments tend to worsen motor symptoms, while the treatment of just these motor symptoms may often worsen or even precipitate psychotic symptoms. Similarly, while anticholinergics have a traditional role in the treatment of some parkinsonian symptoms, they may clearly worsen cognitive and non-cognitive symptoms in Lewy body diseases, whether presenting as dementia with Lewy bodies or indeed as PD dementia. The only currently available treatments used in dementia, i.e. acetylcholinesterase inhibitors, on the other hand, should theoretically be unhelpful for parkinsonian motor symptoms, but are they?

We hope that this collection of expert reviews will provide answers to some of these questions, and will be helpful to the practising clinician, whether psychiatrist or neurologist, and to other professionals dealing with parkinsonian patients. If in

addition the exposition of problems and presentations stimulate research and further development in this fascinating area, we would be especially gratified.

We like to take this opportunity to thank Amanda Pipkin for her conscientious secretarial and organisational support, and the team at Karger in Basle for their help.

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Epidemiology of Psychiatric Symptoms in Parkinson's Disease

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Abstract

Background: Parkinson's disease (PD) is a multifaceted disease characterized by motor symptoms, and often accompanied by autonomous and psychopathological symptoms. This comorbid psychopathology may take the form of affective, motivational, perceptual, and cognitive symptoms, as well as sleep disturbances and sexual problems. **Aim:** To review the prevalence, impact and risk factors of psychopathology in PD. **Methods:** Review of the literature. **Results:** The prevalence and cumulative incidence of psychopathological symptoms is high. The reported prevalence is 17% for major depressive disorder, 34% for anxiety disorder, 17% for apathy, 14% for impulse control disorders, 88% for sleep disturbances and 60% for sexual problems. The cumulative incidence of hallucinations is 60%. Mild cognitive impairment is present in at least 50% with a cumulative incidence of 66% for dementia after 12 years. All psychopathological syndromes have a strong negative impact on a number of disease parameters, other psychiatric comorbidity, and quality of life. All psychopathological syndromes tend to occur with higher frequency in patients with the hypokinetic rigid type of PD. Other risk factors divide into general and disease-specific risk factors, and may vary between the different syndromes. **Conclusion:** Given the prevalence and impact, clinicians need to be constantly aware of the possibility of psychopathology in their PD patients.

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Nowadays, Parkinson's disease (PD) is generally considered a multifaceted disease with a broad spectrum of symptoms. According to the Queens Square Brain Bank diagnostic criteria, motor symptoms such as tremor, rigidity, hypokinesia, and postural instability are obligatory for a diagnosis of PD [1]. In addition to motor symptoms, the disease is often accompanied and sometimes preceded by non-motor symptoms including autonomic and psychopathological symptoms [2]. Autonomous symptoms include orthostatic hypotension, impaired cardiovascular regulation, dysphagia, delayed gastric emptying, urinary incontinence, constipation, dry mouth, disturbed thermoregulation with drenching sweats and sexual problems. Psychiatric symptoms include depression and anxiety, apathy, visual hallucinations and psychosis, impulse control disorders (ICDs), cognitive dysfunction and dementia. Additional symptoms include sleep disturbances, fatigue and pain.

Cluster analyses have shown that all forms of psychopathology occur more frequently in PD patients suffering from hypokinesia and rigidity than in PD patients suffering predominantly from tremor or from postural instability and gait difficulties [3, 4].

The broadness of the spectrum of symptoms can be understood by the disease's widespread pathophysiology in the brain. Braak et al. [5] proposed a staging system for this pathophysiology based on the presence of intraneuronal α -synuclein deposits, known as Lewy bodies. Different cerebral regions that are part of different functional neuroanatomic circuits and different neurotransmitter systems are affected sequentially, with pathology first affecting the olfactory tract and lower brainstem regions, then proceeding upwards to the midbrain, and finally to the basal forebrain and cerebral cortex. In this hypothesis, substantia nigra damage, which is associated with the characteristic motor symptoms of PD, occurs only in mid-stage disease. The diversity of systems affected, and the fact that some of these systems are affected before involvement of the substantia nigra, may explain the diversity of symptoms as well as the fact that some of the non-motor symptoms may precede motor symptoms. The neurobiology of neuropsychiatric symptoms in PD is discussed in the separate chapters. This chapter will provide a brief overview of the basic epidemiology of the psychiatric syndromes in PD that will be discussed in more detail in the other chapters of this volume.

Mood Disorders: Depression and Anxiety

Depression in PD has been the subject of study for a long time. The prevalence rates of depressive syndromes in PD reported in different studies vary widely, ranging from 2.7% to more than 90%, depending on the population studied, the way the diagnosis is established, and the type of prevalence reported (point prevalence, period prevalence) [6]. A recent systematic review of the prevalence rates of the different depressive disorders defined in DSM-IV depression in PD reported an average prevalence across studies of 17% for major depressive disorder, 22% for minor depression and 13% for dysthymia. In addition, 35% of patients showed a clinically relevant level of depressive symptoms without meeting the criteria for any specific depressive disorder [6]. As expected, the prevalence of major depressive disorder in PD patients is lower in the general population (8.1%) than in outpatient and inpatient hospital settings (24.0 and 21.7%, respectively). This is the same for the prevalence of clinically relevant depressive symptoms without a formal diagnosis of depressive disorder, which affects 10.8% in the general population versus 40.4 and 54.3% in hospital outpatients and inpatients, respectively [6].

Depression is linked to other PD symptoms and their severity. In cross-sectional studies, depressed patients have worse motor function and more limitations in activities of daily living (ADL) [7–10]. In addition, depressed PD patients exhibit more

cognitive symptoms [11, 12] and report a lower quality of life [13, 14]. In one study, depression was identified as the most important determinant of quality of life in PD patients [14]. Moreover, depression in the patient not only affects the patient, but is also a predictor of depression in the caregiver [15].

Depression is generally considered the result of multiple interacting risks – and protective factors. These can be divided into general risk factors for depression in the population and specific PD-related or treatment-related factors. In one of the few studies addressing general risk factors for depression in PD, a model consisting of five risk factors for depression in the general population, including age, (female) sex, a history of depression, a family history of depression and somatic comorbidity (other than PD), was able to predict major depressive disorder correctly in 75% of a sample of PD patients [16]. In addition, cognitive decline is associated with a higher prevalence of depressive disorder [17–20]. Specific PD-related variables associated with an increased risk for depression are the presence of motor fluctuations [18], a higher level of disability [19, 21] and more impairment of ADL functions [18, 20, 22]. The use of higher levodopa doses has been associated with increased levels of depression [20, 23], while some studies suggest that dopamine agonists may alleviate depressive symptoms [24, 25]. Depressive symptoms are more prominent in PD patients suffering from non-tremor-dominant forms of the disease [3, 4]. Several studies found an association between right-sided symptoms and the occurrence of depression [16, 21, 22], while one study found an association with left-sided symptoms [26].

Depression preceding the diagnosis of PD occurs with higher frequency than in control patients without a diagnosis of PD [27–29]. Odds ratios for depression preceding the diagnosis of PD vary from 1.2 to 3.1 [27]. In one study, 9% of PD patients suffered from depression in the last 3 years prior to diagnosis. Depression sufferers have a higher chance of being diagnosed with PD later [30].

Unlike depressive disorders, anxiety disorders have long been neglected in the research of psychopathology in PD. Fortunately, this is changing and in the past few years a number of larger scale epidemiological studies have been published. Again, prevalence rates for the different anxiety disorders vary widely across studies. Estimates suggest that up to 40% of PD patients experience substantial anxiety, and up to 34% have a circumscribed anxiety disorder as defined by DSM-IV criteria [31–35]. While earlier studies have described panic disorder as the most frequent anxiety disorder in PD, the more recent larger studies indicate that non-episodic anxiety disorders may occur more frequently. These recent studies report that 4–8% of patients suffer from panic disorder, 2–16% from agoraphobia without panic, 3–21% from generalized anxiety disorder, and 8–13% from social phobia (or social anxiety disorder) [31, 32, 34]. One single study reports on the prevalence of specific phobia (13%) and posttraumatic stress disorder (0%) [34]. In addition, 11.4% of patients suffer from significant anxiety symptoms without meeting the criteria for any DSM-defined anxiety disorder [32], while 12–20% meet the criteria for more than one disorder [32, 34]. This may be an indication of limited construct validity of DSM-defined anxiety

disorders in PD patients. There is a large overlap between depression and anxiety, which is reflected in the fact that 36–65% of PD patients suffering from an anxiety disorder also meet the criteria for a major depressive episode, while only 8% of those not suffering from an anxiety disorder meet these criteria [32, 34].

Anxiety in PD is associated with increased subjective motor symptoms, more severe gait problems and dyskinesias, freezing and on/off fluctuations [35–38]. Anxiety symptoms in PD patients also have a negative impact on health-related quality of life [34, 39]. There are not many studies of risk factors for anxiety disorders, and results from different studies are not always in line. In PD patients, female sex, severity of PD symptoms, the presence of motor fluctuations, as well as a previous history of an anxiety or depressive disorder have been identified as markers for anxiety disorders [31, 32, 34]. The use of a MAO-B inhibitor was associated with a reduced prevalence of anxiety disorders [32].

Anxiety may also precede the diagnosis of PD. One study reports an odds ratio of 2.2 for anxiety disorders and 2.4 for comorbid anxiety and depressive disorder in PD patients compared to control subjects in the years prior to diagnosis [40]. Whereas for depression such an association could only be made in the last few years preceding diagnosis, the increased risk of anxiety disorders was significant even up to 20 years prior to diagnosis of PD.

Apathy

Apathy is commonly observed in PD patients, but unfortunately it lacks a clear definition. Only recently has a set of diagnostic criteria for apathy as a syndrome been proposed. Based on earlier proposals by individual researchers [41–43], a workgroup endorsed by several professional associations, including the European Alzheimer's Disease Consortium and the European Psychiatric Association reached consensus on proposed diagnostic criteria. They defined apathy as a syndrome of reduced motivation, characterized by a deficiency in three symptom domains: activities, cognition and emotion [44]. The proposed diagnostic criteria have recently been validated in patients suffering from a range of neuropsychiatric diseases and in PD patients, where they showed good reliability and validity [45, 46]. So far, only one study involving PD patients has used these criteria and reported a prevalence of apathy of 17% [45]. In earlier studies, 'apathy' is usually diagnosed on the basis of an above threshold score on one of the apathy rating scales, or on the apathy section of the neuropsychiatric inventory (NPI). In these studies frequencies varying from 17 to 70% have been reported, depending on the population characteristics and assessment procedures [43, 47, 48].

In PD, apathy is associated with more severe cognitive deficits, more severe depressive symptoms, and a decreased quality of life [47–50]. Apathy is also considered a predictor of cognitive decline and dementia in PD patients [47].

Psychosis: Delusions and Hallucinations

Psychotic symptoms occur frequently in patients with PD and may affect up to 60% of the patients [51–53]. Psychosis in PD has a wide spectrum of presentations, ranging from ‘lively dreams’ to illusions or ‘misinterpretation of objects,’ ‘feelings of the presence or the passing of others,’ visual hallucinations, hallucinations in other sensory modalities, and delusions. Of those patients suffering from hallucinations, 64% suffer from illusions or sensations of presence or passing of people, 56% have visual hallucinations and 23% have auditory hallucinations [51]. Although longitudinal studies are scarce, it is clear that psychosis in PD tends to be persistent and progressive [54–56]. There is only one report of an increased incidence of psychosis prior to the diagnosis of PD [57].

The impact of psychosis in PD is considerable. It is associated with more severe depression, increased cognitive decline, and earlier nursing home placement [58, 59]. Psychosis is associated with a negative influence on quality of life of the patient [60], and increased caregiver strain [15].

Psychosis in PD is often seen as a ‘drug-induced’ psychosis due to dopaminergic treatment. However, the relation between medication and psychotic symptoms is not a simple one. Psychosis has been described in the pre-levodopa era, and infusion of levodopa in PD patients is not readily associated with incident hallucinations [61, 62]. Some studies find a correlation with higher levodopa equivalent medication doses [52], but most studies do not find such a relation [51, 63, 64]. Risk factors of psychosis in addition to medication are: higher age, higher age at onset, more advanced stage of disease, and disease duration. Moreover, comorbid conditions such as reduced vision [65], depression, cognitive decline and sleep disturbances predispose to psychosis [51, 52, 63, 64, 66].

Sleep Disturbances

Sleep disturbances are common in PD, and may affect up to 88% of patients [67]. They may take different forms. Rapid eye movement (REM) sleep behavioural disorder (RBD), excessive daytime sleepiness and ‘sleep attacks’ have received most attention. Other types of sleep disorders described in PD are insomnia, sleep apnoea, and restless legs syndrome (RLS). These types of sleeping disturbances are not mutually exclusive and may co-occur [68, 69].

RBD is characterized by abnormal behaviour during REM sleep due the absence of the usual atonia of voluntary muscles. Patients may enact their dreams, by which they may bring themselves or their partner in danger. Bruises, lacerations, fractures, etc. have all been reported as a result. The disorder may be present in 15–50% of patients [68, 70]. RBD is probably a predictor of hallucinations [71, 72].

Excessive daytime sleepiness occurs in 15–50% of patients [73]. It often co-occurs with fatigue and is significantly correlated with more severe motor symptoms, more disability, cognitive decline and depression [74]. Sleep attacks occur in up to 30% of

all patients [75]. They have been linked with the use of (any) dopamine agonist, but probably are associated with all dopamine replacement therapy [69]. Due to their occurrence without warning, sleep attacks may have considerable consequences if patients engage in potentially dangerous behaviour, such as driving.

Insomnia may take the form of problems with sleep initiation, sleep maintenance and early awakening. Insomnia may be due to physical discomfort, such as stiffness or muscle aches, nocturia or restless legs. Some 74–88% of patients report a degree of insomnia [67, 76]. Obstructive sleep apnoea syndrome (OSAS) is usually associated with obesity. Polysomnographic studies have shown that 20–50% of PD patients suffer from OSAS [68], often despite normal weight [77], which is tenfold the prevalence in the general population. RLS is a recently recognized syndrome that can occur in patients with PD. The prevalence of this coexistence is uncertain: some studies report a prevalence of 15% [78], while others report that patients may have restlessness, but fail to satisfy diagnostic criteria for RLS [79]. Apart from low serum ferritin, no other predictors of RLS are known [80].

As expected, disturbed sleep may have a great impact on the quality of life of patients [81, 82]. It is a risk factor for cognitive deterioration and dementia [83, 84], more frequent hallucinations [51] and a predictor for nursing home placement [59]. Sleep disturbances in patients also affect caregiver sleep to a great degree [85–87].

Sexual Dysfunction

Sexual dysfunction in patients with PD may take the form of impaired function or as hypersexuality. Hypersexuality can be defined as excessive sexual thoughts or behaviours that constitute an *atypical change from premorbid* sexual behaviour of the patient. It may take the form of inappropriate or excessive requests for sex from the partner, promiscuity, compulsive masturbation, the use of telephone sex lines or (online) pornography, or paraphilias [88]. These behaviours are usually associated with use of dopamine agonists or subthalamic deep brain stimulation, and will be discussed below under ICDs.

Sexual dysfunction is more common than hypersexuality. Although sexual dysfunction increases with age, there is evidence for PD-specific factors since impaired sexual dysfunction was reported in 60% of PD patients, as compared to 37% of matched controls [89]. Men with PD are more likely to report sexual problems than women [90]. Impaired sexual dysfunction in men may take the form of erectile dysfunction or impairment of ejaculation (up to 70%) or diminished libido (44%); reduced libido is reported in 44% of women [91–93]. In men, sexual dysfunction has been associated with testosterone deficiency [94].

Many factors may affect sexual function in PD patients: motor impairment, pain, fatigue, sweating, salivary drooling, side-effects of medication, as well as the changed roles in the relationship [95]. The epidemiology and aetiology of sexual dysfunction in PD has not been extensively studied.

Impulse Control Disorders

ICDs are a range of maladaptive behavioural patterns that are characterized by impulsiveness or compulsiveness. ICDs may take the form of pathological gambling, compulsive shopping, hypersexuality, binge eating, and compulsive medication use (the latter is often called ‘dopamine dysregulation syndrome’ or ‘hedonistic homeostatic dysregulation’). The exact psychopathological nature of ICDs is still under debate. If accompanied by elated mood, hyperactivity and reduced sleep, the behaviour may resemble a hypomanic state; if the behaviour is not associated with hedonic gratification, it may resemble a compulsive disorder; moreover, behaviour in ICDs may resemble that seen in addictive disorders and is sometimes viewed as a behavioural addiction [96].

In the largest study to date, including 3,090 PD patients, ICDs were described in 13.6% of patients. Of these, 5.7% suffered from compulsive buying, 5.0% from compulsive gambling, 4.3% from binge eating disorder, and 3.5% from compulsive sexual behaviour [97]. Of patients suffering from ICDs, 29% suffered from more than one type of ICD simultaneously. The percentages reported in this study are in line with those reported in several smaller studies [88, 97–100]. Compulsive medication use probably occurs in 3.4–4% of patients [96]. Men are more prone to suffer from compulsive sexual behaviour (OR 11.98), and women were more prone to suffer from compulsive buying (OR 1.82) and binge eating (OR 1.75) [97].

The most important risk factor for ICD is treatment with a dopamine agonist. Seventeen percent of patients treated with a dopamine agonist will have ICD. The odds ratio of having an ICD while being treated with a dopamine agonist versus not being treated with a dopamine agonist was 2.72 [97]. The association with dopamine agonists is probably a class effect, since no relevant differences were found between the incidence of inpatients being treated with pramipexole or ropinirole [88, 97, 98]. There was no association with the dose of dopamine agonist [88, 97], but there was an association with the dose of levodopa. When patients were treated with a combination of dopamine agonist and levodopa, compared with a dopamine agonist alone, there was an additional increase in the odds ratio for ICD to 1.42 [97]. Other risk factors for ICDs are younger age, younger age at onset, being unmarried, smoking, a family history of gambling problems, and alcohol use [88, 97].

It is hard to specify the impact of ICD in terms of disease severity, ADL or quality of life. Due to the nature of the syndrome, ICDs can be very disruptive on a relational, financial and social level. Compulsive gambling often leads to serious debts and compulsive sexual behaviours to relational difficulties and separation [88].

Cognitive Impairment and Dementia

Cognitive impairment and dementia are both common in PD. Cognitive impairment may be present early in the course of the disease and be associated with dopaminergic

deficiency in the mesocortical circuit. This ‘mild’ cognitive impairment (MCI) usually takes the form of mental slowing, attentional difficulties and disturbed executive function, including reduced mental flexibility and planning difficulties, while memory remains spared. About 50% of the patients will have cognitive impairment in at least one domain [101, 102]. MCI is a predictor of later dementia in PD [103, 104].

Dementia in PD is characterized by disturbances in a number of cognitive functions, while behavioural symptoms such as affective changes, hallucinations and apathy are frequent [105]. For a diagnosis of Parkinson dementia, a slow cognitive decline is necessary in at least two out of four core cognitive domains (attention, memory, executive and visuospatial function) [105]. Memory impairment is not obligatory for the diagnosis. A systematic review of dementia in PD reported that 24–31% of PD patients suffer from dementia, and that dementia associated with PD constitutes 3–4% of the cases of dementia in the population [106]. However, the cumulative incidence probably gives a better impression of the risk of dementia. Long-term follow-up studies show that the majority of PD patients will eventually develop dementia. Percentages reported vary from moderate percentages, e.g. 38% after 10 years [107], to high percentages: 52% after 4 years, and 78% after 8 years [108]; another study reports that 66% of patients will suffer from dementia after 12 years of follow-up [109], or even 87% after 20 years [110].

Risk factors associated with the occurrence of dementia are higher age, longer disease duration, more severe disease, hypokinetic forms of the disease, more disability, and probably also the existence of depression or psychosis and male sex [105, 107–111].

As is to be expected, dementia has a negative influence on quality of life [112]. Dementia is also a predictor of nursing home admission and mortality in PD [52, 58].

Conclusion

PD is a multifaceted disease, characterized by motor symptoms, autonomous symptoms and psychopathological symptoms. Among these psychopathological symptoms are affective, motivational, perceptual, and cognitive symptoms, as well as sleep disturbances and sexual problems. The prevalence or cumulative incidence of these symptoms is high, and they generally have a large impact on the general level of functioning and quality of life of patients. Given this prevalence and impact, it is important to be aware of these symptoms in clinical practice.

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Depression, Apathy and Anxiety Disorders

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Abstract

Depression and anxiety disorders are among the most common psychiatric comorbidities in Parkinson's disease (PD). Most patients will suffer major depression, minor depression or dysthymia at some stage during the progression of the illness. The presence of major depression suggests a more malignant type of PD as it is associated with a faster cognitive and functional decline, and a faster progression along the stages of the illness. Recent studies suggest some antidepressants, and the dopamine agonist pramipexole may be useful to treat depression in PD. Given the paucity of valid instruments to measure anxiety in PD, its frequency and clinical correlates are less well known. Future studies will focus on separating the generic anxiety disorders, such as generalized anxiety disorder and social phobia, from the anxiety symptoms that may be idiosyncratic to the motor symptoms of PD, such as 'off' period anxiety. Specific psychotherapeutic techniques are currently being developed to treat depression and anxiety in PD.

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Depression, apathy and anxiety disorders are among the most common comorbid psychiatric conditions in Parkinson's disease (PD). Recent studies have consistently demonstrated that depression has a negative impact on patients' quality of life as well as on the motor and cognitive symptoms of the illness. Apathy is being increasingly diagnosed among elderly PD patients, primarily those with dementia. There is less information about the clinical relevance of anxiety in PD, but recent studies have demonstrated a high frequency of both typical and atypical anxiety disorders in PD. The present chapter will review the nosology and diagnostic methodology for depression, apathy and anxiety in PD; we will summarize the epidemiology of these psychiatric disorders and discuss their clinical correlates and putative mechanisms. We will finish the chapter by discussing the most effective treatment modalities for these conditions.

Depression

Phenomenology and Diagnostic Issues

There is no general consensus about the most valid methods to assess and diagnose depression in PD. One of the most important nosological limitations is the overlap between symptoms of depression and symptoms of PD (e.g. motor retardation vs. bradykinesia, poor concentration and bradyphrenia; loss of energy in both depression and PD). A workgroup established by the National Institutes of Neurological Disorders and Stroke, and the National Institutes of Mental Health proposed provisional criteria for depression in PD [1]. The workgroup stressed the need to validate the DSM-IV categories of major depression, minor depression and dysthymia, as well as the concept of subsyndromal depression in patients with PD. They recommended the use of the inclusive approach to symptom assessment (i.e. to consider all symptoms as related to depression, regardless of the overlap with parkinsonism), to distinguish loss of interest/anhedonia from apathy, to consider whether putative depressive symptoms may be the expression of motor fluctuations, to assess depression at consistent times and during the 'on' and 'off' states, and to obtain additional information about mood changes from a next of kin or caregiver. Other investigators reported a relatively low frequency of guilt, self-blame and worthlessness in depressed patients with PD [2, 3].

Starkstein et al. [4] have recently examined the validity, sensitivity and specificity of depressive symptoms for the diagnosis of dysthymia, sub-syndromal depression, and major and minor depression in a series of 173 patients with PD. The main finding was that all DSM-IV clinical criteria for major depression and dysthymia were significantly associated with sad mood. Moreover, there was no significant difference in frequency and severity of depressive symptoms, when PD patients with sad mood were compared with sad mood controls of similar age but without PD. Depression diagnosis based on loss of interest without sad mood was significantly more common in minor than in major depression, suggesting that minor depression in PD may be closer to apathy.

Schrag et al. [5] have recently examined rating scales for depression for use in PD. They concluded that the Hamilton Depression Rating Scale (HAM-D), the Beck Depression Inventory (BDI), the Hospital Anxiety and Depression Scale (HADS), the Montgomery-Åsberg Depression Rating Scale (MADRS) and the Geriatric Depression Scale (GDS) are all useful to screen for depression in PD. To measure severity of depressive symptoms, they recommended the HAM-D, the MADRS, the BDI and the GDS. They further suggested that depression should not be diagnosed based on a cut-off score on a depression scale but based on information provided by semi-structured psychiatric interviews and the use of standardized diagnostic criteria. They further suggested to specify the timing of assessment regarding motor fluctuations and to include collateral information.

Frequency of Depression

The frequency of depression in PD has been reported to range widely from less than 10% to greater than 80%. This variability may be explained by sampling bias

(e.g. patients recruited from the community or attending movement disorders clinics, different assessment methods, and demographic differences, e.g. differences in the proportion of women, elderly patients, and severity of illness). Using the BDI, the Global PD Survey reported significant depression in 50%, although only 1% of the sample reported depressive symptoms to the clinician [6]. Based on GDS cut-off scores, Holroyd et al. [7] diagnosed depression in 15% of 100 consecutive patients with PD. In a series of 1,449 randomly selected outpatients with PD, Riedel et al. [8] reported 25% of depression based on MADRS cut-off scores. Using structured psychiatric interviews in a series of 173 patients attending a movement disorders clinic, Starkstein et al. [4] reported 30% of major depression, 20% of dysthymia and 10% of minor depression. A recent meta-analysis reported a prevalence of 31% of major depression in PD [9]. Other studies reported frequencies of 17 and 21% for major and minor depression, respectively [10].

Clinical Correlates of Depression

Starkstein et al. [11] reported a significant association between major depression, more severe parkinsonism and specific neuropsychological deficits. In two longitudinal studies, these authors demonstrated that depression in patients with PD is associated with faster motor, cognitive and functional decline [12, 13]. Cross-sectional studies demonstrated a significant association between depression and worse quality of life [14], functional capacity and caregivers' quality of life [15, 16], increased mortality [17], increased burden for caregivers [14, 18], motor-related disability [18, 19], lower cognition [7], sleep disturbances and fatigue [20]. Depression was also reported to be a predictor of social and physical functioning in men with PD [21].

Mechanism of Depression

Several studies examined biological correlates for depression in PD. Remy et al. [22] used [¹¹C] RTI (methyl (1R-2-exo-3-exo)-8- methyl-3-(4-methylphenyl)-8-azabicyclo[3.2.1]octane-2-carboxylate)-32 positron emission tomography (PET) to examine in vivo markers of dopamine and norepinephrine terminals in 8 PD patients with major depression and 12 PD patients without depression. Depressed patients showed reduced RTI binding (reflecting a loss of catecholaminergic innervations) in the locus coeruleus, anterior cingulate cortex, thalamus, amygdala and ventral striatum as compared to non-depressed patients. The authors concluded that decreased catecholaminergic innervation in the amygdala and the anterior cingulate may be related to both depression and anxiety in PD, whilst similar decrease in the left ventral striatum may be related to increased apathy. In a recent study, Politis et al. [23] assessed 10 antidepressant-naïve PD patients with major depression, 24 PD patients without depression, and 10 healthy controls using ¹¹C-DASB PET (a compound which selectively binds to the 5-HT transporter). The main finding was that PD patients with the highest depression scores showed increased ¹¹C-DASB binding in the amygdala, hypothalamus, raphe nuclei, and posterior cingulate cortex compared to patients without depression, suggesting that abnormal serotonergic

transmission may play an important role in the mechanism of depression in PD. Further support for the association between serotonergic dysfunction and depression in PD was provided by the finding of a significant association between depression and the S allele of the 5-HT transporter [24], although discrepant findings were recently reported [25].

Palhagen et al. [26] used HMPAO SPECT to examine brain perfusion changes before and after 12 weeks of citalopram treatment in 11 PD patients with major depression and 12 individuals with major depression but no PD. After the 12-week treatment period, there was a significant reduction in regional cerebral blood flow (rCBF) in the left fronto-dorsolateral region among PD patients with major depression, whilst patients with major depression and no PD showed a heterogeneous increase in the right hemisphere rCBF.

Treatment of Depression

Depression is usually undertreated in PD. Among 34% patients with PD meeting diagnostic criteria for depression, about two thirds were untreated for the mood disorder [27]. In the context of the Parkinson Study Group which included 27,410 patients with PD, 26% of the sample was on antidepressants, 51% on selective serotonergic reuptake inhibitors (SSRIs), 41% on tricyclic antidepressants (TCAs) and 8% on other compounds [28].

Four randomized controlled trials (RCTs) have been carried out to examine the efficacy of psychoactive drugs to treat depression in PD and have produced discrepant findings. The first study showed that the TCA desipramine and the SSRI citalopram were more effective than placebo [29], while the second study showed that the TCA nortriptyline but not the SSRI paroxetine was more effective than placebo [30]. A third study that compared the efficacy of the selective norepinephrine reuptake inhibitor atomoxetine with placebo showed no significant difference [31], while an open-label study showed no differences between citalopram and placebo [32]. Finally, a recent RCT showed that the dopamine agonist pramipexole improved depressive symptoms in PD [31]. However, the difference on the BDI between the pramipexole and placebo groups was of only 1.9 points, which is of dubious clinical significance. In conclusion, while TCAs may be useful to treat depression in PD, their side effects and contraindications (especially among individuals with a neurodegenerative condition) may severely restrict their use to a small group of patients, and some antidepressants may exacerbate the physical symptoms of PD [33].

Systematic effectiveness studies of psychotherapy are still lacking. Farabaugh et al. [34] enrolled 8 patients with depression in a 12-week trial of individual cognitive-behavioural therapy (CBT). The authors found a linear decrease in HAM-D scores with remission in 4 of 7 patients. Feeney et al. [35] evaluated CBT outcome for major depressive disorder in 3 people with PD. Using an A-B single case experimental design in which each person acts as their own treatment control, 2 out of the 3 participants made significant treatment gains that were maintained at 6 months' follow-up. In this pilot study, CBT outcome was enhanced when a bereavement model was

added to explain the individual's emotional adjustment to living with PD. A recent small-scale study showed similar positive results. This uncontrolled 15-patient study explored the feasibility of using CBT to treat depression in PD and found that patients experienced significant reductions in depressed mood and negative cognitions over the course of 10–14 weeks of treatment, providing preliminary evidence as to the effectiveness of this approach [36]. Patients improved their ability to negotiate physical limitations, addressed barriers to medication adherence, and learned to pace daily activities appropriately, set more realistic goals, identify coping skills, and modify maladaptive cognitive and behavioural responses to physical symptoms [37, 38]. Modified individual CBT may be an effective treatment of depression, especially for patients with medication intolerance. An RCT is now needed to evaluate the efficacy of CBT in PD.

Apathy

Phenomenology and Diagnostic Issues

Apathy is defined as a syndrome characterized by deficits in goal-directed behaviour and the simultaneous diminution of the cognitive and emotional concomitants of goal-directed behaviour [39]. The construct of apathy was standardized in a set of criteria by Starkstein and Leentjens (table 1).

Partial validation to this set of diagnostic criteria has been provided in a recent publication [40]. The Movement Disorders Society Task Force on Rating Scales for PD constituted an ad-hoc committee to assess psychometric attributes of existing apathy and anhedonia rating scales for use in PD. One of the main limitations to rate symptoms of apathy is the overlap with symptoms of depression and parkinsonism (e.g. loss of interest, energy and pleasure are all prominent in depression and may also result from the motor problems of PD). The committee recommended the use of the Apathy Scale (AS) [41], which was specifically developed and validated in PD patients. The Lille Apathy Rating Scale (LARS) was considered to be well designed for PD and of potential usefulness, whereas there is little information regarding the properties of the Apathy Evaluation Scale (AES) and the Apathy Inventory (AI). One of the main limitations to assess the attributes of apathy scales in PD is the lack of validated diagnostic criteria. Item 4 of the Unified PD Rating Scale (UPDRS) which focuses on 'motivation and initiative' may be used as a screening guide for apathy, given that it has adequate sensitivity and specificity for the clinical diagnosis of apathy in PD [42]. On the other hand, the overlap with both depression and cognitive impairment should be considered when developing new instruments to assess apathy in PD.

Frequency of Apathy

The frequency of apathy varied depending on the instruments used for assessment. Based on cut-off points of severity rating scales, the frequency of apathy was reported

Table 1. Diagnostic criteria for apathy

A	Lack of motivation relative to the patient's previous level of functioning or the standards of his or her age and culture.
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B	Presence, while with lack of motivation, of at least 1 symptom belonging to each of the following three domains: Diminished goal-directed behaviour <ol style="list-style-type: none">1. Lack of effort or energy to perform everyday activities.2. Dependency on prompts from others to structure everyday activities. Diminished goal-directed cognition <ol style="list-style-type: none">3. Lack of interest in learning new things, or in new experiences.4. Lack of concern about one's personal problems. Diminished concomitants of goal-directed behaviour <ol style="list-style-type: none">5. Unchanging or flat affect.6. Lack of emotional response to positive or negative events.7. The symptoms of apathy cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.8. The symptoms are not due to diminished level of consciousness or to the direct physiological effects of a substance.
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to range from 17 to 70% [43–47]. Given the overlap between apathy and depression, the frequency of apathy is significantly lower in the absence of comorbid depression [40, 43]. In one of the first studies to examine the frequency of apathy in PD, Starkstein et al. [43] diagnosed apathy in 42% of a series of 50 patients attending a movement disorders unit. Two thirds of the patients with apathy were also depressed. Kirsch-Darrow et al. [47] compared the frequency of apathy and depression among patients with PD and patients with primary dystonia. The main finding was that apathy without depression was present in 28% of the PD sample but in none of the patients with dystonia. In a recent study, Pedersen et al. [48] examined the prevalence of apathy in a community-based sample that included 232 patients with PD. Using the motivation and initiative item of the UPDRS, the authors diagnosed apathy on 35% of the sample. Similar frequencies were reported by Sockel et al. [49] using the LARS. In a study that included 175 PD patients assessed with the Neuropsychiatric Inventory, Aarsland et al. [50] reported that during a 22-month period the incidence of apathy was 27%, suggesting that most patients with PD will develop apathy at some stage during the progression of the illness.

Few studies have examined the longitudinal evolution of apathy in PD. Dujardin et al. [51] assessed 40 PD patients with neither dementia nor depression, 20 of whom had apathy. Patients with apathy showed more severe cognitive deficits than those without apathy. After a median follow-up of 18 months, 8 of the 20 patients with apathy converted to dementia as compared to 1 of 20 patients in the no apathy group. Cognitive

decline in the group with apathy was most severe on the memory and executive functions domain. Pedersen et al. [52] carried out a 4-year follow-up study of 79 PD patients from a population-based study. At baseline, 14% of the sample had apathy (as diagnosed with the Neuropsychiatric Inventory), and all of them remained apathetic at the 4-year follow-up. About 50% of the patients with no apathy at baseline became apathetic at the follow-up assessment. Compared to patients with no apathy, those with incident apathy had a higher frequency of dementia and depression at follow-up as well as a faster increase in UPDRS motor scores. Butterfield et al. [53] assessed 68 PD patients using the AES and tests of executive functions and memory. Apathy (but not depression) was significantly associated with executive dysfunction and retrograde amnesia.

Clinical and Radiological Correlates of Apathy

In a recent study, Starkstein et al. [43] assessed a series of 164 patients attending a Movement Disorders clinic using the AS, and 32% of the patients met standardized diagnostic criteria for apathy. Patients with apathy were older, had more cognitive deficits, higher depression scores and more severe parkinsonism than PD patients without apathy. On a multiple regression analysis, both the severity of depression and cognitive deficits were significantly associated with more severe apathy. Among patients with neither depression nor dementia, apathy was diagnosed in 13% of the PD group. Dementia is another relevant clinical correlate of apathy in PD. Starkstein et al. [43] reported apathy in 47% of patients with dementia vs. 23% of PD patients without dementia. Similar findings were reported by Dujardin et al. [54] (56% vs. 9%, respectively). Taken together, these findings suggest that apathy identifies a subgroup of PD patients with more severe depression and cognitive deficits, and greater functional impairment.

Few studies examined neuroanatomical correlates of apathy in PD. Reijnders et al. [55] carried out a 3-tesla volumetric MRI study on 55 patients with PD. Using a cut-off on the LARS to diagnose depression, 16% of the patients were diagnosed with apathy. There was no association between apathy scores and severity of motor symptoms or disease duration, but more severe apathy was significantly related with more severe depression. Neuroimaging showed a significant association between higher apathy scores and lower grey matter densities in the bilateral pre-central gyrus, bilateral inferior parietal gyrus, bilateral insula, right posterior cingulate gyrus and right precuneus. The authors suggested that low grey matter density in the premotor cortex may be related to lower motor activation, whilst low grey matter density in the insula may be related to the blunted affect as part of apathy.

Several studies have used PET to examine the metabolic correlates of apathy in PD. Le Jeune et al. [56] showed a significant association between higher apathy scores and decreased glucose metabolism in the bilateral posterior cingulate. Remy et al. [22] showed that increased apathy was associated with decreased ^{11}C -RTI-32 binding (a marker of dopamine and norepinephrine terminals) in the ventral striatum. Drapier et al. [57, 58] reported that patients with apathy had more severe mesolimbic dopaminergic denervation.

Thobois et al. [59]. reported that about half of a sample of patients with PD treated with subthalamic nucleus-deep brain stimulation (STN-DBS) who tolerated a reduction of 80% in anti-parkinsonian drugs developed apathy within the first 6 months after surgery. A subgroup of these patients was assessed with [¹¹C]-raclopride PET, and those with apathy showed greater denervation in the orbitofrontal cortex, dorsolateral prefrontal cortex, anterior cingulate cortex, left thalamus, bilateral globus pallidus and right temporal cortex.

Mechanism of Apathy

Early studies on the impact of testosterone levels in PD demonstrated a significant association between low testosterone levels and increased apathy scores. However, recent studies using more adequate assessments for apathy were unable to replicate those preliminary findings [60].

Apathy has been reported as a relatively frequent complication among patients undergoing STN-DBS. Le Jeune et al. [56] examined 12 PD patients 3 months before and after STN-DBS using the AES and ¹⁸fluorodeoxy-glucose (FDG-PET). In spite of a significant motor improvement with DBS, apathy (but not depression) scores increased significantly. This increment on apathy scores was significantly related to increased metabolism in the right frontal medial gyrus and right inferior frontal gyrus, and decreased metabolism in the right posterior cingulate gyrus and the left frontal medial cortex. The authors speculated that the STN may have a regulatory function in cortico-subcortical connections. Based on these findings, Levy and Czernecki [61] suggested that apathy in PD may result from deficits in basal ganglia-prefrontal cortex interaction coupled with changes in dopaminergic tone.

Treatment of Apathy

There are no RCTs for apathy in PD, and the only therapeutic evidence is based on open label studies. Czernecki et al. [62] reported that dopamine agonists improved motivation in the 'off' state. Ropinirole (1–18 mg/day) was reported to improve apathy in a case series of 8 patients treated during 6 months, and no significant adverse events were reported [63]. Finally, an RCT of atomoxetine (with depression as the primary outcome measure) showed no improvements on apathy scores [31].

Anxiety

Phenomenology and Diagnostic Issues

Whilst anxiety symptoms are common in PD, their frequency has been reported to vary widely. Similar to depression and apathy, this variation may be related to different assessment methods. The MDS Task Force on Rating Scales for PD created an ad-hoc committee to analyze the instruments used to assess anxiety in PD and to determine their psychometric attributes [64]. The main finding was that all the

anxiety rating scales analyzed included items that overlap with depression scales and with motor symptoms of PD.

One diagnostic dilemma is that anxiety was found to be related to the motor fluctuations of PD [64]. Therefore, it may be difficult to ascribe anxiety-like symptoms to a DSM-IV anxiety disorder or to the motor fluctuations of PD, and the most frequently used anxiety scales are unable to capture the phenomenology of atypical anxiety disorders in PD. A critique of anxiety rating scales used in PD (e.g. the Beck Anxiety Inventory, the HADS, the Zung Self-Rating Anxiety Scale, the Spielberger State-Trait Anxiety Inventory, and the Hamilton Anxiety Rating Scale) concluded that none of them is suitable for use in PD. Another suggestion was that patients should be assessed in the 'on' condition given that patients with motor fluctuations may perceive and report anxiety symptoms differently in 'on' vs. 'off' states.

Frequency and Clinical Correlates of Anxiety Disorders

Several recent studies examined the frequency of anxiety disorders in PD. Negre-Pages et al. [65] assessed 422 ambulatory patients with PD and 98 age- and gender-comparable non-PD individuals using the HADS. The authors reported clinically relevant anxiety symptoms in 50% of non-demented PD patients, while the frequency in the control group was 29%. Of note, there was a strong comorbidity between anxiety and depression.

Pontone et al. [66] assessed 127 patients with the SCID and found that 50% had a lifetime anxiety disorder, with a diagnosis of anxiety disorders not otherwise specified being the most frequent diagnosis. About 40% of this group had situational anxiety related to parkinsonism (e.g. fear of falling and fear of freezing). Other patients had anxiety during the 'wearing off' of anti-parkinsonian drugs, whilst still others had panic-like episodes. Patients with lifetime anxiety have a higher frequency of a positive familial psychiatric history, a lifetime personal history of depression, and lower quality of life as compared to PD patients without lifetime anxiety. The comorbidity between anxiety and depression was high (65%), and the current frequency of anxiety disorders was 43%. Thirty percent of patients met DSM-IV criteria for anxiety disorders not otherwise specified, further suggesting that the psychiatric criteria used to diagnose anxiety in PD may not adequately apply to this population. Nineteen percent had a specific phobia, followed by panic disorder (10%) and social phobia (9%). Partial validation to the anxiety disorders was provided by the finding that quality of life was significantly worse for patients with anxiety disorders as compared to those without.

A recent study [67] assessed 79 PD patients using the Mini International Neuropsychiatric Interview and the Spielberger State-Trait Anxiety Inventory. Twenty-five percent of the sample met DSM-IV diagnostic criteria for a current anxiety disorder, 8% met criteria for panic disorder, 13% for social phobia, and 3% for generalized anxiety disorder. There was a significant association between the presence of anxiety disorders and motor complications (e.g. 'on-off' fluctuations and 'freezing'), worse

quality of life, and older age. Finally, the comorbidity between anxiety and depression was 14%.

Leentjens et al. [68] have recently completed a one-year cross-sectional multi-centre study that included a consecutive series of 342 patients with PD assessed with the Mini International Neuropsychiatric Interview and several anxiety rating scales. The main finding was that 34% of patients met DSM-IV diagnostic criteria for at least 1 anxiety disorder, whilst 12% met criteria for 2 or more anxiety disorders. Generalized anxiety disorder was the most common diagnosis, followed by agoraphobia and social phobia. A logistic regression analysis showed that female gender, motor fluctuations, and a lifetime history of anxiety disorders were significantly related to the presence of anxiety. Given the psychometric limitations of the anxiety scales for use in PD, the authors suggested developing an anxiety rating scale specific to PD.

In conclusion, whilst anxiety disorders have been consistently reported to be present in 20–40% of PD patients, the type of anxiety disorder was reported to have a wide variation, from initial studies showing a relatively high frequency of panic disorder, to more recent studies showing non-episodic anxiety disorders to be the most frequent in PD. These discrepancies may be related to the use of different psychiatric instruments and diagnostic criteria for anxiety in PD, full or partial screening for DSM-IV anxiety disorders. The high frequency of anxiety disorders not otherwise specified found in recent studies suggests that the use of DSM-IV criteria may not provide an adequate gold-standard for diagnosing anxiety disorders in PD. Future criteria may consider the fact that both motor and autonomic symptoms of PD may be related to the heterogeneity of anxiety disorders in PD.

Treatment of Anxiety Disorders

There is a paucity of treatment studies of anxiety in PD. Menza et al. [69] carried out an 8-week open-label study that included 10 PD patients using citalopram. They reported a significant decrease in HAM-A scores at study completion. The medication was well tolerated and there were no serious side effects.

Conclusions

Depression is one of the most common non-motor disorders in PD. Cross-sectional studies reported that about 20–30% of patients suffer major depression, whilst longitudinal studies suggest an incidence of about 20%. Therefore, most patients with PD will suffer depression at some stage during the illness. Depression is a marker of a ‘malignant’ type of PD as it is associated with faster cognitive, motor and functional decline and worse quality of life. The mechanism of depression remains unknown, but recent studies suggest dysfunction in specific frontal regions. Recent RCTs demonstrated the efficacy of escitalopram, nortriptyline and pramipexole. Future studies should demonstrate the usefulness of psychotherapy. Apathy is another frequent

non-motor problem in PD and is significantly associated with depression and cognitive deficits. Its mechanism remains unknown, and no treatment has demonstrated adequate efficacy. Whilst anxiety disorders are common in PD, adequate instruments for diagnosis and measure have yet to be developed. Specific psychotherapeutic techniques should also be developed to treat this condition.

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Apathy in Parkinson's Disease

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Abstract

Apathy may be one of the most common behavioural complications of neurodegenerative disorders such as Alzheimer's and Parkinson's (PD) disease and can occur in about a third of those affected by these conditions. Apathy is one of the most underrecognised, underdiagnosed and poorly managed aspects of these diseases. It is defined as a clustering of behavioural, emotional and cognitive symptoms that manifests as diminished initiation and interest and diminished responsiveness to stimuli. Apathy is increasingly being considered as a core symptom of PD and results from underlying disease-related pathological changes. This article outlines various aspects of apathy in PD, particularly focusing on diagnostic criteria, apathy rating scales, underlying pathology, the negative impact of apathy and management strategies.

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The term 'apathy' refers to a loss of motivation and was first used in ancient Greece by the Stoics (*απαθής*, meaning 'without feeling or suffering') to describe a state of indifference or lack of concern towards the external world. However, in the clinical context, apathy has a more specific meaning and instead refers to a clustering of behavioural and emotional symptoms that manifest as diminished interest and involvement in normal purposeful behaviour, flattened affect, diminished emotional responsivity, lack of initiation of non-routine activity and diminished drive to complete activities once started [1]. Apathy may be one of the most common behavioural complications of neurodegenerative disorders such as Alzheimer's (AD) and Parkinson's (PD) disease, and it is one of the most underrecognised, underdiagnosed and poorly managed aspects of these diseases [2, 3]. The consequences of apathy may be significant and may have a negative impact on prognosis, quality of life, level of disability, and carer burden and distress. Management strategies have not been extensively investigated. This chapter provides an outline of various aspects of apathy in PD, including its epidemiology, definitions, method of diagnosis and rating, underlying pathology and the impact that it has on PD sufferers and their carers.

Epidemiology

In treated and untreated PD, apathy has been reported with prevalence estimates between 17 and 42% [1]. In a study using a Norwegian PD database, the rates of apathy in 139 PD sufferers using the Neuropsychiatric Inventory (NPI) was found to be 17% [4]. A more recent study, using an apathy scale specifically designed for PD, the Lille Apathy Rating Scale (LARS), found that 51 of 159 (32%) patients scored above the cut-off for apathy [2]. These figures are slightly lower than in AD, where apathy, as detected by the NPI has been reported in 55–80% [5], and has been described in up to 93% of one sample [6]. In a recent cross-sectional study of 306 patients with various psychiatric diagnoses, revised diagnostic criteria for apathy were validated and revealed an apathy frequency of 27% of the subgroup with PD [7].

Definitions of Apathy and Diagnostic Criteria

Apathy has been defined as a lack of goal-directed behaviour, which can be divided into: (1) diminished or blunted emotions, (2) loss of or diminished initiative, and (3) loss of or diminished interest [8]. Another, but similar, definition is that apathy represents a lack of goal-directed behaviour, cognition or emotion [9]. Other formal definitions generally support the notion of apathy as a multi-dimensional construct, rather than merely a symptom secondary to other medical, psychiatric or neurologic conditions [reviewed in 10].

Initially outlined by Marin et al. [11] and modified and operationalised for PD by Starkstein et al. [12], more recently revised diagnostic criteria proposed by a task force from Europe, Australia and North America [13] have been validated in a series of patients with different types of dementia, as well as major depression and schizophrenia [7, 13]. These criteria are based on loss of motivation that persists over time (at least 4 weeks) as well as the presence of at least two of three dimensions of apathy: reduced goal-directed behaviour, goal-directed cognitive activity, and emotions. Evidence for change in each of the three dimensions is derived from observed reduction in either self-initiation of behaviour within the dimension or response to an external stimulus that taps into the dimension. Symptoms should cause clinically significant impairment in various functional domains and should not be due to another condition that may resemble apathy. In the validation study, the NPI apathy domain score with a cut-off of 3 [14] was used as a reference point, and inter-rater reliability was found to be high. The most commonly observed domains in those with apathy were a reduction in goal-directed cognitive activity, followed by goal-directed behaviour. As in the other diagnostic groups, ‘initiation’ symptoms were more frequent in PD, compared with the ‘responsiveness’ symptoms. In a study examining PD alone, there was a high percentage of agreement between the diagnosis of apathy using the criteria of Robert et al. [13] and the cut-off score for apathy on both the LARS (81%)

Table 1. Diagnostic criteria for apathy validated in PD [13, 15]

For a diagnosis of apathy, the patient should fulfil the criteria A, B, C and D

A. Loss of or diminished motivation in comparison to the patients' previous level of functioning and which is not consistent with his age or culture.

B. Presence of at least one symptom in at least two of the three following domains for a period of at least 4 weeks and present most of the time.

Domain B1 – Behaviour:
Loss of, or diminished, goal-directed behaviour as evidenced by at least one of the following:
Initiation symptom: loss of self-initiated behaviour (i.e. starting a conversation, doing basic tasks of day-to-day living, seeking social activities, communicating choices)
Responsiveness symptom: loss of environment-stimulated behaviour (i.e. responding to conversation, participating in social activities)

Domain B2 – Cognition:
Loss of, or diminished, goal-directed cognitive activity as evidenced by at least one of the following:
Initiation symptom: loss of spontaneous ideas and curiosity for routine and new events (i.e. challenging tasks, recent news, social opportunities, personal/family and social affairs).
Responsiveness symptom: loss of environment-stimulated ideas and curiosity for routine and new events (i.e. in the person's residence, neighbourhood or community)

Domain B3 – Emotion:
Loss of, or diminished, emotion as evidenced by at least one of the following:
Initiation symptom: loss of spontaneous emotion, observed or self-reported (i.e. subjective feeling of weak or absent emotions, or observation by others of a blunted affect)
Responsiveness symptom: loss of emotional responsiveness to positive or negative stimuli or events (i.e. observer reports of unchanging affect, or of little emotional reaction to exciting events, personal loss, serious illness, emotional-laden news).

C. These symptoms (A–B) cause clinically significant impairment in personal, social, occupational, or other important areas of functioning.

D. The symptoms (A–B) are not exclusively explained or due to physical disabilities (e.g. blindness and loss of hearing), to motor disabilities, to diminished level of consciousness or to the direct physiological effects of a substance (e.g. drug of abuse, a medication).

and the NPI apathy sub-score (86%) [15]. Diagnostic criteria of apathy are outlined in table 1.

Apathy Rating Scales

The measurement of apathy in PD first became properly validated following the proposal of Marin et al. [11] of diagnostic criteria for apathy as a 'pure' syndrome. These criteria were later expanded by Starkstein et al. [12] to apply to various neurodegenerative

disorders, including PD, and were informally accepted in PD research as well as in the clinical setting. Two apathy scales were subsequently designed specifically for use in PD populations. The first is the Apathy Inventory (AI) [10], which is an informant-rated scale that is scored in a similar manner to the Neuropsychiatry Inventory [16], i.e. frequency \times severity; it assesses three components of apathy: emotional blunting, lack of initiative and lack of interest. The LARS [17] is the most recent scale developed for assessing apathy in PD. Gallagher et al. [18] used the LARS to determine the usefulness of the Unified Parkinson's Disease Rating Scale (UPDRS), part I [19], as an apathy screening and diagnostic instrument by rating both scales in 74 PD sufferers. Using the LARS cut-off, 20% of the sample had apathy. The apathy item on part I of the UPDRS was sensitive (73%) in detecting apathy symptoms in PD, but was not sufficient to make a diagnosis of a full apathy syndrome.

In 2008, the Movement Disorder Society undertook a comprehensive critique of all apathy scales relevant to PD and proposed recommendations, based on scale properties [20]. Only Starkstein's Apathy Scale (AS) [21], which is an abbreviated version of Marin's original Apathy Evaluation Scale (AES) [11], was recommended by the consensus group to assess apathy in PD. Selected apathy rating scales are outlined in more detail in table 2. More recently, a review of 15 apathy scales, not specific to PD, was undertaken. This review found that the most psychometrically robust measure for assessing apathy across any disease population was the AES as well as the apathy subscale of the NPI [22].

Pathology of Apathy

In 1973, Singer [23] concluded that the apathy syndrome in PD was an example of 'premature social aging'. However, subsequent studies, such as that of Pluck and Brown [1], which found that high levels of apathy in PD compared with their age- and disability-matched osteoarthritis sample, supported the notion that apathy is most likely part of the disease process, in particular, disruptions to the frontal-subcortical circuit, and not a psychological response to disability or loss of role. Studies in non-PD patients with apathy, who have had basal ganglia lesions, have highlighted the potential underlying pathophysiology of apathy in PD. For example, in a case series of 16 patients with bilateral focal lesions of the putamen, caudate nucleus or pallidum, a syndrome of 'auto-activation deficit' (AAD) was observed. AAD is a term initially used to describe a particular type of apathy related to basal ganglia lesions [24]. The Alexander and De Jong neural loop most likely to be involved is the limbic loop, including the anterior cingulate cortex (ACC), to ventral striatum, globus pallidus and thalamus, and returning to the ACC [25]. The ACC may also have a role in depression, reward, executive function and goal-directed behaviour and is therefore a plausible substrate for apathy [13, 26]. As apathy and anhedonia are closely linked, and pleasure and reward seeking are associated with ventral tegmental area

Table 2. Selected apathy rating scales relevant to PD

Type of measure	Description	Use in PD	Comment
AS Administration: self-rated	Abbreviated version of the original AES-C; 14 items rated on a 4-point Likert scale (higher score is worse apathy); clinically significant apathy is a score of ≥ 14 (range 0–42); sensitivity 66% and specificity 100%)	Specifically designed for use in PD, and has also been used in stroke and AD	Key scale recommended by the Movement Disorders Society working group on apathy scales in PD; considered to have good face validity, internal consistency, inter-rater and test-retest reliability [20]
AES-C Administration: clinician-rated measure	First scale to quantify the syndrome of apathy using a psychological definition of apathy; 18 items rated on a 4-point Likert scale (higher score is worse apathy); clinically significant apathy is a score of ≥ 38	Has been used in PD; good internal consistency but has not been correlated with key markers of disease severity [20]; more cognitively impaired PD sufferers score higher on the scale [1]	AES was developed in three versions: an informant version, a patient version, and a clinician version.
<i>NPI, apathy subscore</i> Administration: Informant rated	Based on the ‘frequency \times severity’ scale; several descriptors; range 0–12 (higher is worse apathy); clinically significant apathy is >3	Validated for use in PD [14]	A revised version of the NPI for clinician rating [71] is available with an updated apathy domain
LARS Administration: structured clinical interviewing	33-item scale, based on 9 domains and 4 subscales; includes: everyday productivity, interests, initiative, novelty seeking, motivation, emotional response, concern, social life and self-awareness; score ranges from -36 to $+36$ (positive scores indicate more severe apathy)	Different apathy profiles in PD have been defined using the LARS [2]	Used in validating clinical diagnostic criteria for apathy in PD [7, 15]
AI Administration: informant rated	Based on 3 dimensions of apathy: emotional blunting, lack of initiative and lack of interest; each dimension is rated on the ‘frequency \times severity’ scale		It also has a patient version

Table 3. Main neuroimaging studies investigating cerebral metabolism in apathy in AD

Authors	Participants	Apathy scale used	Type of imaging findings	Regions of interest implicated in apathy
Ott et al. [72]	40	AES	SPECT Tc-99m	Temporoparietal cortex
Craig et al. [73]	31	NPI	SPECT Tc-99m	Prefrontal and anterior temporal cortex
Benoit et al. [74]	20	NPI	SPECT Tc-99m	Anterior cingulate cortex + inferior frontal, medial orbitofrontal and lingual gyrus
Benoit et al. [75]	30	NPI (cut-off >2)	SPECT Tc-99m	Anterior cingulate cortex + inferior frontal, medial orbitofrontal and lingual gyrus
Benoit et al. [76]	30	AI	SPECT Tc-99m	Bilateral superior orbitofrontal gyrus
Robert et al. [43]	31	Interest and Initiative subscores of the AI (score >2)	SPECT Tc-99m	Anterior cingulate cortex (correlated with loss of interest and initiative)
Lanctot et al. [77]	51	NPI (cut-off >1)	SPECT Tc-99m	Anterior cingulate cortex + medial orbitofrontal cortex
Marshall et al. [78]	41	Scale for the Assessment of Negative Symptoms- Alzheimer's disease	PET F-18	Anterior cingulate cortex (bilateral) + medial orbitofrontal cortex

and nucleus accumbens activity in PD, apathy too may be caused by disruption of these pathways. A few functional imaging studies have investigated apathy and the dimensions of diminished interest or initiative in AD. Key findings are summarised in table 3.

Dopamine, a key neurotransmitter involved in motivation and reward and the core neurochemical lesion in PD, is likely to have a significant role in apathy. Apathy varies according to the extent of motor fluctuation in PD patients, consistent with a contribution of dopamine [27]. The importance of dopamine is documented in non-

PD apathy as well. For example, in subjects diagnosed with AD and dementia with Lewy bodies, those with apathy (according to the NPI) and AD had lower striatal levels of dopamine transporter (DAT) [28]. Similarly, serotonin (5-HT) may have a role in apathy, particularly in PD depression [29]. Interestingly, apathy may be a result of depression treatment due to the interplay between 5-HT and dopamine. This may result in the so-called ‘SSRI-induced apathy’ syndrome [30, 31], which may be taken as a model for the role of 5-HT in PD apathy. Finally, various lines of converging evidence have suggested that the cholinergic deficit in PD, and particularly dementia in PD (PDD), may be even more marked than they are in AD. This deficit has been demonstrated in the ACC, suggesting a link with apathy, as well as by the evidence that cholinesterase inhibitors have a beneficial effect on apathy [32].

Psychiatric Co-Morbidity and Apathy

Apathy frequently occurs with other psychiatric diagnoses in PD. For example, in the Norwegian PD database, factor analysis of the NPI revealed that apathy covaried with anxiety [4], as it did with anxiety and depression in other studies [1, 21, 33]. In PD, the overlap of depression and apathy may be particularly high or even exclusive compared with other neurodegenerative conditions [34]. It may be related to the shared role that serotonin has in mediating both depression and apathy [29].

The nature of the co-occurrence of depression with apathy has frequently been debated. Indeed, apathy was initially attributed to being a symptom of depression in the same way that anhedonia is a symptom of depression [34]. Diagnostically, it can be difficult to distinguish an apathy syndrome from depression. In spite of this, it has also been demonstrated that if using carefully validated rating scales for apathy and depression and excluding items of overlap, it is possible to discriminate the entities [2, 36]. Furthermore, there are a handful of studies that have shown a significant level of discrepancy between apathy and depression. For example, in AD, a longitudinal study of 65 patients found that apathy and depression had different natural histories and that it is clearly possible to discriminate between them [37].

Cognition and Apathy

In 1922, Naville [38] described a clinical profile in PD consistent with what today would be considered ‘bradyphrenia’, or slowness of thinking. This consisted of a constellation of symptoms including fatigue, lack of initiative, slowness of thinking, poor persistence in tasks, mild memory problems and deficits in attention and interest. This syndrome is most likely a combination of the effects of motor impairment, or bradykinesia, and the underlying cognitive deficits and apathy syndrome that are well recognised as being part of PD today. In examining the cognitive profile in apathy,

it is tempting to speculate on the direction of causality. That is, does the cognitive profile, which is most often described as being a 'dysexecutive syndrome' inform and drive the behavioural syndrome of apathy, or vice versa? According to some authors, apathy is only one of several behavioural signs of executive dysfunction [39]. With impairment in executive function, problems typical of an apathy syndrome, such as with initiation and task completion, may emerge and have significant impact on the ability to function successfully and independently in situations lacking a clear structure. However, with the current state of knowledge, this relationship can at best be described as being 'bidirectional'.

A handful of studies have explored the associated cognitive profile in apathy, although few studies have done this specifically in the context of PD. The majority of non-PD studies have used rather blunt and non-specific global instruments such as the Mini-mental State Exam (MMSE), and this has led to some conflicting results. In spite of this, the consensus is emerging that global cognitive impairment is more commonly observed in those with apathy compared with those without [33]. In PD specifically, the few studies in the area have had generally consistent findings. Starkstein et al. [21] used a relatively extensive neuropsychological battery in 50 PD sufferers, 21 of whom scored above the cut-off on the AS (15 also had depression). They found no effect of apathy on the MMSE, but lexical fluency and time to complete Trails B were significantly worse in those with apathy. There were no differences found in tests of visuomotor tracking, set shift, concept acquisition, or auditory attention. Interestingly, those with apathy performed overall worse in time-dependent tasks (FAS and Trails B), but if this was corrected for, performance was equivalent to non-apathetic PD sufferers. The authors suggested that this finding supported a link between apathy and bradyphrenia. Pluck and Brown [1] compared the cognitive profile of PD sufferers with 'high' apathy (n = 17) with those with 'low' apathy (n = 28) as determined by a cut-off score of 38 on the AES-C. Of the high apathy group, only 13 did not have dementia, but the group was analysed as a whole. The key findings supported the notion of executive function being differentially impaired in the high apathy group. Specifically, slowness in performance was seen in the Stroop test, but also on executive tasks less dependent on speed of visual processing. Studies in AD have revealed that those with apathy had significantly worse word list learning, verbal fluency, set shifting and naming than a comparable group without apathy [40, 41].

Impact of Apathy on Prognosis

Prospective longitudinal studies suggest that the presence of an apathy syndrome can worsen prognosis and is associated with a faster rate of cognitive and functional decline [12, 42, 43]. In a 4-year follow-up of a cohort of over 350 AD patients, the rate of apathy was noted to increase as the disease progressed, and those with apathy declined faster and had a more severe course compared with those without apathy

[12]. Robert et al. [43] followed a group of 251 patients with amnesic mild cognitive impairment for a year, and found that those who converted sooner to dementia had initial higher rates of apathy. In a group of non-demented PD patients followed-up at a median period of 18 months, more apathy sufferers had converted to dementia compared with those who did not have apathy at baseline [42]. Furthermore, for the group who had not yet converted to dementia at follow-up, higher apathy was associated with more significant cognitive decline. Thus, it appears that apathy may be associated with more aggressive forms of AD and PD. It is not yet clear whether early intervention and amelioration of apathy will alter this poor prognosis.

Apathy may also have negative effects on physical aspects of AD and PD. Core features of apathy may include lack of initiative and interest, which can manifest in decreased motor behaviour and withdrawal from usual physical activities and hobbies, including activities of daily living. This was elegantly shown by ambulatory monitoring of the extent of motor activity in AD patients with apathy compared with those without apathy, demonstrating significantly less movement in those with apathy [44]. Sedentary behaviour in elderly demented people can lead to secondary physical complications such as deep vein thrombosis, urinary and respiratory infections and increased frailty. Although there is a growing recognition that exercise may be beneficial to those with a neurodegenerative disease, in the context of apathy, such potentially beneficial non-specific interventions as exercise may be difficult to implement. Other physical complications associated with apathy in dementia may be a decline in weight and nutritional status, as demonstrated in a study of over 600 community-dwelling AD sufferers where poor nutritional status was significantly associated with the presence of apathy [45].

The negative impact of apathy on disability levels and overall functional decline in PD can be significant. In a sample of 99 non-demented PD patients with apathy, clinician-rated apathy was strongly and significantly associated with higher levels of disability, as determined by activities of daily living rating scores [46]. In this study, a multivariate regression analysis revealed that apathy, together with later stage of disease and more cognitive impairment, accounted for 56% ($p < 0.001$) of the variance predicting disability. These findings are consistent with the literature in AD, where numerous studies have found higher levels of impairment in ADLs in those with apathy or depression [8, 45, 47, 48].

The effect of apathy on carers needs to be considered since the role of carers in chronic degenerative diseases such as AD and PD is significant. Psychiatric symptoms such as depression in the PD sufferer have been strongly associated with carer distress [4, 49], and this appears to be the case with apathy as well. However, the impact on carer burden of apathy has not been as well studied other than in those with significant cognitive impairment and dementia [50]. In our own study of 71 non-demented PD sufferers and their carers, a strong correlation between level of self-reported apathy ($\rho = 0.41$; $p < 0.001$) and carer burden, as measured by the Zarit Burden Inventory was found [51].

Management of Apathy

The cornerstone to managing apathy is recognising its presence, differentiating it from depression or other differential diagnoses, and developing an individualised care plan that is based on multidisciplinary input. Differential diagnoses, other than depression include the undertreatment of motor symptoms of PD, hypoactive delirium, sleep disturbances with excessive daytime sleepiness, medication side effects and disease progression. Other medical conditions, besides PD, may also present with an apathy-like syndrome and need to be ruled out. In particular, these can include systemic conditions common in the elderly such as thyroid disease, B₁₂ or folate deficiency, cardiac conditions and malignancies.

If reversible causes of apathy have been excluded and the diagnosis of apathy is made, both non-pharmacological and pharmacological interventions need to be considered. Non-pharmacological approaches generally depend on motivated carers to activate and interest the affected person and provide external sources of stimulation to overcome the loss of internal drive and motivation. Occupational therapists and activity coordinators may develop specialised programs that can be continued by carers. Fostering physical activity through exercise may be helpful, but this often requires much dedication from carers to undertake such programs: the apathy sufferer may resist such interventions. A current French study examines the effectiveness of staff education in non-pharmacological intervention methods to manage apathy in older people with dementia in nursing home settings. This study involves a trainer providing guidance on structured activities designed to stimulate and involve the residents and is an example of an intervention that can be undertaken at a relatively low cost and with few adverse effects [Robert, pers. commun.].

From a pharmacological perspective, there is little evidence to guide therapeutic choice, although there is some evidence supporting the use of cholinesterase inhibitors in alleviating apathy symptoms in AD. In particular, studies with donepezil, the most commonly prescribed cholinesterase inhibitor, have shown reduction in apathy in AD as measured by the NPI [52, 53] or the AS [54]. Apathy was not specifically examined as an outcome measure in the few small studies of donepezil in PD [e.g. 55]. On the other hand, rivastigmine, the only cholinesterase inhibitor licensed for the treatment of PDD, does appear to be beneficial in this condition, as well as in AD and dementia with Lewy bodies [56–58]. Finally, galantamine, another cholinesterase inhibitor has been shown to be of benefit in improving clusters of behavioural symptoms comprising apathy [59]. There is no evidence in PD specifically. Memantine, an N-methyl D-aspartate receptor antagonist, does not appear to have a role in treating apathy in AD or PDD [60–62].

Evidence to support the use of drugs other than cholinesterase inhibitors is rather limited. Stimulants such as methylphenidate may be effective, but they carry significant risk of precipitating psychosis in PD or causing insomnia or appetite loss,

particularly if cognitive impairment or advanced disease is present. Modafinil, a non-stimulant wakefulness-promoting agent, may have a role in treating both excessive daytime sleepiness and apathy [63]. However, robust evidence for its efficacy in PD specifically is lacking.

Dopamine-enhancing medications have long been of interest in alleviating the symptoms of apathy. For example, there is evidence that bupropion, a dopaminergic antidepressant, is effective in enhancing motivation [64]. Amantadine, an N-methyl-D-aspartic acid receptor antagonist, which may indirectly enhance dopaminergic transmission, may have a role in alleviating frontal-type behavioural disturbances in dementia, and is generally well tolerated in elderly patients. It too may have a role in improving apathy; however, the evidence for this in PD and AD is not extensive [65, 66]. Dopamine agonists, particularly pramipexole, which has the most specific D3 receptor activity, may be helpful, and increasing the dose of agonists in apathetic PD sufferers may improve apathy and mood symptoms. A recent meta-analysis of seven randomised controlled trials suggested that of the 70 PD patients with some degree of motivational loss, 63.2% had improvement in motivation with pramipexole compared with 45% of those on placebo (odds ratio = 2.06) [67]. This approach, however, needs to be undertaken cautiously since many apathy sufferers will be older, have advanced disease and therefore may be unable to tolerate the cognitive and psychiatric side effects of higher doses of dopamine agonists. Another approach may be to increase the overall daily dopaminergic load with levodopa and other, better tolerated dopamine replacement therapies. Finally, the role of antidepressants in the treatment of apathy needs to be considered. Since the overlap of depression and apathy is high, and some antidepressants (e.g. sertraline, venlafaxine) are slightly stimulating, PD patients with depression and apathy may benefit from a course of antidepressants. However, since as seen above there is some evidence that SSRIs may cause apathy, patients on SSRIs need to be closely monitored for worsening, or emergence of apathy symptoms. Other antidepressants which may have a role in treating apathy are the monoamine oxidase inhibitors. These are used clinically in some centres, but the evidence supporting their use is very limited.

Another intervention that may be of interest for treating apathy in PD is deep brain stimulation. Current evidence is too conflicting for any clear recommendations to be made [68–70].

Conclusion

We have highlighted various aspects of apathy in neurodegenerative disorders such as PD. The significant negative impact that the presence of apathy can have in AD, as well as in PD, has been outlined. There is a need for more detailed prospective studies to examine these and other apathy-related issues further, as well as trials of pharmacological and non-pharmacological interventions for the management of apathy.

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Disorders of Visual Perception in Parkinson's Disease and Other Lewy Body Disorders

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Abstract

Visual disturbances are common in Parkinson's disease, Parkinson's disease dementia, and other Lewy body disorders. Patients may report a wide range of symptoms from double and blurred vision to complex visual hallucinations and illusions. Investigations have shown impairments in virtually all aspects of vision from contrast sensitivity to object recognition and spatial orientation. Increasing visual disturbance, particularly the presence of hallucinations, is associated with poorer quality of life and increased risk of institutionalization and death. Increasing cognitive impairment, the use of medication with anticholinergic effects, sleep disturbance and poor eyesight are potential risk factors. Reduction and rationalization of medication may be as important as starting additional pharmacological therapies, which are currently limited in efficacy, and offset by negative effects on motor symptoms. Imaging and neuropathological studies suggest that multiple abnormalities in the distributed visual system, both in the dorsal and ventral visual streams, as well as in their associated frontal projections and regulatory systems play a role in the pathogenesis of visual disturbances in Lewy body disorders. The varied nature of visual symptoms and wide distribution of pathology through brain visual systems argues against a simple one-to-one correlation between specific visual symptoms and discrete cortical areas.

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In this chapter, we aim to review the phenomenology, the course, the pathophysiology and the treatment of the most common visual symptoms in Parkinson's disease (PD) and other Lewy body disorders; in particular the overlapping syndromes of PD dementia (PDD) and dementia with Lewy bodies (DLB). Given the overlap between the latter two, we will refer to them as a single symptom complex (PDD/DLB), unless there are specific reasons for distinguishing between them (see chapter 11).

In his original description of the disease which now bears his name, Charles Parkinson emphasised that 'the senses and intellect are uninjured'; a statement which biased perceptions of the non-motor symptoms of PD until relatively recently. Even

though early descriptions of clinical parkinsonism [1] reported visual hallucinations (VH), they were generally ascribed to comorbid disorders or to the side effects of treatments given – opium, ergot derivatives and anticholinergic drugs (atropine, scopolamine and belladonna) were all popular – rather than being recognised as a core feature of the disease. Similarly, the high rate of psychiatric symptoms in encephalitis lethargica after the 1918 influenza epidemic led to the conclusion that this was a disorder different from PD, rather than broadening the view of what constituted PD. In line with this purely motor view of PD, the frequently reported visual symptoms were initially attributed to medication use when research intensified in the 1970s following the introduction of first levodopa and then direct dopamine agonists [for a discussion see 2].

Several factors have brought visual symptoms to the focus of attention in Lewy body disorders. Patients have been living longer. This led to an increase in the prevalence of poor cognition and eyesight, two of the major risk factors for hallucinations and other disturbances. Increased clinical interest and consequent better ascertainment has overcome the understandable reluctance of patients to report seeing things not seen by other people. Patients often do not disclose VH, fearing the response of doctors or worrying about being diagnosed ‘insane’ [3]. As a result of greater ascertainment, there has been increasing recognition of the substantial burden of disability and distress that these symptoms cause for patients and families [4]. Particularly since DLB was identified as a common disorder in the 1990s, research has emphasised on the overlapping pathology between classical motor symptom PD and the multi-symptom complexes of distributed Lewy body pathology.

Clinical Disorders of Vision in Parkinson’s Disease

In patient surveys, large proportions of PD and virtually all PDD/DLB patients report some disturbance of vision. Symptoms include complaints about dry eyes, photophobia, diplopia, difficulties with reading, difficulties estimating spatial relations, or freezing when passing narrow spaces. Although, as a group, PDD/DLB patients perform worse on just about every measure of visual function – visual acuity, contrast sensitivity, motion and colour perception are all impaired in PD [for review see 5, 6] – there is substantial individual variation [7].

The causes of such symptoms and signs can rarely be established with confidence. Potential explanations include reduced blink rate, oculomotor abnormalities or reduced retinal contrast sensitivity. Alternatively, they may be an expression of cortical dysfunction manifesting as visuoperceptual, visuospatial and attentional impairment, or general perceptual slowing. As these factors usually co-exist, it can be difficult to disentangle the purely ‘perceptual’ from ‘lower level’ disturbances of visual and motor function.

Validated questionnaire and interview-based assessments of some visual symptoms, specifically hallucinations, are now available, but these are restricted in the range of

visual and other symptoms investigated [8]. Commonly used structured assessments, for example the Neuropsychiatric Inventory or Unified Parkinson's Disease Rating Scale, provide minimal detail on the types of symptoms seen in PD. The North-East Visual Hallucination Interview [9] assesses the VH phenomenology and associated cognitions and emotions more specifically. It is validated for use in the elderly as well as those with cognitive impairment. It has also been used in PD samples with studies due to be published soon. Until a wider range of assessments are available, a careful clinical assessment remains the most generally useful way of ascertaining symptoms.

Cortical visual processing depends upon two overlapping, but distinct, networks – the dorsal (occipitoparietal, 'vision for action') and ventral (occipitotemporal, 'vision for perception') streams. There is now considerable evidence that the disease process in PD and DLB impacts on both of these streams, influencing the nature of the visual symptoms reported by patients.

In terms of putative disturbances in the ventral stream, hallucinations, generally formed, and of figures and animals, occur both in population- and hospital-based studies of PD with a prevalence of 20–40%, rising to 60–80% in studies of patients with PDD and DLB (see chapter 2). Once present, VH are often persistent and progressive, and cause increasing neuropsychiatric impact. They are strong predictors of nursing home placement and even mortality [4].

There are many anomalous visual experiences [10] which are often loosely included in the same category as VH in clinical studies of PD. They include a sensation of movement in the visual periphery (passage hallucinations), a sense of presence in the room (extra-campine hallucinations) and illusory misperceptions of a visual stimulus. Illusory misperception, feelings of presence and passage often co-occur with VH, but also exist in isolation, and may not have the same predictive value in terms of the development of PDD [11].

VH are not unique to PD and DLB and are seen in a variety of normal and other neurological, psychiatric and ophthalmological conditions, especially psychosis, delirium, and eye disease [for reviews see 12, 13]. In eye disease, a broad range of hallucinatory experiences are reported by psychologically normal people, i.e. the Charles Bonnet syndrome. In this condition, patients experience a variety of visual phenomena from simple visual disturbances (flashes of light) through to well-formed VH of people, animals and panoramic scenes. Suggesting that processes underlying hallucinations in different disorders may not be entirely distinct, poor visual acuity and contrast specificity are identified as risk factors for VH in PD and PDD/DLB [14, 15].

Vivid nocturnal hallucinatory experiences are also seen in some patients with brainstem disorders, where they are referred to as 'peduncular' hallucinations, and transient hallucinations are also seen in the hypnopompic (waking up) and hypnagogic (falling asleep) state in narcolepsy, and indeed in the general population, too. Peduncular hallucinations share phenomenological features with the 'presence' hallucinations seen in PD and PDD, and raise the possibility of links between sleep

disorders, brainstem dysfunction and the development of hallucinations in PD [for example 16].

Disturbances in spatial perception, for example depth perception, orienting, and motion perception [17] may be due to dysfunction in the dorsal visual stream, although the association between the extensive dorsal stream dysfunction described later and specific visual symptoms in PD remains relatively unexplored.

Associations with Other Features of Parkinson's Disease

Cognition

The increase in the frequency of VH between PD and PDD/DLB suggests a role for cognitive impairment as a risk factor for hallucinations. PDD/DLB patients suffering VH perform less well on visuoperceptual tasks than PDD or DLB patients without VH [7, 18]. Indeed, even in non-demented PD patients, differences in cognitive profiles can be demonstrated between hallucinators and non-hallucinators in terms of executive function, visuoperceptual abilities and sustained attention [11, 19–26].

Medication

Once assumed to be a consequence of dopaminergic therapy, evidence now suggests that there is no clear association between levodopa dose and VH, although dopamine agonists as a class are associated with a small increased risk of VH [2, 27]. There are historical reports of hallucinations complicating late-stage PD in the pre-levodopa era, and DLB patients frequently experience florid VH without previous exposure to dopaminergic therapy. Anticholinergic medication may potentiate VH [28] and further evidence against a 'pure' dopaminergic hypothesis is provided by the improvements seen in PDD hallucinators when treated with cholinesterase inhibitors.

Sleep Disturbance

Several studies have suggested that REM sleep behavioural disorder (RBD) is an independent risk factor, along with cognitive impairment, for developing VH in PD [16]. However, clear correlation between RBD, VH and motor and non-motor outcome has not been confirmed in other studies. Goetz et al. [29] found that although sleep disorders (sleep fragmentation, vivid dreams/nightmares, acting out of dreams) co-occurred with VH in a 10-year longitudinal study of PD patients, they did not predict their development.

Other Psychiatric Symptoms

Mood disorder, and delusional syndromes may co-exist with hallucinations; perhaps reflecting the role of other factors. Insight, for example, may be compromised by cognitive function [11]. Delusional misidentifications, for example Capgras and Fregoli type syndromes, may similarly reflect the combination of cognitive and perceptual factors.

Pathophysiology

Neuroimaging

Different modes of neuroimaging have been used to examine the structural and functional consequences of neurodegeneration in PD and PDD. Figure 1 summarises these findings.

Bruck et al. [30] demonstrated hippocampal and prefrontal cortex atrophy in non-demented PD patients compared with healthy controls, the former being associated with memory deficits and the latter with attentional impairments on cognitive testing [30]. More diffuse, but subtle, atrophy has also been detected in superior parietal, occipital, fusiform and parahippocampal regions of non-demented PD patients, correlating with visuospatial and visuo-perceptual impairments [31]. Greater reductions in grey matter density in limbic, paralimbic and neocortical regions are evident in PD hallucinators compared with non-hallucinators, suggesting a link not just with cognitive profile but also visual symptoms [32, 33].

Atrophy is more pronounced in studies of PDD and DLB. Hippocampal, parahippocampal, frontal, parietal and occipital regions are all affected [34], although those cortical areas involved in dorsal and ventral stream visual processing seem particularly vulnerable [35, 36]. Diffusion tensor imaging, which provides a measure of the integrity of neural connectivity, suggests that communication between precuneus, posterior cingulate and posterior parietal regions is damaged in PDD and DLB [37, 38].

Single-photon emission computed tomography (SPECT) studies, measuring regional perfusion, provide functional as well as structural measure of cortical integrity. SPECT studies in DLB and PDD have demonstrated reductions in occipital and posterior parietal perfusion [39, 40] associated with cognitive and behavioural features such as attentional deficits and hallucinations [41]. In addition to this occipitoparietal change, greater hypoperfusion in inferior temporal and fusiform regions is described in hallucinators compared with non-hallucinators [42, 43]. Subtle perfusion changes are even demonstrable in parieto-occipital regions in PD patients with mild cognitive impairment compared with cognitively normal PD patients [44]. MR spectroscopy and positron emission tomography highlight reductions in metabolic activity in occipital [45], temporal and frontal areas [46].

fMRI has been employed to study the neuroanatomical substrate of cognitive impairment and associated symptoms in PD. During stroboscopic and kinematic stimulation of the visual pathway, PD hallucinators show an altered pattern of activation in the visual pathways, with reduced activity in occipital and parietal, and increased activation in frontal, subcortical and visual association areas compared with non-hallucinators [47]. DLB patients demonstrate reduced activation in ventral occipitotemporal regions for face perception tasks and reduced activation of lateral occipitotemporal cortex for visual motion tasks [48]. Results from face recognition and visual pop-out tasks in PD hallucinators and non-hallucinators highlight the role

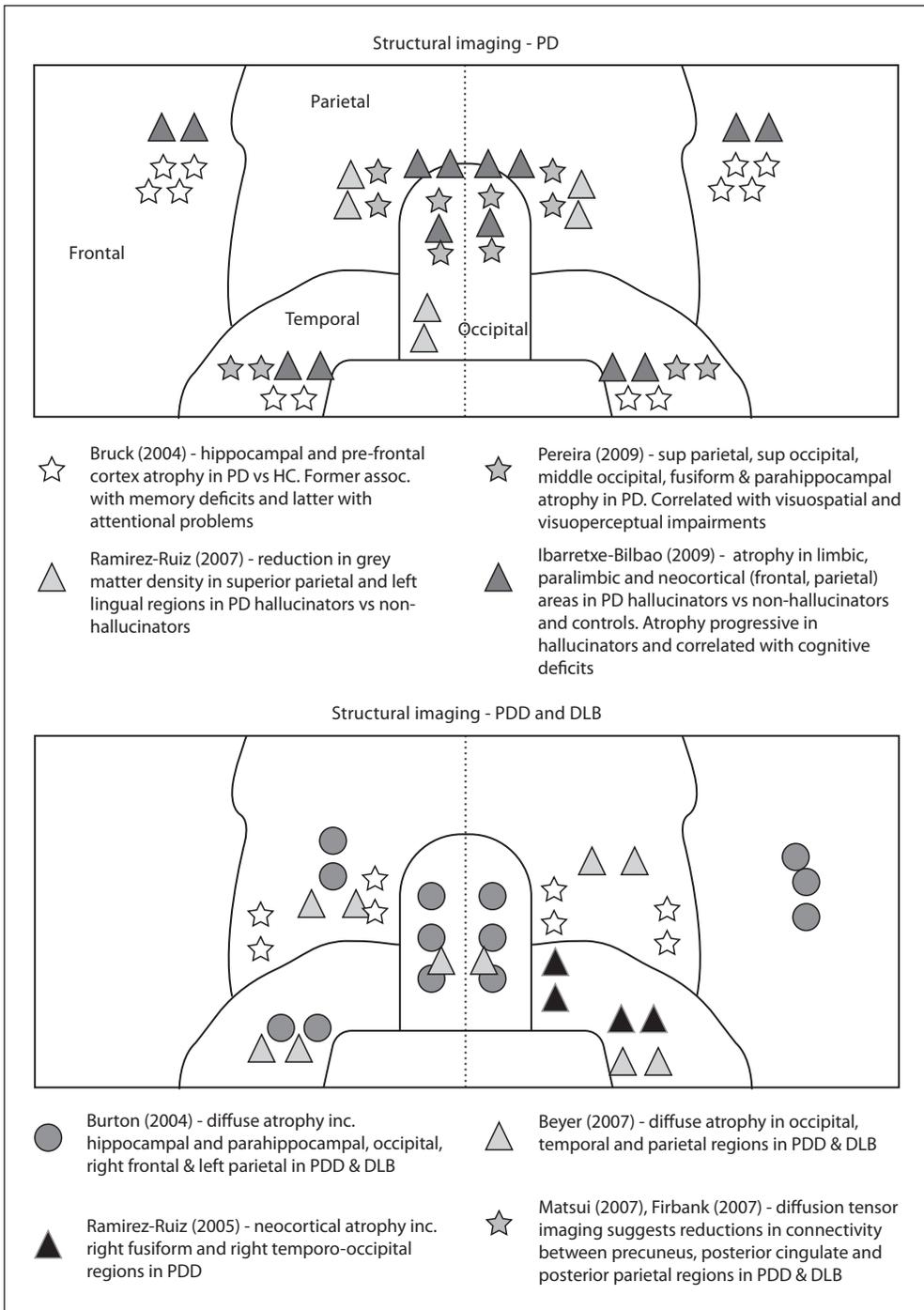
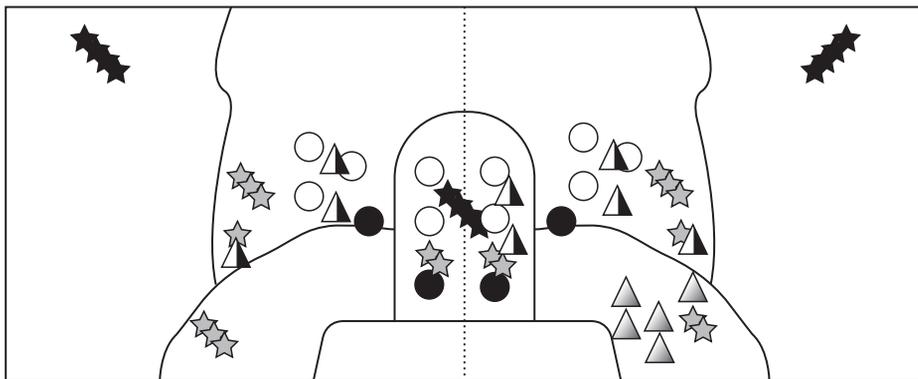


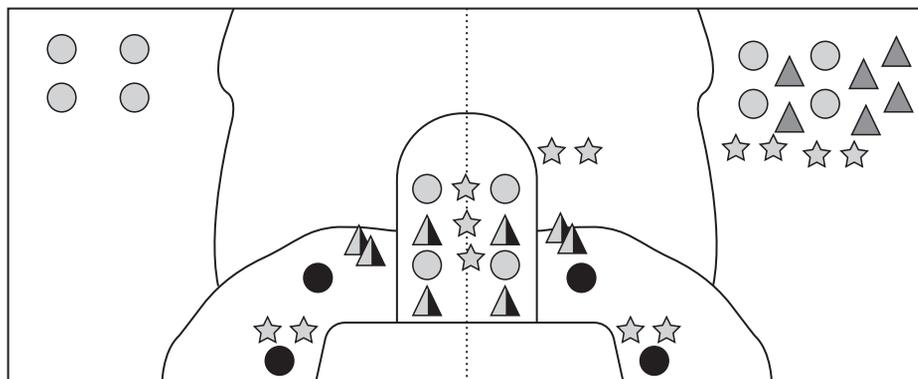
Fig. 1. Imaging studies. In this depiction, the lobes of the brain have been flattened out to allow a better appreciation of the principal regions affected in Lewy body disorders. Each symbol relates to a separate study; more symbols indicate more severe pathology or dysfunction. Note the bias toward involvement of the medial temporal, occipitoparietal and prefrontal regions, which holds even in those studies focussing on early stage disease. HC = Healthy controls; PIGD = postural instability gait difficulty; TD = tremor dominant; PD-MCI = PD-mild cognitive impairment; PPC = posterior parietal cortex.

Perfusion imaging - PD, PDD and DLB



- Abe (2003) - reduced regional cortical blood flow (rCBF) in occipital and PPC (PD vs HC)
- ☆ Matusi (2006) - PD and PDD hallucinators and non-hallucinators. Reduced perfusion in inferior parietal lobe, inferior temporal gyrus, precuneus and occipital lobe
- ★ Mito (2006) - reduced perfusion in anterior cingulate and occipital cortex, more marked in PLGD vs TD phenotype
- O'Brien (2005) - cognitive and behavioural features associated with perfusion changes in post. cingulate, thalamus and inferior occipital regions (PDD & DLB)
- ▲ Oishi (2005) - hypoperfusion in right fusiform region and hyper-perfusion in sup. and middle temporal gyri in PD hallucinators
- ▲ Nobili (2009) - PD-MCI vs PD demonstrates reduced perfusion in posterior parietal cortex, right occipital region and precuneus

Functional MRI - PD, PDD and DLB



- Sauer (2006) - fMRI during face perception and visual motion tasks. Reduced activation in DLB (ef.AD) in ventral occipital-temporal regions for former and lateral occipital-temporal regions for latter
- ▲ Holroyd (2006) - PD hallucinators and non-hallucinators. Increased activation in association visual cortex and reduced activation in primary visual cortex
- ☆ Meppelink (2009) - Visual pop-out task demonstrates reductions in occipital and ventral stream activation in PD hallucinators. Also subtle parietal and frontal hypoactivation.
- Stebbins (2004) - stroboscopic and kinematic stimuli in PD hallucinators and non-hallucinators. Altered pattern of activation with posterior activation in non-hallucinators and frontal/sub-cortical activation in hallucinators
- ▲ Ramirez-Ruiz (2008) - face recognition task in PD hallucinators and non-hallucinators. Reduced activation of right pre-frontal areas and anterior cingulate and increased activation of right inferior frontal gyrus in hallucinators

of pre-frontal, cingulate and temporal regions in this task, with hallucinators showing reductions in activation [49, 50].

Neuropathology

In PD and PDD/DLB, there is structural and neurochemical pathology in virtually all parts of the visual system from the retina to frontal cortex, as well as in the brainstem and thalamic regulatory systems which project to visual areas [5]. Cholinergic and dopaminergic deficits are particularly consistent. Two studies have examined the neuropathology in Lewy body dementia (PDD and DLB) specifically with VH. Consistent with both is an association between α -synuclein burden in the medial temporal lobe (particularly the amygdala) and VH in life [51, 52]. Synuclein and amyloid may thus disrupt a distributed system beyond its capability to self-stabilise, rather than having an effect in a critical location.

Models of Visual Hallucinations

In recent years, a number of models have been proposed which link disturbances in brain function with VH. Current models of normal visual perception see the subjective experience of vision as resulting from an internal, sparse, functional, predictive, dynamic representation of the visual input that the brain would receive if that representation were correct. Given this conceptualization, it is perhaps not surprising that disturbance in any part of this system can produce misperceptions. With potentially different causes in different patients, or even within the same one, there may thus not be a single final pathway for hallucinations in PD.

Arnulf et al. [53] proposed the first PD-specific model in 2000 suggesting that hallucinations reflected the intrusion of dreams into the waking state. In spite of the associations of VH with disturbed sleep and dreaming, more recent evidence suggests that these may reflect co-incidental disturbances in closely related but separate systems rather than causal links. Phenomenological differences between dreams and hallucinations further suggest that other models may fit the data better [54].

In 2005, Collerton et al. [13] and Diederich et al. [55] separately published similar interactive models which locate the generation of VH in the faulty interaction between top down internal representations and bottom up sensory input.

Collerton and collaborators developed the Perception and Attention Deficit (PAD) Model to account for VH across many disorders: a combination of attentional and perceptual impairments leads to the intrusion of an expected but incorrect perception which is not then disconfirmed because of poor perceptual function. Thus, the perception with a hallucinatory element is possible because it provides a better match for distorted visual input than does a purely veridical perception. Other risk factors, for example alertness, poor vision, and medication act through these attentional and perceptual pathways. The cognitive data noted earlier, which indicate that

attentional and perceptual impairments are associated with hallucinations, provide some support for the PAD model. It is also broadly consistent with functional imaging data suggesting abnormalities in the ventral visual stream, but there are conflicting results from imaging of frontal cortex, perhaps reflecting the difficulty in capturing the dynamic changes associated with specific hallucinations instead of the relatively static factors which generally increase the risk of hallucinating. Because of the intermittent nature of hallucinations, virtually all studies have been of subjects who are prone to hallucinations but who are not actively hallucinating at the time of imaging.

Diederich's Activation, Input, Modulation Disturbance Model [28, 55] suggests more direct roles for alertness and sensory input than does PAD, but similarly locates the disturbance at the interface between internal and external factors within the perceptual process. Given the conceptual overlap between these two models, similar levels of experimental support exist for both.

Treatment

Reduction or cessation of medications, particularly those with cholinergic effects, is the first consideration when managing hallucinosis in most disorders [56]. In Lewy body disorders, it is usually possible to rationalise anti-parkinsonian therapy, aiming to remove those drugs with the greatest tendency to cause neuropsychiatric disturbance (anti-cholinergics, amantadine). It may also be appropriate to simplify the therapeutic schedule by stopping weak anti-parkinsonian medications, such as monoamine oxidase type B inhibitors (selegiline, rasagiline), and aiming for levodopa monotherapy wherever possible. With such changes, a worsening of motor symptoms is to be expected, and patients and carers must be counselled accordingly. In some patients, motor fluctuations may necessitate the institution or continuance of catechol-O-methyl transferase inhibitors (entacapone, tolcapone). There is no clear link between levodopa dose and the development of VH, but the direct synthetic dopamine agonists as a class do appear to be associated with VH as well as a wide range of behavioural symptoms. Very few PDD/DLB patients tolerate direct dopamine agonists (e.g. pramipexole, ropinirole), and for this reason they should be avoided.

If medication reduction is impossible or ineffective, atypical antipsychotics may be effective. Clozapine has the best evidence base, but its use is limited by side effects and the risk of agranulocytosis [28]. Clozapine is also licensed in the US for the treatment of tremor and can have a beneficial effect on motor symptoms in some PD patients. Cholinesterase inhibitors are effective in PDD by enhancing cognition and reducing psychiatric symptoms [57]. Hallucinators respond better than non-hallucinators to rivastigmine, perhaps reflecting the relatively greater cortical cholinergic deficits in those PDD and DLB patients with hallucinations [57]. Cholinesterase inhibitors may therefore have a role as 'antipsychotic' medication in PDD patients. There is no

evidence base for the use of cholinesterase inhibitors to treat hallucinations in PD patients without dementia or with milder cognitive impairments.

Practical manipulations such as improving lighting or vision, and modifying sleep or activity patterns may be tried [56]. There is no systematic evidence of effectiveness, but patients often use such techniques themselves [58], and there is little likelihood of harm. Cognitive behavioural treatments analogous to those used in psychosis may be useful to reduce the distress associated with hallucinations, but they lack a current evidence base.

Future Directions

Future progress is likely to come from combined methods which link a specific focus on a particular visual symptom with risk factors, structural and functional imaging, and treatment effects. Clinicians may benefit from improved clinical scales for the assessment of visual symptoms in PD patients with or without dementia. Furthermore, clinical algorithms on how to diagnose and treat visual symptoms in PDD and DLB are likely to improve diagnostic accuracy and management. More effective treatments that do not compromise motor function are needed.

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Psychosis and Parkinson's Disease

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Abstract

Parkinson's disease (PD) psychosis is a common phenomenon that affects quality of life, caregiver burden, and disability in patients with PD. Although there may be an increased risk of psychosis inherent to the disease itself, current research suggests that dementia, advancing age, and concomitant medication use increase the risk of psychosis in PD. Symptoms of psychosis in this population may include hallucinations, delusions, paranoia, false sense of presence, and illusions. Early intervention may be important for delaying progression of psychotic symptoms. Treatment options for PD-related psychosis include reduction of dopaminergic therapy, switch to levodopa, simplification of polypharmacy and addition of an atypical antipsychotic, such as quetiapine and clozapine.

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Parkinson's disease (PD) is a chronic, progressive neurodegenerative disorder characterized by tremor, bradykinesia, rigidity, and postural instability. The presence of psychotic symptoms, or PD psychosis (PDP), is a recognized symptom cluster, and has serious consequences for patients. Psychotic symptoms experienced by PD patients may include hallucinations (primarily visual, but also auditory), illusions, paranoia, delusions, and a milder 'false sense of presence'. Psychotic symptoms are associated with poorer quality of life, disability, caregiver distress and worse outcomes including mortality and nursing home placement [1, 2]. Given the impact of psychosis on this chronic, progressive neurodegenerative disease, current research aims to further understand the epidemiology of psychotic symptoms, the risk factors for psychosis, and most appropriate treatments.

The prevalence of psychotic symptoms varies widely in the literature and may be as high as 60% in the PD population [3–6]. A recent population-based study of PDP revealed an incidence of 797 per 1,000 person-years. At the end of the 12-year study period, 60% of patients had developed psychotic symptoms [7]. The difficulty in assessing the frequency of this condition may be related to a lack of consensus on methods to define what constitutes PDP, subsequent use of multiple rating scales in the literature, and differences in study design and patient population. An expert

consensus group has published a proposed definition of PDP to distinguish it from the Diagnostic and Statistical Manual-IV (DSM-IV-TR) classification of 'psychosis due to a general medical condition'. It defined PDP as psychotic symptoms for at least one month, not due to another cause, with subtypes relating to presence or absence of dementia, insight, and use of dopaminergic medications [8].

Multiple rating scales have been used to screen for psychotic symptoms including: Brief Psychiatric Rating Scale (BPRS), the Clinical Global Impression of Improvement (CGI), Parkinson's Psychosis Rating Scale (PPRS), and Unified Parkinson Disease Rating Scale Thought Disorder (UPDRS-TD) [9]. In addition to the complexity of multiple rating scales, in general, trained clinicians must complete the screening and there are not validated 'cutoffs'. Attempts are being made to both clarify definitions of PDP as well as to establish and validate rating scales. Further epidemiology of neuropsychiatric symptoms in PD is covered in a previous chapter.

Features of Parkinson's Disease Psychosis

PDP typically arises later in the course of the disease, approximately 10 years after initial diagnosis of PD. Symptoms typically arise in the context of retained insight and clear sensorium [10]. Over time, symptoms such as visual hallucinations or delusions tend to recur and progress and insight is lost. Prominent hallucinations early in the course of the disease may suggest Lewy body dementia, Alzheimer's disease, or a pre-existing psychiatric disorder [11].

Hallucinations

Unlike hallucinations seen in primary psychotic disorders such as schizophrenia, which are typically auditory and persecutory or grandiose in nature, in PDP, hallucinations are more often visual, with persistent images (animals, people, inanimate objects) superimposed upon the natural environment [4]. Patients with PDP can also demonstrate 'false sense of presence' hallucinations in which the person has the strong sensation of being in the presence of another person, either known or unknown, in the absence of external stimuli (table 1). Often insight is maintained early in the course. Preliminary studies suggest that over 80% of patients with 'benign hallucinations' progress to frank psychotic symptoms, suggesting that these less severe symptoms should be monitored [10]. Further evaluation of visual and sensory disturbances is covered in the next chapter.

Delusions

Delusions are fixed, false beliefs. The average age of patients displaying delusions is younger than those with hallucinations [12]. The types of delusions seen in patients with PD may vary and are typically paranoid in nature (table 1). There are case reports of patients with Othello syndrome, or pathologic jealous delusions of marital infidelity

Table 1. Psychotic features by disorder

	Primary psychotic disorder	PDP
Hallucinations	Most often auditory, occasionally somatic; persecutory in nature	Primarily visual with persistent images superimposed on a normal environment, false sense of presence and illusions also common
	Typically no insight	Insight generally retained early
Delusions	Paranoid, bizarre (being followed, mistreated, poisoned, mind-reading, ideas of reference, thought broadcasting, thought insertion, thought withdrawal), religious, grandiose (special powers)	Paranoid in nature typically related to jealousy, infidelity, abandonment, parasitosis
Mania	Can be present	Typically not present

that followed PD diagnosis. Psychotic symptoms were treated with reduction in dopamine agonist and/or the addition of an antipsychotic [13, 14]. There are also case reports of delusional parasitosis resolving with cessation of dopamine agonists [15].

Etiology of Psychotic Symptoms

PD is characterized by the loss of dopaminergic neurons with cell bodies residing in the substantia nigra pars compacta with resultant decreased dopamine release in the basal ganglia. The etiology of psychosis is less understood and may involve dysfunctional dopaminergic and serotonergic, and possibly cholinergic, pathways. Indeed, drugs that block dopaminergic receptors can cause extrapyramidal symptoms.

Risk factors for PDP include: exposure to dopaminergic medications, advancing age, increasing impairment in executive function, dementia, increasing severity and duration of PD, comorbid psychiatric symptoms such as depression and anxiety, daytime fatigue, sleep disorders, visual impairment, and polypharmacy [16]. The presence of psychosis in patients with PD is a strong predictor of institutionalization. A study comparing PD patients still living at home with those in nursing care facilities found a 16-fold higher likelihood of hallucinations in the institutionalized group [17]. Another review of a population of PD patients with psychosis found that after 2 years, hallucinations were linked to dementia (68%), nursing home placement (42%) or death (25%) [18].

Inherent to Disease

The incidence of psychotic symptoms in patients with untreated PD is considered to be low; however, there are little data on the natural course of untreated PD. Historically,

Table 2. Odds of psychosis with dopaminergic agonists [20]

Dopamine agonists	Odds ratio (confidence interval)	Odds ratio adjusted for age, sex, dementia
Pergolide	2.22 (1.01–4.87)	2.01 (1.22–5.45)
Ropinerole	1.18 (0.60–2.32)	1.05 (0.55–2.11)
Pramipexole	0.52 (0.22–1.24)	0.94 (0.33–1.66)
Cabergoline	0.32 (0.16–0.63)	0.65 (0.39–1.09)
Levodopa	0.14 (0.07–0.26)	0.11 (0.06–0.19)

the lack of prospective studies, accompanied by a wide use of anticholinergics and ergot compounds, has confounded assessment of prevalence of hallucinations in the natural course of PD prior to the levodopa era. However, per historical accounts, there may be some increase in hallucinations in late-stage PD, especially in the context of dementia and depression [19]. The mechanism of hallucinations in untreated PD remains unknown, and in the modern treatment era, is not feasible to study clinically.

Psychosis and Dopamine Agonists

The majority of PDP symptoms are felt to be secondary to treatment with dopamine agonists, as the prevalence of psychotic symptoms dramatically rises with the addition of dopamine agonists. This is parsimonious and consistent with the general idea that psychosis is a consequence of increased dopaminergic transmission in the mesolimbic dopaminergic pathway. In a cross-sectional retrospective study of PD patients with psychosis vs. age-matched controls without psychosis, there was a positive correlation found between psychosis and dementia, number of medications, and pergolide intake [20]. In terms of medications, the adjusted odds ratio was calculated to be the highest with pergolide (2.01) and the lowest with levodopa (0.11) [20] (table 2). This lack of association with levodopa is further supported by data showing that the relationship of PDP symptoms with mean levodopa and levodopa-equivalent may not be always established [21].

Another study using the administrative health care databases of Ontario, Canada, examined 10,347 individuals 66 years of age or older following recent initiation with dopaminergic therapy. The estimate for the cumulative probability of requiring an antipsychotic at 7 years was 35%; 499 individuals (4.8%; 5.2/100 person-years) were prescribed an antipsychotic within 1 year of starting dopaminergic therapy. This also suggests a role for dopaminergic treatment in the development of psychosis [22].

Diagnosis and Treatment of Psychotic Symptoms in Parkinson's Disease

Diagnosis of PDP is largely clinical and is facilitated by collateral histories from care-takers and/or family members. There is current work to establish validated measures

to assess PDP. It is important when evaluating psychotic symptoms in a patient with PD to first rule out other causes for the symptoms such as delirium. Fluctuating level of consciousness, marked decline in cognitive performance, increased confusion, and disorientation from baseline in the context of medical illness are the hallmark signs of delirium. In psychosis, baseline memory, orientation, and cognition are usually unimpaired. Delirium is common in PD patients due to their comorbid medical problems and multiple medications. Distinguishing delirium from drug-induced psychosis may be difficult, especially in a patient with comorbid dementia at baseline [23].

The presence of prominent visual hallucinations, especially if accompanied by stupor, early in the course of parkinsonism should also alert the physician to consider a diagnosis of Lewy body dementia. Parkinsonism and psychotic symptoms may also arise in the context of Alzheimer's disease. The possibility of an independent psychotic disorder should also be considered, especially if the hallucinations are primarily auditory with paranoia, or if there is accompanying mania.

Psychotic symptoms can be debilitating and precipitate moves to higher levels of care in individuals with PD. Because psychotic symptoms tend to progress, early intervention may halt or slow progression [24]. Treatment for PDP aims to reduce psychosis without worsening the movement disorder. As medications used to treat PD can cause psychotic symptoms, and antipsychotics can cause extrapyramidal symptoms, treatment of psychotic symptoms in PD can be complex. There is always the concern that targeting the psychotic symptoms with D2 blockers will worsen symptoms of parkinsonism.

An initial first strategy is to simplify the drug regimen to lowest effective doses and minimize polypharmacy with adjuvants (especially anticholinergic medications, amantadine, and MAO-B inhibitors) [25]. If this fails to reduce psychotic symptoms, use of additional medication can be considered. Most commonly, atypical antipsychotics are used. Thus far, only two medications have been shown to be effective in PDP with minimal worsening of motor function: clozapine and quetiapine. Clozapine, in doses less than 50 mg/day, is considered to be safe and effective in reducing PDP symptoms [26]. A four-week, randomized, double-blind placebo controlled study of 60 patients with PD exposed to clozapine, followed by 12-week open period and one month discontinuation, showed that a mean dosage of 35.7 mg significantly reduced psychotic symptoms without significant worsening in motor function. This effect was lost upon discontinuation of the drug [27].

Clozapine is considered to be the gold standard treatment for psychosis in schizophrenia; however, it carries a serious adverse event of agranulocytosis in 1%. Consequently, weekly monitoring of white blood cell counts is required in the first 6 months of treatment and biweekly thereafter. Quetiapine carries less risk of leucopenia, but may not be as efficacious as clozapine for treatment of psychotic symptoms [9, 28]. A recent study that randomized age- and disease duration-matched subjects (n = 30) to quetiapine or placebo (n = 28) for a 3-month period did not show a beneficial effect for the treatment of psychosis in PD, although the withdrawal rates were high [29]. A long-term study of quetiapine use in PDP examined 35 patients (mean

age \pm SD, 76.1 ± 5.9 years; mean disease duration \pm SD, 10.3 ± 5.3 years; 19 with dementia) over a 24-month period. Nonresponding patients ($n = 15$) were switched to clozapine, with a positive response in 12 patients (80%). In long-term follow-up, 31% of parkinsonian patients with psychosis treated with quetiapine were still on this medication at 24 months [30].

A systematic review suggests that clozapine is effective for PDP. Data on quetiapine therapy for PDP are conflicting, with open label trials showing some efficacy; however, more rigorous RCTs have failed to show effects for quetiapine [31]. Other studies have shown no statistically significant differences between quetiapine and clozapine in head-to-head trials; however, the data are limited [9].

Other atypical antipsychotics, such as risperidone, aripiprazole, olanzapine, and ziprasidone may have limited effectiveness in targeting psychotic symptoms, but demonstrate motor worsening and should generally be avoided to treat PDP [25]. High potency first generation antipsychotics, such as haloperidol and fluphenazine, are contraindicated.

Antipsychotics have serious limitations. They can have serious side effects including postural hypotension, dizziness, drowsiness, metabolic side effects, lowered seizure threshold to name a few. Clozapine has the additional serious risks of agranulocytosis and cardiac involvement (cardiomyopathy and myocarditis). Because both clozapine and quetiapine carry black box warnings for increased mortality with use in the elderly, other agents have been examined, to a limited degree, to target PDP, including cognitive enhancers, and antidepressants. The acetylcholinesterase inhibitor rivastigmine has been shown to be effective in reducing hallucinations in a double-blind, placebo-controlled trial. Reports on donepezil, tacrine, and galantamine are inconsistent, concerning effects on psychotic and motor symptoms, and it is not clear that cognitive enhancers have a role in PDP in the absence of dementia [25]. Memantine, an NMDA receptor antagonist that also has similar affinity for the D2 receptors and can trigger psychosis in some PD patients, is currently not recommended [32].

Antidepressants have been used in patients with comorbid depression, psychosis and PD with variable effects on psychotic symptoms, but little effect on the movement disorder and are not a standard recommendation [25].

Nonpharmacologic treatments for PDP are also being studied. A small study with patients whose psychotic symptoms were refractory to antipsychotic medication underwent electroconvulsive therapy (ECT) with significant decreases in psychotic symptoms as measured by the BPRS as well as improvement in the Hoehn and Yahr staging [33].

Conclusion

Psychotic symptoms are a common phenomenon experienced by patients with PD that can have serious consequences on quality of life and caregiver burden. Efforts

to define the spectrum of PDP symptoms and diagnostic criteria are in progress and will help facilitate more accurate assessment of the epidemiology of PDP. Clinicians are advised to routinely screen for psychotic symptoms in the office and modify PD treatment accordingly, or consider the addition of an atypical antipsychotic such as quetiapine or clozapine.

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Sleep in Parkinson's Disease and Dementia with Lewy Bodies

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Abstract

Sleep disturbance in Parkinson's disease (PD) and dementia with Lewy bodies (DLB) is common and can have a debilitating effect on quality of life due to the effects of daytime somnolence on cognition, motor function, potential for injury and capacity to manage activities of daily living. Sources of excessive daytime sleepiness in PD and DLB often include sleep fragmentation, side effects of medications, and sleep disorders that disrupt night-time sleep continuity. The parasomnia of REM sleep behavior disorder has also been shown to be an early feature of PD and DLB and a risk factor for dementia in PD. Dysfunction of the dopamine nigrostriatal and mesolimbic systems is involved in Lewy body disease, but several other neurotransmitter systems have Lewy body pathology and neuronal loss that may be responsible for abnormal sleepiness and REM sleep behavior disorder in these conditions.

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Excessive daytime sleepiness refers to a tendency to doze off or fall asleep in situations where one is expected to maintain wakefulness. Daytime sleepiness is a serious clinical issue in Parkinson's disease (PD) and dementia with Lewy bodies (DLB). In PD, excessive somnolence is associated with cognitive impairment, dementia, interference with activities of daily living, and increased risk of driving accidents [1, 2]. In a study of 3,078 men, those with excessive daytime sleepiness were three times more likely to develop PD, a finding not related to insomnia, mood or cognitive function, indicating somnolence may precede PD [3]. Excessive daytime sleepiness is now part of the proposed criteria for dementia associated with PD [4], and disturbed arousal is a common feature of DLB and appears related, in part, to the core feature of fluctuations in DLB [5, 6].

The estimated frequency of abnormal sleepiness in PD ranges from 15 to 81% [7–9]. In the early stages of DLB later confirmed by autopsy, we found the frequency of abnormal sleepiness to be 61% and greater than an age- and dementia-matched AD cohort.

Polysomnography and Multiple Sleep Latency Tests

In PD, overnight sleep studies using polysomnography reveal increased sleep fragmentation and a reduction in total sleep time, slow wave sleep and lower sleep efficiency [10]. Although nocturia, dyskinesia, dystonia, parkinsonism severity, and wearing off phenomena may fragment night-time sleep and result in daytime sleepiness, these factors do not entirely account for reduced sleep efficiency or daytime sleepiness [11, 12]. We found a similar pattern in a cohort of 78 DLB patients in the early and middle stages of DLB, and 50% of the sample had sleep efficiency less than 70%. Although about half the sample met criteria for obstructive sleep apnea (OSA) or periodic limb movements of sleep (PLMS), 76% of the sample had five or more spontaneous arousals an hour, not accounted for by respiratory or motor issues. This suggests that a component of the sleep fragmentation in DLB may have a primary neurologic basis.

The 'gold standard' for the objective assessment of daytime sleepiness uses the Multiple Sleep Latency Test (MSLT). The MSLT is a daytime polysomnographic study that records initial sleep latency (ISL) with four or five sequential laboratory-based nap opportunities spaced every 2 h. The mean value for the initial sleep latencies across the naps is the mean ISL. Mean ISL values less than 10 min are considered abnormal, and values less than 5 min reflect severe daytime somnolence. In a sample of 24 PD patients, despite normal nighttime sleep efficiency, the mean ISL for daytime naps was abnormally low (mean 9.2 ± 6.4 min), and the mean ISL in 42% of the 125 nap opportunities the mean ISL was clearly pathologic (≤ 5 min) [11]. Similarly, an MSLT study of 54 PD patients found more than half fell asleep within 5 min [13]. These findings provide objective evidence of abnormal daytime sleepiness in PD.

We carried out polysomnography and daytime MSLT in 31 DLB and 16 AD patients matched for gender and mild to moderate dementia [14]. Results revealed both groups had a mean night-time sleep efficiency of 70%, but the DLB group was more likely to fall asleep on the MSLT, and those that did fall asleep, did so faster than the AD group. Specifically, mean ISL <10 min occurred in 81% of DLB vs. 44% of AD ($p < 0.01$), and mean ISL <6 min occurred in 61% of DLB versus 19% of AD ($p < 0.01$). These data are similar to the studies of PD and provide objective confirmation of abnormal daytime sleepiness in DLB.

Sleep Attacks and Medication Side Effects

In the last 10 years, the phenomena of sleep attacks in PD, defined as an event of falling asleep suddenly, unexpectedly and irresistibly while engaged in some activity (e.g. during a meal, telephone call, driving a car) have received a great deal of attention.

Compared to levodopa, the ergot agonists (e.g. bromocriptine, pergolide) and non-ergot D2-D3 dopamine agonists (e.g. pramipexole and ropinerole) show an increased risk of daytime sleepiness and episodes of unintended sleep [15–17]. With

the exception of a dose-related effect, levodopa is generally not sedating in PD or DLB [9, 18, 19]. In a sample of 6,620 PD respondents to a questionnaire, 42.9% reported the sudden onset of sleep that was predicted by exposure to a non-ergot dopamine agonist [20]. Factors contributing to sleepiness with dopamine agonists include older age, male gender, history of sleep problems, cognitive impairment, dysautonomia and an overall higher dopaminergic load [20, 21]. Unlike levodopa, the ergot and non-ergot dopamine agonists are more likely to aggravate cognitive impairment and may elicit or intensify hallucinations [22].

Polysomnography data reveal that sleep attacks are objectively characterized as intrusions of non-REM stage 1 and 2 sleep, and a subset are represented by microsleep episodes, which last 15–120 s [23]. Whether sleep attacks are truly abrupt and occur in the absence of a history of sleep disturbance is a point of contention, particularly since patients often have reduced awareness of daytime sleepiness [11, 24] and microsleep episodes are often not perceived by patients [23].

Profound cholinergic neuronal loss in the basal forebrain and severely depleted choline acetyltransferase levels occurs in DLB and in PD with dementia [25]. Further reduction of an already vulnerable system may trigger delirium or delirium-like features [26]. Patients with parkinsonism are often given drugs with anticholinergic properties (e.g. amantadine, antihistamines, antidepressants, medication for incontinence, siallorhea), and patients with DLB or PD with dementia exposed to anticholinergics are at greater risk for confusional episodes, greater functional impairment and the development or worsening of psychosis. Therefore, it is prudent to limit or eliminate the anticholinergic load in patients with DLB or PD with cognitive impairment, and to consider a cholinesterase inhibitor in an effort to augment existing cholinergic availability for the diffuse connectivity of the basal forebrain.

Sleep Disorders

When considering sleep disturbance in PD and DLB, it is important to consider an underlying sleep disorder as the potential culprit or as an exacerbating factor. Treatment of a known sleep disorder may improve nighttime sleep continuity and daytime functioning.

Insomnia

Insomnia refers to difficulty initiating or maintaining sleep and is a common complaint in normal elderly. A study of over 9,000 normal elders >65 years showed that 42% reported difficulty initiating and maintaining sleep, and follow-up 3 years later revealed an annual incidence rate of about 5% [27]. In a sample of 39 DLB and PD with dementia, insomnia was reported in 47% of the cases [28]. In a study of 231 patients with PD, insomnia from delayed sleep initiation was reported in 23–30% and from frequent awakenings in 23–43% [29], similar to the population rates. Over an

8-year follow-up, the complaint of insomnia in PD did not increase over time [29]. Factors associated with insomnia include mood, disease duration, female gender, vivid dreaming, trouble turning in bed, and nocturia [29, 30]. The causes of insomnia may also be related to non-PD related factors; underlying sleep disorders involve arousals due to motor, respiratory or circadian disturbance.

Restless Legs Syndrome

The diagnosis of restless legs syndrome (RLS) requires four essential features: (1) the urge to move the legs, usually accompanied by uncomfortable sensations in the legs (2) onset or worsening of symptoms during periods of rest or inactivity, (3) partial or total relief by movement at least as long as the activity continues and (4) worsening of symptoms in the evening or at night [31]. In the general population of individuals over 65 years of age, RLS occurs with a prevalence of about 8–10% [32] and typically interferes with sleep by causing insomnia. The same frequency of RLS is found in PD [33], though some argue that this is an underestimate since both use the same first-line treatment which may mask its appearance in PD. This seems unlikely though, since the dopaminergic dose needed to optimally treat RLS is much lower than that typically administered for PD, and when RLS does occur in PD, the extrapyramidal signs tend to precede the RLS by several years [34]. Also, although dopamine replacement therapy may help both conditions, RLS is known to respond to opioids, gabapentin and iron replacement therapy, which is not the case for PD. In one study of 303 consecutively treated idiopathic PD subjects, low serum ferritin levels predicted the occurrence of RLS in 20.8% of the group [35]. Moreover, idiopathic RLS is not associated with substantia nigra neuronal loss or Lewy body pathology [36]. In contrast, the hypothalamic dopaminergic diencephalic area that extends to the spinal cord has been considered, especially given mouse model findings of increased locomotion with 6-hydroxydopamine lesions to that region, and improvement of that increased locomotion with ropinirole [37].

Periodic Limb Movements of Sleep

About 80% of patients with RLS also have PLMS, but those with PLMS do not necessarily have RLS. PLMS are repetitive, stereotypic flexion movements of the legs that occur semi-rhythmically (up to 5 s in duration) separated by an interval of usually 20–40 s. They may cause arousals that fragment sleep and result in daytime somnolence. The treatments that are beneficial to RLS are also generally efficacious and well tolerated in those with PLMS. In PD, fragmentation of sleep due to PLMS is not correlated with the severity of daytime sleepiness, suggesting that although it is present and should be addressed, it is not likely the sole or primary source of daytime somnolence in PD [13, 38].

Obstructive Sleep Apnea

Sleep-related breathing disturbance, such as OSA, may cause sleep fragmentation, oxygen desaturation and associated daytime somnolence. Males are disproportionately

represented in those with OSA, a pattern also seen in PD and DLB. In a sample of elderly community-dwelling men, the degree of frailty was associated with the nocturnal respiratory disturbance index with estimated rates of sleep-disordered breathing at about 24% in those with few or no signs of frailty, and 35% in those considered frail [39]. In PD, OSA has been observed in 20–30% of PD patients [40], suggesting rates of sleep-disordered breathing in PD are similar to rates in the normal population.

The apnea/hypopnea index (AHI) refers to the number of times per hour the patient demonstrates breathing cessation or partial obstruction. Several studies of PD demonstrate a mean AHI <10, indicating overall mild sleep-disordered breathing [12, 41, 42], but there is substantial inter-subject variability in PD with some demonstrating moderate to severe apnea, but many show no apnea at all [10, 13]. In one study, 36% of the sample had an AHI >10 [43] and another sample had 21% with AHI >15 (moderate to severe OSA) [40]. Therefore, a subset of patients with PD may be at greater risk for OSA despite normal body mass index (a primary predictor of OSA in the general population), and potential explanations include reduced tone in upper airway muscles, irregular respiratory flow oscillations, use of sedating medications, or perhaps dysfunction of the autonomic regulatory mechanisms for respiration [10, 40].

In DLB, our experience parallels that of PD, and reveals 37% with an AHI >10, 15% with an AHI >15 and no difference compared to AD [14]. Similarly, OSA occurs in a subset of patients but does not account for the overall excessive daytime sleepiness observed in DLB [14]. Nonetheless, it is important to screen for and treat sleep apnea in PD and DLB, in an effort to improve daytime alertness.

Circadian Dysrhythmia

Disrupted sleep architecture with reduced time spent in slow wave sleep (deep sleep) or altered circadian rhythm (associated with nocturnal melatonin peak) is not consistently found in PD and DLB [42, 44, 45]. Patients with hallucinations and cognitive impairment are more likely to have circadian dysrhythmia compared to healthy controls, but this relationship is not strong enough to account for the daytime somnolence in DLB [46].

Mechanism of Arousal in Parkinson's Disease and Dementia with Lewy Bodies

Lewy body disease affects the brainstem and hypothalamic sleep-wake centers, and the pathology affects multiple neurotransmitter systems [47]. Saper et al. [48] have provided data and a theoretical framework for a neuroanatomic flip-flop switch that regulates the transition from sleep to wakefulness. It includes mutually inhibitory elements responsible for sleep initiation, and brainstem nuclei that promote arousal. One hypothesis for the daytime somnolence in PD and DLB may be associated with the disruption of the wakefulness centers, but perhaps also to damage to the mechanism that switches and maintains wakefulness, presumed to reside in the hypothalamic hypocretin neurons. Involvement of the latter may lead to difficulty keeping the

arousal switch ‘in place’ which may result in trouble maintaining wakefulness and/or frequent brief transitions of sleep into wakefulness, or microsleeps.

REM Sleep Parasomnia in Parkinson’s Disease and Dementia with Lewy Bodies

REM sleep behavior disorder (RBD) was first described by Schenck et al. [49] and is characterized by a loss of normal muscle atonia during REM sleep associated with coordinated limb movements (i.e. punching, kicking, pushing, arm and leg movements that look like running or jumping) that mirror dream content. The actions made during REM sleep can be quite vigorous and themes often include defending oneself or others [50], though not exclusively [51], and may be associated with injuries. There seems to be far greater male representation in RBD, though it is unclear whether this reflects a referral bias, hormonal effects or a genetic relationship to the underlying pathology. The treatments of choice are clonazepam and more recently, melatonin [52].

It is important to distinguish RBD from other parasomnias or sleep disorders through polysomnography for proper intervention and to ensure that other sleep conditions are not present that may mimic RBD or that may be exacerbated with the use of clonazepam. For example, severe OSA may include flailing of the limbs and hollering, and nocturnal wandering, confusional arousals and sleep walking (which typically arise from non-REM stages of sleep), may also be hard to distinguish from RBD without polysomnography. Patients are often unaware of their sleep behavior, and it is crucial to obtain information from a bed partner or somebody who has witnessed the patient’s sleep.

RBD occurs with disproportionately greater frequency in DLB, PD and multiple system atrophy, also referred to as the synucleinopathies [53, 54]. In PD, the frequency of RBD is estimated to range between 46 and 58% [53, 55]. In DLB, the frequency of co-occurring RBD has been reported to be about 75% in autopsy-confirmed DLB [56]. In contrast, RBD in AD is quite rare, and occurred in only 2% of a clinical sample of 371 patients with AD or amnesic MCI [53] and in 0% of an autopsy-confirmed AD sample of 81 cases [56].

RBD often antedates the onset of the other clinical features by years and even decades [57–59]. The estimated 5-year risk of developing PD or DLB in a cohort with idiopathic RBD is 17.7%, and the 12-year risk is 52.4% [60]. Including RBD in the new DLB criteria improves diagnostic accuracy and leads to a 6-fold increase in the odds that the patient has autopsy-confirmed DLB [56]. When RBD is present with dementia but not parkinsonism or visual hallucinations, the cognitive pattern is indistinguishable from DLB and differs from AD. The pattern is characterized by impaired attention and visuoperceptual skills but relatively preserved memory and naming [59]. Patients with RBD and PD dementia show a similar cognitive pattern [61].

Follow-up of a subgroup of an RBD with dementia cohort revealed the eventual development of parkinsonism and/or visual hallucinations. Similarly, in Schenck

and Mahowald's original RBD cohort [62], after 7 years of follow-up, 65% showed an eventual development of parkinsonism or dementia. In a group of 8 prospectively studied patients with RBD and MCI followed longitudinally, results revealed 7 developed DLB clinical features and all 8 had autopsy confirmation of DLB [63].

RBD in PD has been associated with orthostatism and non-tremor predominant (akinetic-rigid) parkinsonism [64, 65]. Those with PD and RBD are more likely to have cognitive impairment and an earlier onset of dementia than PD patients without RBD [61, 66, 67].

Results to date indicate that RBD and cognitive impairment may be an early harbinger of DLB and may be predictive of PD with dementia. Nonetheless, not all cases of idiopathic RBD develop cognitive impairment and/or parkinsonism, and it is not known whether there are protective factors that may keep the condition isolated in the brainstem.

The presumed pathophysiologic mechanism of RBD, based on the cat model, involves damage to the descending pontine-medullary reticular formation (including the gigantocellular medullary nuclei) that leads to a loss of the normal REM sleep inhibition of the spinal alpha-motor neurons. Smaller lesions in this region produce REM sleep without atonia, while larger lesions result in more elaborate motor behavior [68]. Some lesions in humans have been associated with polysomnography-verified RBD [50, 69], and two separate case reports of patients with idiopathic RBD revealed isolated brainstem Lewy body pathology with no evidence of dementia, parkinsonism or psychiatric features [69, 70]. Thus, RBD provides a reliable window into brainstem pathology and when combined with cognitive difficulties, is a predictor of DLB or PDD. Idiopathic RBD is a unique biomarker because it is treatable, and when it represents early neurodegenerative disease, the RBD is often present many years before the onset of the parkinsonism or dementia. Thus, RBD provides the potential for early detection for clinical trials and for early therapeutic and preventative intervention for DLB and PDD, once such therapies become available.

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Sexual Problems in Parkinson's Disease

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Abstract

Sexual dysfunction (erectile dysfunction) is a common non-motor disorder in Parkinson's disease (PD). In contrast to motor disorder, sexual dysfunction is often not responsive to levodopa treatment. Among brain pathologies, hypothalamic dysfunction is mostly responsible for the sexual dysfunction (decrease in libido and erection) in PD, via altered dopamine-oxytocin pathways, which normally promote libido and erection. Phosphodiesterase inhibitors are used to treat sexual dysfunction in PD. These treatments might be beneficial in maximizing the patients' quality of life.

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Parkinson's disease (PD) is a common movement disorder associated with the degeneration of dopaminergic neurons in the substantia nigra. In addition to the movement disorder, patients with PD often show non-motor disorders. The non-motor problems of PD include neuropsychiatric disorders, sleep disorders, sensory symptoms, and autonomic disorders. Sexual dysfunction is one of the most common autonomic disorders [1]. Studies have shown that sexual dysfunction has great significance in relation to quality of life measures [2]. It is particularly important to note that, unlike motor disorder, sexual dysfunction is often not responsive to levodopa, suggesting that it occurs through a complex pathological mechanism; for this reason, add-on therapy is required to maximize patients' quality of life. This chapter reviews sexual dysfunction in PD, with particular reference to neural control of the genital organs, symptoms, objective assessment, and treatment.

Neural Control of Erection

Normal Erection

Sexual dysfunction is not uncommon in PD [2, 3]. Studies have shown that sexual dysfunction has great significance in relation to quality of life measures. How-

ever, the detailed mechanism of sexual dysfunction in PD has not been well explored.

The genital organs primarily share lumbosacral innervation with the lower urinary tract. Erection is a vascular event [4] occurring secondarily after dilatation of the cavernous helical artery and compression of the cavernous vein to the tunica albuginea [4]. Helical artery dilatation is brought about by activation of cholinergic and nitroergic nerves; this activation facilitates nitric oxide secretion from the vascular endothelium. Ejaculation is brought about by contraction of the vas deferens and the bladder neck, in order to prevent retrograde ejaculation, by activation of adrenergic nerves. Sexual intercourse in healthy men can be divided into 3 phases: (a) desire (libido), (b) excitement and erection, and (c) orgasm, seminal emission from the vas deferens, and ejaculation from the penis. Erection can be further classified into 3 types by the relevant stimulation: (1) psychogenic erection (by audiovisual stimulation), (2) reflexive erection (by somatosensory stimulation), and (3) nocturnal penile tumescence (NPT; associated with rapid eye movement sleep). 'Morning erection' is considered the last NPT in the night-time.

Hypothalamic Neurons and Dopamine

Among the 3 types of erection, reflexive erection requires an intact sacral cord, particularly the intermediolateral (IML) cell columns. Pathology studies have shown that involvement of the IML nucleus is common in MSA, whereas it is uncommon in PD. Therefore, reflexive erection can be affected in patients with MSA. In patients with a suprasacral spinal cord lesion, reflexive erection might be preserved, whereas psychogenic erection is severely disturbed because of a lesion in the spinal pathways to the sacral cord. Libido and erection are thought to be regulated by the hypothalamus; particularly the medial preoptic area (MPOA) and the paraventricular nucleus (PVN; fig. 1) [5]. Electrical or chemical stimulation in the MPOA/PVN evoked erection and mating behaviors in experimental animals; both were abolished by destruction of these areas. Somatosensory input from the genitalia ascends in the anterior spinal cord and project to the MPOA/PVN via the thalamic nuclei. Erotic visual input from the retina is thought to reach the MPOA via the mammillary body. Recent neuroimaging studies have shown that penile stimulation or watching pornography activate these areas in humans [6]. NPT [7] seems to be regulated by the hypothalamic lateral preoptic area [8]. The raphe nucleus and the locus ceruleus are candidate areas participating in the regulation of NPT. Oxytocinergic neurons in the hypothalamic PVN are thought to facilitate erection by projecting directly to the sacral cord, and by projecting to the midbrain periaqueductal gray and Barrington's nucleus (identical to the PMC). Serum oxytocin concentration increases during masturbation in healthy men.

In experimental animals, dopamine is known to facilitate erection and mating behaviors. The MPOA/PVN receives projections from the nigral dopaminergic neurons [4, 5]. A microdialysis study showed that the dopamine concentration in

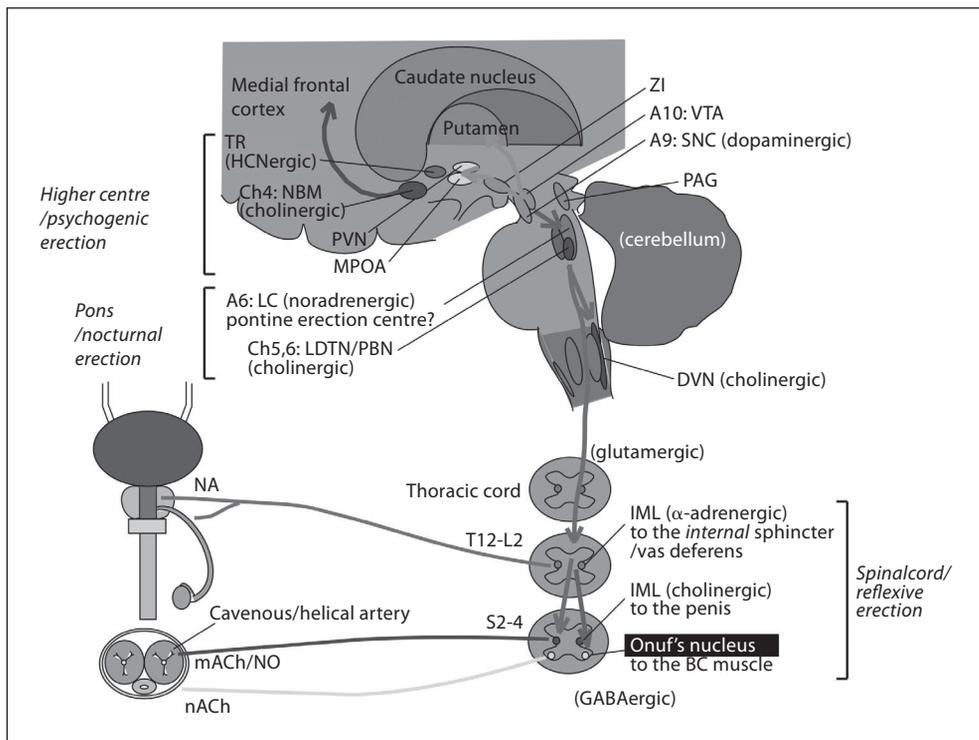


Fig. 1. Neural circuitry relevant to erection. PAG = Periaqueductal gray; LC = locus coeruleus; NBM = nucleus basalis Meynert; A = adrenergic/noradrenergic; ZI = zona incerta; VTA = ventral tegmental area; SNC = substantia nigra pars compacta; DLTN = dorsolateral tegmental nucleus; PBN = parabrachial nucleus; IML = IML nucleus; GABA = γ -aminobutyric acid; T = thoracic; L = lumbar; S = sacral; NA = noradrenaline; Ach = acetylcholine; NO = nitric oxide.

the MPOA was increased by sexual stimulation. It is reported that dopamine D1/D2 receptors in the hypothalamus participate in erection, whereas only D2 receptors participate in ejaculation. Pathology studies have shown that the hypothalamus is affected in PD [9]. Recently, a polymorphism in the dopamine D4 receptor gene has been shown to contribute to individual differences in human sexual behavior [10]. Prolactinergic neurons are thought to be inhibitory to sexual function. Serum prolactin levels increase after orgasm in healthy men. Prolactin-producing pituitary tumors often cause gynecomastia and erectile dysfunction in male patients. Hyperprolactinemia occurs after the use of sulpiride, metoclopramide, and chlorpromazine (all dopamine receptor antagonists). Therefore, dopaminergic neurons seem to facilitate oxytocinergic neurons, whereas they inhibit prolactinergic neurons. Some de novo PD patients have hyperprolactinemia [11], which may contribute to erectile dysfunction in those patients.

Sexual Dysfunction in Parkinson's Disease

Sexual Symptoms

The reported prevalence of sexual symptoms in patients with PD ranges from 37 to 65% [12–14]. Only few previous studies have looked at sexual symptoms in PD and control subjects. Jacobs et al. [12] studied 121 men with PD (mean age 45 years) and 126 age- and sex-matched community derived controls. Patients were more dissatisfied with their present sexual functioning and relationship, whereas no differences were found for the frequency of sexual intercourse itself. Erection and ejaculation were not explored. Sakakibara et al. [2] analyzed sexual function of 84 PD patients (46 men, 38 women, age 35–70 years old) and 356 healthy control subjects (258 men, 98 women, age 30–70 years old) [2]. As compared with the control group, the frequency of dysfunction in PD patients was significantly higher for decrease in libido (84% men, 83% women), decrease in sexual intercourse (55% men, 88% women), decrease in orgasm (87% men), and decrease in erection (79%) and ejaculation (79%) in men. Therefore, sexual dysfunction is significant in PD. The majority of patients had onset of the sexual dysfunction after the appearance of the motor disorder. This is in contrast to patients with MSA, who often have sexual dysfunction before the onset of motor disorder.

Comparing the results between four age subgroups (subjects in their 30s, 40s, 50s, and 60s) in the control group, the frequencies of sexual intercourse and of orgasm were significantly lower in older individuals [2]. In the PD group, only the frequency of orgasm was lower in older men ($p < 0.05$). Comparing the results between both sexes in the control group, decrease in libido and orgasm was more common in women ($p < 0.01$). In the PD group, there was no significant difference in sexual function items. Bronner et al. [14] reported that use of medications (selective serotonin reuptake inhibitors used for comorbid depression), and advanced PD stage contributed to the development of ED.

Rigiscan

In healthy men, sexual intercourse is thought to be carried out by integrating affective, motor, sensory, autonomic, and other factors. In male patients with PD, depression, motor disorder, and pain inevitably lead to sexual dysfunction. In contrast, it has been difficult to determine to what extent autonomic factors contribute to the sexual dysfunction in PD. However, erectile dysfunction often precedes motor disorder in multiple system atrophy, and abnormal NPT is not uncommon in PD. These findings strongly suggest that the disorder does in fact contribute to sexual dysfunction in PD. Rigiscan[®] (Timm Medical Technologies, Eden Prairie, Minn., USA) is an objective measure for erectile dysfunction, which allows both tumescence and rigidity measurement; and it is suitable for assessing NPT.

Only few data have been available concerning the relationship between NPT and dopamine. However, in experimental animals, administration of levodopa elicited

erection and yawning together. Animals with experimental parkinsonism showed fewer rapid eye movement stages during sleep than did control animals.

Treatment of Erectile Dysfunction in Parkinson's Disease

Dopaminergic Drugs

It is possible that levodopa and other antiparkinson medication may affect sexual function in PD. However, it is not entirely clear to what extent levodopa ameliorates sexual dysfunction in PD. In contrast, subcutaneous apomorphine injection is used to ameliorate fluctuating symptoms in PD. It has also been used to treat erectile dysfunction in the general population [15] and in patients with PD [16], although the dose is different (general population, initial 2 mg and up to 3 mg [15]; PD, 4 mg [17]). Apomorphine is thought to stimulate dopamine D2 receptors, and activate oxytocinergic neurons in the PVN. Nausea is a common side effect of this drug. Cabergoline [18] and pergolide [19] are also reported to improve sexual dysfunction in PD. In contrast, pathological hypersexuality may occur together with [20] or without delirium [21], which is attributed to the dopamine dysregulation syndrome (impulse control disorder) in this disorder. DBS in the STN has produced either improved sexual well-being [22] or transient mania with hypersexuality [23] in patients with PD.

Phosphodiesterase-5 Inhibitors

When dopaminergic drugs do not help, phosphodiesterase-5 inhibitors, e.g. sildenafil, vardenafil, etc., become the first-line treatment in PD [24, 25]. These drugs inhibit nitric oxide degradation and facilitate smooth muscle relaxation in the cavernous tissue. When treating PD patients with postural hypotension, these drugs should be prescribed with extreme caution [24, 25].

Conclusions

This article reviewed the current concepts of sexual dysfunction in PD. Central nervous system pathology is clearly associated with sexual dysfunction (decrease in libido and erection) in PD. Phosphodiesterase inhibitors are used to treat erection dysfunction. These treatments are beneficial in maximizing patients' quality of life.

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An Update on Impulse Control Disorders in Parkinson's Disease

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Abstract

The impulse control disorders associated with dopaminergic medication in Parkinson's disease provide a clear and unequivocal demonstration of the biological basis of behavioural addiction. These behaviours can be dramatic, resulting in significant financial and social consequences, with functional impairments, and include pathological gambling, compulsive shopping, hypersexuality, binge eating, punding (complex prolonged, purposeless, and stereotyped behaviour) and compulsive medication use.

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The impulse control disorders (ICDs) associated with dopaminergic medication in Parkinson's disease (PD) provide a clear and unequivocal demonstration of the biological basis of behavioural addiction. These behaviours can be dramatic, resulting in significant financial and social consequences, with functional impairments [1], and include pathological gambling, compulsive shopping, hypersexuality, binge eating, punding (complex prolonged, purposeless, and stereotyped behaviour) and compulsive medication use.

Epidemiology

The recent multicentre cross-sectional DOMINION study surveying 3,090 PD patients demonstrated that the ICDs are common, occurring in 13.6% of patients with behaviours in descending frequency as follows: compulsive shopping (5.7%), problem gambling (5.0%), binge eating disorder (4.3%) and compulsive sexual behaviour (3.5%) [2]. Patients reporting single ICDs were common, with multiple ICDs occurring in >25%. More recently, behaviours such as hoarding [3], kleptomania [4] and impulsive smoking [5] have been reported.

The DOMINION study confirmed a class effect of dopamine agonist (DA) and an association with higher levodopa, but not DA, dose [2]. A follow-up of the DOMINION study also highlighted a potential association between ICDs and amantadine [6], commonly used in the treatment of dyskinesia. However, this remains to be clarified, given the results of the randomised crossover amantadine study, which demonstrated efficacy of amantadine in the treatment of pathological gambling in PD [7].

Untreated PD appears not to be protective or causative, but may still interact with medication, thereby provoking the development of an ICD. Treated PD patients were more likely to have pathological gambling than general hospital controls [8]. Untreated PD patients did not differ in their frequency of ICDs compared with non-PD controls [9]. Furthermore, ICDs have been reported in other neurological disorders requiring dopaminergic medication, including restless legs syndrome [10], progressive supranuclear palsy [11] and multiple sclerosis [12]. Larger and prospective studies are required to determine the exact role of PD and the nature of its relationship with ICDs.

Younger PD patients are consistently demonstrated to be at greater risk, consistent with observations in the general population, but also raising the possibility of specific PD genotypic or phenotypic influences. The association with current or former smoking highlights the overlap with other substances of abuse. An association with a family history of gambling, and that demonstration of gender differences, with males expressing hypersexuality and females compulsive shopping, may speak towards either biological or social influences. Social factors are likely to be at play, given the association with being single, and living in the United States rather than in Canada [2]. The case-control arm of the DOMINION study compared 564 PD patients with and without ICDs and confirmed an association with depression, anxiety and obsessive compulsive symptoms, as previously observed [1]. Novelty seeking and impulsivity, both previously demonstrated to be elevated in PD patients with ICDs, appear differentially associated with behavioural subtype. Pathological gamblers and compulsive shoppers have higher novelty seeking and make more impulsive choices relative to binge eating and hypersexuality, emphasizing pathophysiological differences and the need to study subtype differences in the ICDs [1].

Pathophysiology

There are several pointers towards a specific relevance of dopaminergic medication in ICDs in PD that are outlined in the following section.

On a broader level, converging evidence suggests a mechanistic overlap between levodopa-induced behavioural ICDs and motor dyskinesias. The overlap reflects the engagement of the different behavioural and motor domains of corticostriatal circuitry [reviewed in 13]. ICDs in PD are associated with an oscillatory theta-alpha activity (mean frequency 6.71 Hz) in the ventral subthalamic nucleus, and there is electroencephalographic coherence with non-motor prefrontal regions that is distinct

from that observed with dyskinesias; these are in contrast associated with a higher theta-alpha peak frequency (mean 8.38 Hz), dorsal localisation and coherence with motor regions [14]. Dyskinesias are also more common in patients with punding [15] and multiple ICDs [1]. On another level, the behaviours of ICDs, punding and compulsive medication use, together with dyskinesia, have also been postulated to reflect hyper-dopaminergic activity and apathy, whereas the symptom of depression has been thought to reflect hypo-dopaminergic activity. Patients with ICDs or compulsive medication use (21/63) presumably with hyper-dopaminergic activity had a complete resolution of symptoms with marked decreases in the dose of dopaminergic medication following subthalamic deep brain stimulation surgery. Furthermore, depression (17/63) and apathy (34/63) were very common in the larger group of post-operative patients with markedly low dopaminergic tone, and apathy correlated with mesolimbic dopaminergic denervation [16]. That the DA, pramipexole, is effective for depression in PD [17] is consistent with this concept. This links with the 'overdose' theory, stating that behavioural function has a U-shaped relationship with dopaminergic activity, where optimal function follows a mid-level, eudopaminergic, tone, and impaired function is associated with both low and high tone [18]. Dopaminergic medication targeted at ameliorating the extensively degenerated motor dorsal striatal function in PD may result in an overdose of the relatively preserved ventral corticostriatal function.

The effects of acute versus chronic DA administration and subsequent neuroadaptations are likely also to be of great relevance. In rodents, acute DA challenge decreases dopaminergic firing in a dose-dependent manner, due to D2 autoreceptor stimulation, yet dopaminergic firing normalises with chronic DA administration, likely to be secondary to D2/D3 autoreceptor downregulation [19]. Furthermore, chronic administration of DAs enhances serotonergic firing, probably via 5HT_{1A} autoreceptor downregulation. The effects of the dopamine agonist withdrawal syndrome are also enhanced in PD patients with ICDs [20], emphasising the role of neuronal supersensitivity. The effects of exogenous dopamine may also influence function via tonic stimulation or interference with phasic endogenous signalling.

On this background, we discuss the emerging evidence on reward, incentive, behavioural regulation and risk. PD patients on medication engaged in a gambling type task have greater striatal dopamine release [21]. More specifically, two studies have demonstrated that PD patients with ICDs appear to learn faster from rewards [22, 23], possibly related to enhanced ventral striatal phasic prediction error and reward prediction activity. This may be of relevance to an early acquisition stage and is also relevant to forming learned associations with cues. The evidence for impaired learning from loss outcomes is more equivocal [22, 23]. PD patients with ICDs have greater striatal dopamine release [24] and greater striatal activity [25] to heterogeneous visual reward-related cues as compared with levodopa or neutral cues, supporting an incentive salience process. However, another study did not demonstrate any motivational differences, as measured by reaction time, in a reward incentive task

[26]. These studies provide evidence to support enhanced 'bottom-up' striatal engagement. Some evidence for impaired 'top-down' prefrontal regulation is beginning to emerge. Apomorphine decreases activity in the orbitofrontal and rostral cingulate cortices in PD patients with pathological gambling [27], and patients have decreased functional connectivity between the striatum and anterior cingulate [28].

PD patients with ICDs have greater risk-taking biases [23, 29] relative to PD controls, associated with lower ventral striatal [30], orbitofrontal and anterior cingulate activity [29]. This is consistent with the expression of pathological behaviours, which represent a choice with both positive rewarding, and financially and socially negative, outcomes. DAs have differential effects on the different facets of impulsivity in PD patients with ICDs. DAs increase impulsive choice in PD patients with ICDs [1, 26, 31], shifting the preference towards small, immediate rewards and away from larger, delayed rewards. This effect has been suggested to be related to an impairment in waiting [26], but may also reflect the effect of DA on the subjective valuation of larger rewards [1]. DAs appear to enhance the rapidity of decision making or reflection impulsivity in PD patients with ICDs [31], thus decreasing the evaluation of conflicting or difficult choices. However, there have been no differences reported in the Stroop task [32], which probes inhibition of a verbal pre-potent response and response selection and engages the anterior cingulate cortex.

Recent evidence implicates impairments in working memory, including both visuospatial working memory [31] and memory for digit span [23]. That digit span was impaired both on and off medication suggests a potential overdosing of the dorsolateral corticostriatal circuitry when on medication, and from endogenous dopamine activity when off medication.

Vulnerability towards these disorders may also be associated with genetic polymorphisms. The D3 dopamine receptor p.S9G and GRIN2B c.366C > G was recently identified as a risk factor for ICDs [33]. This is consistent with the role of D3 receptors, expressed predominantly in the ventral striatum, in reward and emotional processes. In primate studies, levodopa administration results in aberrant D3 receptor expression in the dorsal striatum [34]. Similarly, levodopa with concurrent DA administration increases the risk for ICDs [2].

Clinical Issues

Patients and caregivers should be warned about the risk of ICDs at treatment onset and actively questioned on follow-up. Patients with a premorbid history of substance or behavioural addiction may be at a greater risk for the development of these disorders. A 5-min questionnaire, the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease, has been validated for screening of ICDs in PD [35]. Observational follow-up studies suggest that a decrease or discontinuation of the DA, if tolerated, may be helpful for some patients [36]. A recent randomised crossover

trial demonstrated the efficacy of amantadine [7]; however, a contradicting report of increased risk of ICDs associated with amantadine suggests that its role is not yet fully established [6]. The efficacy of subthalamic stimulation in ICD patients, which allows for a decrease in the total dopaminergic dose and the discontinuation of the offending DA, is not yet resolved, given the contradictory published reports. However, the recent demonstration of a complete resolution of ICDs in a prospective study, in which dopaminergic medication was dramatically decreased [16], suggests that retrospective studies showing a post-operative worsening of symptoms [37] may represent inadequate post-operative titration of medication. Notably, ICD patients with PD may be at greater risk of post-operative suicidal behaviour [29]; careful pre-operative selection and post-operative follow-up are indicated.

Conclusion

Recent advances in the understanding of ICDs in PD provide greater insight into the mechanisms underlying this disorder and into basic questions about human behaviour. Such work brings us closer towards developing better preventative and treatment strategies.

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Neuropsychological Features of Early Cognitive Impairment in Parkinson's Disease

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Abstract

Cognitive impairment can be evident even in the earliest stages of Parkinson's disease (PD). Executive dysfunction due to disruption of dopaminergic frontostriatal circuitry is well recognised, but deficits also occur across other domains, including memory and visuospatial function, and these deficits may have a non-dopaminergic basis. There is growing interest in the concept of mild cognitive impairment in PD, which may have important prognostic implications in terms of predicting the development of dementia. Cognitive impairment in early PD is heterogeneous, and hence particular subtypes of mild cognitive impairment might have particular prognostic significance. This chapter will review the prevalence of neuropsychological deficits in early PD, and discuss whether these deficits have any functional impact on the day to day life of PD patients. We will then consider the most appropriate neuropsychological tools to use in early PD given the limitations of current instruments and difficulties in neuropsychological testing in this patient group. Longitudinal data exploring the evolution of early cognitive deficits over time and their relationship with later occurring dementia will then be discussed. Finally, we will review current knowledge about the underlying pathophysiology of cognitive impairment in early PD, which has important implications for better understanding the neurobiological basis of PD-associated dementia.

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Cognitive deficits are detectable with neuropsychological testing from the earliest stages of Parkinson's disease (PD) [1, 2]. They may be reported by the patient or carer, but in some instances are subclinical. There is growing interest in early cognitive impairment in PD, with the recent proposal of a diagnostic term for this aspect of the disease, namely PD-associated mild cognitive impairment (PD-MCI) [3], analogous to the MCI which is thought to be a precursor of Alzheimer's disease [4]. Whilst these impairments may be problematic in their own right with a direct impact on the patient's daily life, they may also have important prognostic value by identifying those patients who are likely to go on to develop dementia.

This chapter will review the frequency of early cognitive impairment in PD, discuss the profile of cognitive domains typically affected, and consider the behavioural consequences of these early cognitive deficits. We will then discuss the most appropriate neuropsychological tools to use in this population, an issue which remains under debate. A small number of longitudinal studies have attempted to explore the relationship between early cognitive deficits and later occurring dementia, and these prognostic data will be discussed. Finally, we will consider the underlying pathophysiology of early cognitive impairment in PD that has implications for understanding how dementia in PD evolves and for the development of future therapeutic strategies.

Epidemiology

A number of studies have investigated the prevalence of cognitive impairment in non-demented PD patients; most estimates are in the region of 20–40% [1–3, 5–7]. Even amongst those with normal Mini-Mental State Exam (MMSE) scores, 29% have detectable cognitive deficits, highlighting the need for detailed neuropsychological testing in early PD [7]. The prevalence of early cognitive impairment depends on a number of factors, including whether the cohort is incident (i.e. only includes newly diagnosed patients) or prevalent (includes all patients with the diagnosis, no matter when diagnosed), hospital or community based, the selection of neuropsychological tests employed, and the criteria used to define cognitive impairment. Large-scale, community-based incident cohorts with comprehensive neuropsychological test batteries would provide the most accurate estimates, but these are lacking.

The number of impaired tests required and the cut-off levels for impairment also have a major impact on estimated prevalence, as demonstrated in a recent study which assessed 20 neuropsychological measures across 4 cognitive domains in 119 non-demented PD patients [8]. This study reported that prevalence figures varied from 14% when using 2 scores in 1 domain at 2 standard deviations below normal, to 89% of patients (and 70% of healthy controls) when using 1 score from 1 domain at 1 standard deviation below normal. The authors suggest that 2 scores below 1.5 standard deviations from the normative mean, either within 1 domain (30% prevalence) or across 2 domains (37% prevalence) are the most suitable criteria to adopt.

The most reliable data on the prevalence of early cognitive impairment in PD come from a recent large multicentre analysis including 1,341 PD patients, which reported a frequency of 25.8% (CI 23.5–28.2) [9]. The authors adopted criteria similar to those proposed above, with 1.5 standard deviations below the normative mean taken as the cut-off for impairment and impairment within 1 domain being sufficient, with test scores averaged within each domain. However, only 3 cognitive domains were specified (attention/executive, memory, visuospatial), not all centres had data on all 3 domains, and in some centres, performance on a domain was determined on the basis of a single neuropsychological test.

Profile of Cognitive Deficits

Neuropsychological deficits in early PD occur across multiple domains including executive function, attention, memory and visuospatial function, but language deficits are less commonly reported.

Of the range of cognitive deficits described in PD, the most commonly described are impairments of executive function, i.e. planning, organizing and regulating goal-directed behaviour. These deficits are similar to those seen in patients with frontal lesions and are thought to represent a dysfunction of dopaminergic frontostriatal circuitry. They are demonstrated on neuropsychological tests sensitive to frontal lobe dysfunction, including planning tests based on the 'Tower of London' task and tests of spatial working memory [10, 11]. Deficits in sustained attention (e.g. in vigilance tasks) are reported only rarely in non-demented PD patients and have been interpreted as reflecting difficulties with executive control [12]. However, PD patients do tend to be impaired from an early stage in attentional set shifting, i.e. in altering behaviour according to changes in the relevance of stimuli [13]. This may reflect a degree of 'cognitive rigidity', i.e. the difficulty in disengaging from one task and engaging in a new task, particularly whilst still being distracted by a previously relevant dimension.

Impairment of explicit memory (a temporolimbic function) in early PD has been widely reported [1, 2, 5, 14]. Performance of PD patients in recall tasks is improved by semantic cueing or probing, unlike in Alzheimer's disease, and PD patients are said to perform relatively better on recognition tests than free recall [15, 16]. These findings have led to the suggestion that the memory deficit in PD lies in retrieval rather than storage of information, possibly reflecting a deficiency in internally cued search strategies due to the dysexecutive syndrome [17]. In support of this hypothesis, it has been reported that memory performance test scores in patients with PD correlate with executive performance scores [16]. However, more recent work demonstrates that executive dysfunction and temporal lobe-based deficits can occur independently in PD [1]. Furthermore, memory impairment in PD seems to be more heterogeneous than originally thought, with some patients exhibiting problems with retrieval memory whilst others have deficits in encoding [18, 19].

Visuospatial and constructional deficits are a well-recognised component of the dementia of PD. They are less commonly reported in early PD but do seem to occur in some patients [2, 5, 14, 20]. Whilst such deficits are widely thought to reflect parietal lobe dysfunction [21], it has been suggested that impaired performance on visuospatial tasks in PD may be related to problems with sequential organization of behaviour [22]; in other words, may be at least partly attributable to frontal executive dysfunction rather than pure parietal pathology.

Language deficits are not commonly reported in PD, although there are isolated reports of deficits in sentence comprehension [23], naming ability [2] and language expression [14]. This apparent rarity of language dysfunction in PD may reflect the fact that this domain is often neglected in neuropsychological batteries.

Verbal fluency deficits, both semantic (category, e.g. animals) and phonemic (lexical, e.g. for letters FAS) are well reported in PD [24]. The appropriate neuropsychological domain within which fluency deficits belong is a matter of debate, as the tasks rely on executive search and retrieval strategies and psychomotor speed as well as semantic memory and language expression. A meta-analysis including 4,644 patients concluded that PD patients are more impaired on semantic fluency than phonemic fluency, and suggested that these deficits are particularly associated with semantic memory [24]. This pattern of verbal fluency dissociation is more akin to the cortical dementias, such as Alzheimer's and semantic dementia [25], rather than the subcortical dementias, such as progressive supranuclear palsy [26] where phonemic fluency deficits predominate.

Whilst some authors have argued that seemingly disparate aspects of cognitive dysfunction in PD including memory impairment, visuospatial dysfunction and impaired verbal fluency are largely explained by the dysexecutive syndrome with a neuropathological substrate in frontostriatal circuits, it seems more likely that cognitive impairment in PD is heterogeneous. A population-based study of newly diagnosed PD patients (CamPaIGN) identified subgroups with differing patterns of cognitive impairment in the very early stages of the disease [1]. 142 patients were classified into 4 distinct groups: no cognitive impairment (n = 92); frontostriatal type impairment (n = 17); temporal lobe type impairment (n = 12) and global impairment (n = 21). Cluster analysis techniques have also been adopted to investigate heterogeneity of cognitive dysfunction in PD, reporting 3 separate subgroups, memory/attention, executive/motor and visuospatial [27]. Furthermore, studies attempting to define MCI in PD report impairment in single domains more commonly than multiple domains [3, 9]. The multiple aetiopathologies underlying the cognitive deficits in early PD will be discussed below.

Neurobehavioural Correlates

It remains unclear how much of an impact early cognitive deficits have on behaviour and day-to-day functioning in typical PD patients. Although a cross-sectional study of 124 non-demented PD patients has reported an independent association between neuropsychological test performance and health-related quality of life in a multivariate analysis, the cohort was not representative of idiopathic PD, with 64% of the patients being young onset (<50 years) [28]. Given that cognitive impairment in early PD is heterogeneous, one might anticipate that different deficits will have differing consequences in terms of their impact on activities of daily living (ADL). A small study of 39 idiopathic PD patients, exploring correlations between cognitive and motor function and ADL, found that executive deficits were associated with impairment in instrumental ADLs, e.g. shopping, preparing meals and handling finances, which require planning and organisation, whereas timed motor tasks were more associated

with physical ADLs, such as eating and dressing. However, their neuropsychological assessments were restricted to the trail making test and the digit ordering test, both assessing executive function [29]. A further study explored capacity to consent in 20 PD patients with cognitive impairment compared with 20 elderly controls [30]. The PD group were significantly impaired across all domains of a standardised competency measure, of which executive dysfunction was identified as the most important neuropsychological predictor.

Testing for Cognitive Deficits

There is no clear consensus about the best cognitive tools to use in early PD. This is likely to contribute to the heterogeneity of impairments reported in this field. Neuropsychological tests can be divided into global screening instruments, including those used across a range of disorders as well as those specific to PD, and tests which are designed to probe particular neuropsychological domains.

Global Screening Assessments

Global screening assessments can be useful to identify whether a patient is performing at a suboptimal cognitive level. They are commonly used in clinical practice, and are not designed for any particular disease. They include the MMSE [31], Addenbrooke's Cognitive Exam-Revised (ACE-R) [32] and the Montreal Cognitive Assessment (MoCA) [33]. These tools assess multiple cognitive domains, with the ACE-R and MoCA providing individual domain scores. However, they have been criticised for their lack of sensitivity to detect deficits commonly reported in early PD and are not ideally suited to pinpoint the specific nature of any impairment. The MMSE, in particular, has never been systematically validated for use in PD, although it has been widely used in both clinical and research settings primarily because the scale is brief, and requires minimal training to administer. However, with a maximum score of 30, the MMSE is prone to floor effects in patients with severe cognitive impairment and ceiling effects for patients with MCI [34]. The MMSE also lacks sensitivity to cognitive dysfunction in PD. In particular, many scale items assess verbal memory and language, areas not thought to be dramatically affected in early PD, at the expense of measures of executive function, which is known to be impaired in a significant proportion of early PD patients. Furthermore, research has shown that a cut-off of ≤ 24 (which is used clinically to indicate dementia) shows a strikingly low sensitivity for the diagnosis of PDD [35].

In recent years, the MMSE has been used less frequently as other cognitive screening instruments have been validated for use in PD. One such scale is the MoCA. While still brief to administer, the MoCA includes more items assessing executive function, and has been shown to be sensitive to global cognitive impairment in both early PD (receiver operating characteristic area under the curve, ROC AUC: 87–91%) and later

in the disease for detecting PD dementia (ROC AUC: 78–90%). Although the specificity of this scale as a diagnostic measure is suboptimal, it far exceeds that of the MMSE [36]. Longer scales such as the ACE-R have used the MMSE as a starting point and expanded on it by incorporating small sections from other cognitive batteries such as Visual Object and Space Perception [37]. As a result, the ACE-R provides a more comprehensive summary of cognitive functioning in five domains: attention/orientation, memory, fluency (executive function), language and visuospatial. Although this test takes much longer to administer (approximately 25 min) than the MMSE, it has been used extensively in clinical practice [38]. The ACE-R has been validated against the Mattis dementia rating scale as a tool for evaluating dementia in a PD population [39]. Importantly, the ACE-R is also able to distinguish the cognitive profile of non-demented PD patients from other neurological conditions [McColgan and Williams-Gray, unpubl. data].

More recently, PD-specific scales have been developed such as the Scale for Outcomes of Parkinson's Disease – cognition (SCOPA-cog) [40] and the Parkinson's Disease-Cognitive Rating Scale (PD-CRS) [41]. The SCOPA-cog was originally designed as a tool for comparing groups of PD patients in a research setting [40], although it is now commonly used as a screening tool for PD dementia. Because the SCOPA-cog was created specifically for use in PD patients, it is weighted heavily for frontostriatal function. It has been successfully validated [40, 42] and shown to demonstrate better discriminative ability than the MMSE [40]; however, this was only true when comparing mild/moderate PD (Hoehn & Yahr = 2) to late PD (Hoehn & Yahr = 4/5), and it was relatively insensitive to the deficits experienced in very early PD [43]. The PD-CRS was designed to capture the full spectrum of cognitive deficits seen in PD and includes tasks which assess 'instrumental-cortical' functions and 'frontal-subcortical' functions. It reliably differentiates between cognitively intact PD patients and those with either PD-MCI or PDD as well as between those with PD-MCI and PDD. A cut-off score of ≤ 64 yields high sensitivity when screening for PDD [41], but no cut-off score has been reported for PD-MCI as yet.

Domain-Specific Neuropsychological Tests

Executive function refers to the mental processes necessary for the realization of goal-directed behaviour; these processes are thought to rely upon the functional integrity of the prefrontal cortex [44]. A wide array of tests have been used to assess executive dysfunction in early PD, including tests of planning such as the Tower of London [45] or Cambridge Neuropsychological Test Automated Battery (CANTAB) Stockings of Cambridge tests [46], tests of set-shifting behaviour such as the Wisconsin Card Sorting Test [47], and several variations of the verbal fluency tasks including tests of phonemic and semantic fluency [48]. Tests of attention measure the brain's ability to filter relevant and irrelevant information in response to given criteria. The concept of 'attention' overlaps strongly with the executive function of 'working memory'. It is difficult to delineate tasks that only measure attention in the absence of working memory. In PD, attention is typically measured through standardised tests such as the

Stroop colour-word test, the digit span test (forward and backward) and the Reitan Trail-Making test (part A and B) [45].

Visuospatial function is typically assessed using figure copying or drawing tests, which are known to be impaired by parietal lobe lesions [21]. The pentagon copying task derived from the MMSE has been reported to have predictive value for later occurring dementia in PD [20]. The clock drawing task has also been widely used in PD; points are attributed for the accuracy of the drawing, in particular the inclusion of all necessary features and the appropriate spacing of the numbers [49]. Clock drawing performance probably relies on a range of neuropsychological functions including executive as well as visuospatial function, although a study of 133 patients with focal brain damage indicated that the strongest neuroanatomical correlates of clock drawing performance were predominantly in the parietal cortex [50].

In terms of assessing memory performance, word list learning tests with delayed recall and recognition conditions, such as Rey's Auditory Verbal Learning Test, the California Verbal Learning Test and the Hopkins Verbal Learning Test [45] are preferable to prose recall tests which can be relatively unreliable. Tests of non-verbal memory in this population are problematic as most visual memory tasks rely on recognition memory which is less sensitive to early memory decline. The Brief Visuospatial Memory Test-Revised [51], however, allows for the assessment of any motor impairment which can then be considered when interpreting the data. Language is reported to be relatively preserved in PD patients with cognitive impairment [52], but confrontation naming tasks such as the Boston Naming test and the Graded Naming Test [53] are useful measures of language ability in early PD.

As with many other movement disorders, evaluating the cognitive profile accurately can be difficult in patients with PD. Cognitive tasks often rely on a degree of manual dexterity (e.g. clock drawing tasks), or need complex and prolonged motor responses (e.g. Rey Osterrieth Complex Figure), so that performance can be confounded by motor impairment in PD. The picture is further complicated by the use and timing of anti-PD medication, especially dopaminergic agents. Patients should therefore be assessed when 'ON'.

Bradykinesia can disadvantage patients in timed tasks which require the patient to maximise performance within a given time frame, such as the Stroop test, or in tests of verbal fluency. Additionally, the subtle delay introduced by motor slowing to immediate recall tasks such as the initial stages of the Hopkins Verbal Learning Test and the Digit Span test can add an additional memory load that affects performance. In tests with reaction time, detailed measurement is needed to ensure that bradykinesia is not misinterpreted as cognitive slowing. Computerised test batteries, such as the CANTAB, try to address this by measuring components of reaction time, allowing the researcher to differentiate between motor (movement time) and cognitive (movement initiation time) slowing. The graded nature of most tasks in the battery reduces the probability of floor and ceiling effects. CANTAB has been widely used to evaluate executive function in early PD, with multiple studies reporting problems with planning, measured

by the Stockings of Cambridge [10] and One-Touch Stockings [54], and attentional set shifting, measured by the Intra-/Extradimensional Shift task [55].

Finally, depression and apathy, which are commonly reported in early PD, are both associated with increased cognitive impairment, particularly in the domain of executive function [56, 57]. These neuropsychiatric symptoms should ideally be screened by using appropriate tools, and caution should be exercised when interpreting the data from neuropsychological assessment in patients who exhibit these features.

At present, there is little consistency in the tests used to identify cognitive impairment in early PD. The choice is vast, and the research supporting the sensitivity and specificity of tests in this population is limited. Ultimately, cognitive batteries are designed based upon convention, preference and availability rather than scientific grounding. A more coherent approach to cognitive testing in PD is necessary and may help to reduce some of the heterogeneity currently reported.

Prognosis

MCI in PD is a risk factor for later dementia [58]. However, studies evaluating the prognosis of global MCI are likely to be too simplistic to yield meaningful results. There is considerable evidence that early cognitive impairment in PD is heterogeneous [1, 2, 9], and hence it is important to establish whether domain-specific impairments have particular prognostic value for dementia. Given the relatively recent emergence of the concept of MCI in PD, there is still a lack of longitudinal data exploring the relationship between MCI subtypes and dementia, although one small study has reported that amongst 59 patients followed up over 4 years, single-domain non-amnesic MCI and multiple-domain MCI were associated with later development of dementia, whereas amnesic MCI was not [58].

A number of previous longitudinal studies have investigated the relationship between performance in individual neuropsychological tests and later dementia with varied and inconsistent results: executive deficits [59–61], impaired verbal fluency [60, 62], visuospatial deficits [60] and memory and language dysfunction [61, 63] have all been suggested as useful prognostic markers. These findings are limited by the selection of neuropsychological tests employed, as well as by the nature of the cohorts studied: these cohorts included patients of widely varying disease duration, most collected from hospital settings not representative of the general population.

The CamPaIGN study has investigated how cognitive function evolves over time in a newly diagnosed PD cohort. The authors attempted to recruit all patients within Cambridgeshire, UK, over a 2-year period using multiple sources in hospitals and the community [1]. The resulting cohort of 122 patients underwent detailed neuropsychological testing and has been followed up longitudinally, with data at 3.5 and 5.2 years from diagnosis being published so far [20, 64]. Analyses at both time points have shown that two neuropsychological tests performed at baseline, namely

semantic fluency (<20 words in 90 s) and pentagon copying, are significant predictors of dementia, independent of age and other potential confounding factors. Suboptimal scores in these neuropsychological predictors plus age greater than 71 years resulted in an odds ratio of 8/11 versus 1/34 patients (OR: 88; 95% CI 8–962) for the development of dementia at 5.2 years. There was a dissociation between semantic and phonemic fluency, with the latter having no association with later occurring dementia. This implicates the more temporal lobe-based semantic memory system as the critical predictor, rather than frontally based search and retrieval strategies which are common to both fluency tasks. Hence, the best neuropsychological predictors of dementia in this study were ‘posterior cortical’, whilst there was no apparent association between ‘frontostriatal’ executive deficits and later occurring dementia. In fact, there was no clear deterioration in executive function over time. This work suggests that there may be at least two distinct cognitive syndromes in early PD which evolve differently: frontostriatal executive deficits which are common but do not necessarily worsen over time, and more posterior cortical deficits which herald decline to dementia (fig. 1). These cognitive syndromes appear to differ not only in terms of prognosis, but also in terms of their underlying pathophysiology, as discussed in the next section.

Other studies have provided additional support for the hypothesis that there is dissociation between early frontostriatal executive and posterior cortical cognitive syndromes [41, 65]. For example, a large meta-analysis of 25 longitudinal studies involving 901 PD patients has explored differences in the progression of impairment in multiple cognitive domains. Over a mean follow-up period of 29 months, significant cognitive decline occurred in global cognitive ability, and in the domains of visuospatial function and memory, but not in executive function [65].

A potential concern with all longitudinal studies to date is that they have used DSM-IV criteria to diagnose dementia, which are biased towards more posteriorly based cognitive deficits, in that memory impairment is an absolute requirement for the diagnosis in addition to impairment in one other cognitive domain. It could therefore be argued that the identification of posterior cortically based deficits as neuropsychological predictors of cognitive decline and dementia is simply a reflection of this diagnostic bias towards more posterior deficits. PD-specific dementia criteria have recently been proposed [52], which require impairment in any 2 cognitive domains (attention, executive, visuospatial, memory): they are likely to be adopted in future studies and will circumvent this argument. Diagnostic criteria for MCI in PD are also currently under development and should be helpful to ensure that future longitudinal studies adopt more consistent methods for examining and categorising early cognitive impairment in PD.

Pathophysiology

The majority of postmortem studies report that Lewy body deposition in limbic and cortical areas is the best correlate of dementia in PD [e.g. 66, 67], although Alzheimer’s

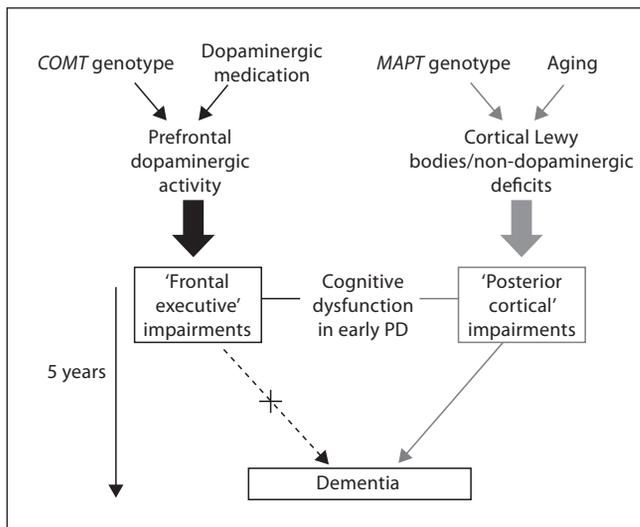


Fig. 1. Schematic representation of hypothesised aetiological pathways leading to cognitive dysfunction in early PD and their relationship to the development of dementia 5 years later. The findings of the CamPaIGN study suggest that 'frontal executive' impairments in early PD are a consequence of a hyperdopaminergic state in the prefrontal cortex which is in turn modulated by *COMT* genotype and dopaminergic medication. These deficits were not associated with subsequent global cognitive decline and dementia over 5 years of follow-up. In contrast, it is proposed that early deficits on more posteriorly based cognitive tasks do not have a dopaminergic basis, but reflect Lewy body deposition in posterior cortical areas, which is in turn influenced by *MAPT* genotype and the ageing process. Reproduced with permission from Williams-Gray et al. [20].

type neurofibrillary tangles and amyloid- β plaques also appear to contribute [66]. Postmortem studies examining MCI in PD are very limited for obvious reasons; one report has specifically examined the relationship between pathological findings at post-mortem and subtypes of MCI [68]. The authors studied 8 cases with parkinsonism: all went through a stage of MCI, 7 developed dementia prior to death, 6 had neocortical-predominant Lewy body disease and 2 had limbic-predominant Lewy body disease, with only 1 case having co-existing Alzheimer's disease. They found no clear relationship between Lewy body pathology and subtype of MCI. The obvious disadvantage of such studies is that they cannot prospectively examine the evolution of cognitive deficits in the early stages of PD. Hence, alternative methods including genotype-phenotype correlation studies, structural and functional brain imaging, and pharmacological manipulation of neurochemical systems must be relied upon.

A number of candidate genes have been considered as potential factors influencing cognitive decline in PD. APOE, whose $\epsilon 4$ allele is strongly associated with Alzheimer's disease, has been well studied in this respect, but a recent large meta-analysis including 4,198 PD cases and 10,066 controls did not support a clear association between APOE- $\epsilon 4$ and dementia, and longitudinal analysis of a subset of cases

revealed no association between this allele and rate of cognitive decline [69]. The α -synuclein gene is another obvious candidate, and studies of kindreds with autosomal dominant forms of PD carrying α -synuclein gene missense mutations or triplications reveal that these abnormalities in α -synuclein genotype are associated with early onset PD with dementia [70–73], but there has been no convincing evidence of a relationship between genetic variation in α -synuclein and early or late cognitive dysfunction in idiopathic PD. One gene which has proved more interesting however is the micro-tubule-associated protein tau (MAPT) gene. A common inversion polymorphism of chromosome 17 containing the MAPT gene (H1 versus H2 haplotype) is known to have a small effect on susceptibility to PD (OR 1.4, $p = 2 \times 10^{-19}$), but the CamPaIGN study has suggested that MAPT H1 variant has a much more profound effect on longitudinal cognitive decline in PD (fig. 2) [74]. The odds of developing dementia are reported to be 12 times greater in those carrying the H1/H1 genotype after correction for age [20], thus implicating the MAPT H1 variant as by far the most important genetic factor contributing to cognitive heterogeneity in PD reported to date. Furthermore, there is evidence that this variant has a functional impact, increasing transcription of 4-repeat tau in PD-affected brains [20]. These data implicate protein aggregation in the dementing process of PD, particularly when interpreted in the light of recent studies suggesting a synergistic interaction between α -synuclein and tau in Lewy body formation (fig. 1) [75, 76].

Earlier in this chapter, we have discussed evidence suggesting that executive deficits in early PD evolve differently to posterior cortically based deficits, implying a different aetiological basis, and this is supported by a number of neuroimaging studies. A structural MRI study has demonstrated that executive and more posterior type impairments in early PD do differ in terms of their anatomical basis, with impairment on tasks of sustained attention correlating with prefrontal atrophy, whereas verbal memory impairment correlates with hippocampal atrophy [77]. Indeed, it is well established that executive deficits are related to dysfunction within frontostriatal dopaminergic systems: functional neuroimaging studies have demonstrated reduced blood oxygen level-dependent activation in dorsolateral and ventrolateral prefrontal cortices, caudate nuclei and right putamen during performance of a working memory task in executively impaired PD patients compared with those with no cognitive impairment [78], and PET studies have demonstrated that reductions in striatal ^{18}F -fluorodopa uptake correlate with impaired executive performance [79, 80]. However, if dopaminergic deficits do underlie the executive syndrome in PD, one might expect an improvement in executive function with levodopa. In fact, levodopa withdrawal studies report seemingly contradictory results, with dopaminergic medication improving performance on certain frontally based cognitive tasks, but leading to impairment on others [81]. This may in part be explained by the concept of an inverted U-shaped relationship between executive performance and dopaminergic activity in the prefrontal cortex, with not only low but also high prefrontal synaptic dopamine levels causing impaired performance [82] (fig. 3). Such a relationship is

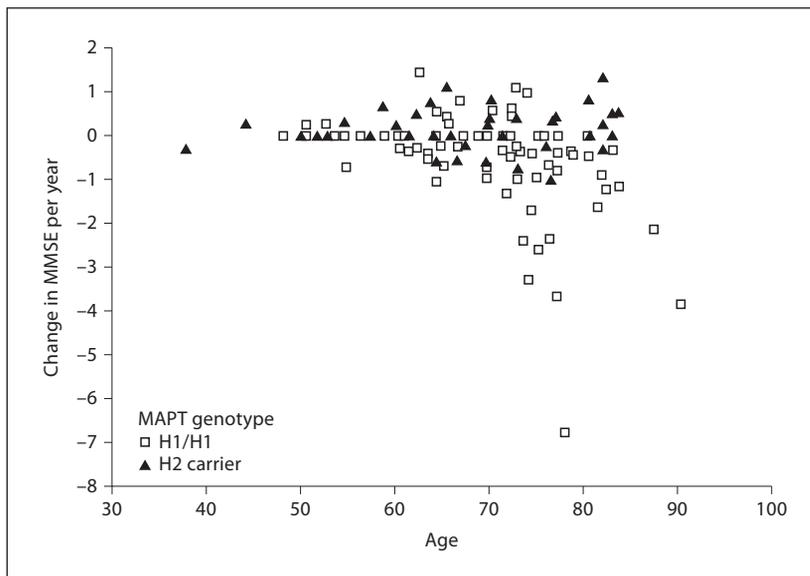


Fig. 2. Correlation between age and cognitive decline (change in MMSE per year) over 3.5 years depending on MAPT genotype amongst 108 incident PD patients. There is a strong correlation in H1 homozygotes, with a clear tendency to cognitive decline over the age of 70 years (Kendall's $\tau_b = -0.35$, $p = 2 \times 10^{-5}$), whereas cognitive performance remains unchanged in H2 carriers, regardless of age ($\tau_b = 0.11$, $p = 0.36$). Reproduced from Goris et al. [74].

consistent with experimental work involving D1 receptor-mediated modulation of dopaminergic transmission in animals [83–85] and is supported by behavioural and functional imaging studies in humans with genetically determined differences in prefrontal dopamine [86].

Evidence to support the importance of the inverted U relationship in the dysexecutive syndrome of PD comes from studies investigating a common functional polymorphism (val¹⁵⁸met) in the catechol o-methyltransferase gene. This polymorphism alters the activity of the dopamine-regulating COMT enzyme by 40% in human cortex [87], and has a particular influence on dopamine levels in the prefrontal cortex where the expression of dopamine transporters is low relative to the striatum [88]. The low activity met/met genotype, putatively associated with higher prefrontal dopamine levels, is associated with improved performance on working memory and planning tasks in healthy controls [89], but in contrast the met/met variant is associated with impaired performance on the Tower of London planning task in early PD, and this effect is greatest in those exposed to dopaminergic medications [54]. Furthermore, functional imaging studies in early PD have demonstrated that the low activity met allele is associated not only with impaired behavioural performance on working memory and attentional set shifting tasks, but also with underactivation of a frontoparietal executive network [90, 91]. When combined with evidence from

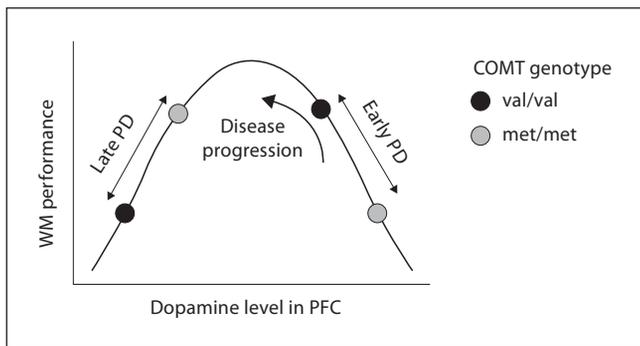


Fig. 3. Hypothesised inverted U-shaped relationship between working memory (WM) performance and dopaminergic activity in the prefrontal cortex (PFC). Evidence from behavioural and functional imaging studies in PD patients suggests that position on the curve is determined by both disease state and *COMT* val¹⁵⁸met genotype. Early PD patients are postulated to be on the downslope of the curve with Val homozygotes (high-activity COMT) being closer to the peak than Met homozygotes (low-activity COMT). As disease progresses, however, patients are expected to shift to the left. Reproduced with permission from Williams-Gray et al. [20].

¹⁸F-dopa-PET studies suggesting a hyperdopaminergic state in the PFC in early PD [92–94], this work suggests that early PD patients are on the right-hand side of the inverted U-shaped curve, where higher prefrontal dopamine levels have a detrimental effect on executive performance (fig. 3). Hence, it seems that in early PD, executive deficits may relate to an upregulation of dopaminergic activity in the prefrontal cortex relative to the striatum, and are influenced by *COMT* genotype as well as exogenous dopaminergic medication. In later disease, dopamine levels in the PFC fall [95], and one would expect patients to shift from the right to the left hand side of the inverted U-shaped curve. Indeed, cross-sectional comparisons do indicate an alteration in the direction of the relationship between *COMT* genotype and executive performance in later versus early PD, and longitudinal analysis of 70 PD patients from the CamPaiGN cohort indicates that *COMT* met/met individuals show an improvement in executive performance over 5 years of disease progression in contrast to other genotypic groups, as predicted by the inverted U-shaped curve [20]. There may thus be a dynamic relationship between dopaminergic activity in frontostriatal networks and executive performance in PD which is dependent on disease duration, *COMT* genotype and medication.

Whilst less well explored, other neurotransmitter systems are also likely to be involved in cognitive dysfunction in early PD. As yet, there is little good evidence to support a role for noradrenergic and serotonergic deficits, although they have been implicated in mood and attention [17]. Cholinergic deficits do seem to be an important contributor to cognitive dysfunction in PD. Not only has cell loss in the nucleus basalis of Meynert been demonstrated in PD [96, 97], but associated cortical cholinergic deficits have been found, and a correlation between these pathological

findings and level of cognitive impairment has been reported in several studies [e.g. 98–100]. A double-blind pharmacological study has demonstrated that low-dose scopolamine, an anticholinergic, causes memory impairment in PD patients but not in healthy controls, suggesting a pre-existing subclinical cholinergic deficit in PD [101]. Functional PET studies have also confirmed a cortical cholinergic deficit in PD compared to controls, which is most pronounced in PD dementia cases [102, 103]. This has led to the use of cholinesterase inhibitors as therapeutic agents for PD dementia, although with only very modest effects [104]. Thus, although it seems very likely that cholinergic deficits are involved in the dementing process in PD and are likely to be implicated in posterior cortical deficits in early disease, there is a lack of evidence for direct correlation between cholinergic deficits and impairment in particular neuropsychological domains.

Conclusions

Early cognitive impairment probably affects around a quarter to a third of PD patients, with estimates varying according to the nature of the cohort studied and the neuropsychological criteria adopted. Agreement is yet to be reached on the most appropriate method of diagnosing ‘mild cognitive impairment’ in PD, but establishing a clear definition is important to allow selection of patients for therapeutic trials, as well as to facilitate comparison between future studies. Neuropsychological deficits in early PD include executive dysfunction, deficits in attentional shifting, poor verbal fluency, impaired explicit memory and visuospatial dysfunction. Some older cognitive screening instruments such as the MMSE are insensitive to executive deficits, and thus not well placed to assess cognition in early PD, but PD-specific screening tools have been recently developed to circumvent this problem.

Longitudinal data suggest that different types of cognitive impairment in early PD evolve in different ways. Specifically, we propose that frontostriatally based executive deficits, which are dependent on prefrontal dopaminergic activity, fluctuate and in some cases improve over time, whereas more posterior cortically based deficits herald global cognitive decline and later-occurring dementia. Genetic variation in tau, cortical Lewy body deposition, and cholinergic deficits, have been implicated in this posterior cognitive syndrome.

The direct impact of early cognitive deficits in PD on day-to-day behaviour and function is yet to be established. The focus of research to date has been on their prognostic value in terms of predicting later-occurring dementia. Interest in the concept of MCI in PD is growing, but given the heterogeneity of early cognitive deficits in PD in terms of their pathophysiology and evolution over time, subtyping of PD-MCI is essential in future longitudinal studies.

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Parkinson's Disease with Dementia

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Abstract

Parkinson's disease with dementia (PDD) is now recognised as a major clinical consequence of idiopathic Parkinson's disease (PD). Indeed the cumulative prevalence of dementia in PD is very high; up to 80% of patients will develop dementia within 10 years of their Parkinson's diagnosis. The consequences of PDD, including the associated neuropsychiatric, autonomic and sleep symptoms, are profound. With increased survival in PD accurate diagnosis and appropriate management of PDD in neurological, movement disorder and psychiatric services is increasingly important. In this chapter we explore the epidemiology of PDD, risk factors for its development as well as clinical features, diagnostic issues, prognosis and management. We conclude with a synthesis of current theoretical considerations and research into the aetiology of PDD.

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An Essay on the Shaking Palsy by James Parkinson is remarkable in its inclusive and thorough description of the motor symptoms of Parkinson's disease (PD) [1]. However he stated that it was a condition which left the 'senses and intellects' 'uninjured', and this belief was perpetuated for a significant part of the 20th century.

However perhaps consequent to the development of dopaminergic treatment and increased survival of PD patients, it has now become increasingly recognised that cognitive and neuropsychiatric dysfunction is an integral part of PD. Indeed there is now evidence to indicate that the majority of people with PD will develop so-called Parkinson's disease with dementia (PDD) within 10 years of diagnosis [2]. Furthermore with the spotlight of modern enquiry, including genetic, neuroimaging and detailed neuropsychological studies, subtle deficits have been observed even in the earliest stages of PD (see chapter 10 for further elaboration).

There is now also a convergence of opinion [3] that PDD shares a common aetiological basis with a closely related condition, dementia with Lewy bodies (DLB) but that they represent different points along a Lewy body disease spectrum. DLB was defined on the basis of people presenting primarily with dementia, who had

varying degrees of parkinsonism (often falling short of full PD) and who had alpha-synuclein (Lewy body) pathology at autopsy. Traditionally DLB and PDD have been separated on clinical grounds, though clinical, imaging, cognitive, therapeutic and pathological studies suggest considerable overlap between DLB and PDD. Indeed both PDD and DLB are now often collectively referred as the Lewy body dementias (LBDs). In this chapter, we focus on PDD, although we draw upon evidence and data from studies in DLB as appropriate. We explore the epidemiology of diagnostic classification and neuropsychiatric features of PDD as well as briefly cover management of this complex condition. We conclude with a discussion on the proposed aetiology including neuropathological findings and recent genetic determinations. Interest in PDD has burgeoned over the past decade [4], and there is now a significant literature on the condition. This chapter thus provides more of a taster for the reader rather than an exhaustive text; for example, we do not discuss recent innovative developments in LBD biomarkers, as this is beyond the scope of this chapter, but would refer the reader to reviews such as Burn [5] and Johansen et al. [6] on the subject. For an in-depth exploration of all aspects concerning PDD, we would suggest Emre [7], which provides a comprehensive clinical and research overview of PDD. A similarly structured text edited by O'Brien et al. [8] provides a detailed description of DLB.

Epidemiology of Parkinson's Disease with Dementia

Prevalence and incidence rates of PDD have varied depending upon the methodologies applied in particular surveys, imprecision in definitions of dementia and cognitive impairment, as well as pathological heterogeneity in the patient populations studied. Nevertheless a comprehensive recent systematic review [9] of the available literature found a mean point prevalence of 31.3% (29.2–33.6 95% confidence interval) of dementia in PD patients, with community prevalence of PDD in the over 65s between 0.3 and 0.5%.

As discussed in chapter 10, it is becoming increasingly recognised that cognitive impairment is present even in the earliest stages of PD; for example, it was shown that between 19 and 24% of newly diagnosed PD patients had a mild degree of cognitive impairment [10, 11]. These deficits appear to progress over time, and it has been suggested that the mean duration from onset of PD to the development of PDD is around 10 years. A longitudinal study based in Norway suggested that the cumulative prevalence was up to 78% after 8 years of follow-up [2]. Consistent with this are the incidence rates of PDD from longitudinal community-based cohorts which are at least four to six times that of the rate of dementia in age-matched controls with approximately 10% of PD patients developing dementia annually [9, 12].

A variety of risk factors for the development of dementia in PD have been described, and these are summarised in table 1.

Table 1. Risk factors for PDD

Risk factor	Comments
Age	This is a major risk factor for PDD; it may play a major role in aetio-pathology of PDD by interacting with disease processes in non-dopaminergic structures [13].
Parkinsonism	The severity of motor manifestations, in particular, the symptoms of rigidity, and the so-called postural instability gait disorder (PIGD), appear particularly important [14–17].
Gender	PD incidence is twice as common in men as women, but it is not clear if male gender predisposes PD patients to the development of PDD.
Pre-existing mild cognitive impairment	Individuals with mild cognitive impairment at diagnosis of PD are at greater risk of subsequent development of dementia, although those with amnesic mild cognitive impairment do not. See chapter 10 for further elaboration.
Neuropsychiatric symptoms	Neuropsychiatric symptoms in general [18–20] are associated with cognitive impairment in PD. Specific associations with cognitive impairment and dementia include depression and visual hallucinations; the former may be a prodrome of PDD [21] while the latter associated with a much higher rate of cognitive decline and greater risk of dementia in PD. Common underlying aetio-pathologies may contribute to both the neuropsychiatric symptom and cognitive dysfunction; for example, there is an association between cortical Lewy body disease in the temporal lobe with visual hallucinations and dementia [22].
Genetics	Family history of PD does appear to increase the risk of dementia in PD [23]. The presence of apolipoprotein E4 genotype, unlike AD, does not appear to increase the risk for PDD development [24–27]. However MAPT gene with H1/H1 haplotype may be a risk factor. Gene-dose effect with triplication of the associated alpha-synuclein gene has been suggested to give rise to familial variants of PDD, whereas duplication is associated with motor PD alone [28]. Recent autopsy studies have demonstrated that 4–10% of PD patients have evidence for glucocerebrosidase (GBA) mutations. GBA deficiency arising as a result of an autosomal recessive mutation is more typically thought of as the cause of Gaucher's disease. However it has recently been suggested that GBA mutations represent the most common genetic risk factor for the development of PD or LBDs [29] in Lewy body dementias although this finding needs confirmation.
Smoking	Whether smoking is protective or risk factor for the development of PDD is not clear as longitudinal findings have been contradictory [24, 30].

Diagnostic Classification of Parkinson's Disease with Dementia

Consensus operational criteria for PDD [31] have recently been developed (see tables 2 and 3), which take account of the constellation of signs and symptoms that are prototypical to PDD. The criteria make two major diagnostic separations: probable PDD

Table 2. Features of dementia associated with PD

I. Core features
1. Diagnosis of PD according to Queen Square Brain Bank criteria
2. Dementia syndrome with insidious onset and slow progression developing within the context of established PD disease and diagnosed by history, clinical, mental examination, defined as: <ul style="list-style-type: none">• Impairment in more than one cognitive domain.• Representing a decline from premorbid level• Deficits severe enough to impair daily life (social, occupational, or personal care), independent of the impairment ascribable to motor or autonomic symptoms.
II. Associated clinical features
1. Cognitive features <ul style="list-style-type: none">• Attention: Impaired. Impairment in spontaneous and focused attention, poor performance in attentional tasks; performance may fluctuate during the day and from day to day.• Executive functions: Impaired. Impairment in tasks requiring initiation, planning, concept formation, rule finding, set shifting or set maintenance; impaired mental speed (bradyphrenia).• Visuospatial functions: Impaired. Impairment in tasks requiring visual-spatial orientation, perception, or construction.• Memory: Impaired. Impairment in free recall of recent events or in tasks requiring learning new material, memory usually improves with cueing, recognition is usually better than free recall.• Language: Core functions largely preserved. Word finding difficulties and impaired comprehension of complex sentences may be present.
2. Behavioural features <ul style="list-style-type: none">• Apathy: decreased spontaneity; loss of motivation, interest, and effortful behaviour• Changes in personality and mood including depressive features and anxiety• Hallucinations: mostly visual, usually complex, formed visions of people, animals or objects• Delusions: usually paranoid, such as infidelity, or phantom boarder (unwelcome guests living in the home) delusions• Excessive daytime sleepiness
III. Features which do not exclude PDD, but make the diagnosis uncertain
<ul style="list-style-type: none">• Co-existence of any other abnormality which may by itself cause cognitive impairment, but judged not to be the cause of dementia, e.g. presence of relevant vascular disease in imaging• Time interval between the development of motor and cognitive symptoms not know.
IV. Features suggesting other conditions or diseases as cause of mental impairment, which, when present make it impossible to reliably diagnose PDD
<ul style="list-style-type: none">• Cognitive and behavioural symptoms appearing solely in the context of other conditions such as:<ul style="list-style-type: none">• Acute confusion due to<ul style="list-style-type: none">(a) Systemic diseases or abnormalities(b) Drug intoxicification

Table 2. Continued

Major depression according to DSM-IV

- Features compatible with 'probable vascular dementia' criteria according to NINDS-AIREN (dementia in the context of cerebrovascular disease as indicated by focal signs in neurological exam such as hemiparesis, sensory deficits, and evidence of relevant cerebrovascular disease by brain imaging AND a relationship between the two as indicated by the presence of one or more of the following: onset of dementia within 3 months after a recognised stroke, abrupt deterioration in cognitive functions, and fluctuating, stepwise progression of cognitive deficits).
-

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Table 3. Criteria for the diagnosis of probable and possible PDD

Probable PDD

- A. Core features: Both must be present
 - B. Associated clinical features:
 - Typical profile of cognitive deficits including impairment in at least two of the four core cognitive domains (impaired attention which may fluctuate, impaired executive functions, impairment in visuospatial functions, and impaired free recall memory which usually improves with cueing)
 - The presence of at least one behavioural symptom (apathy, depressed or anxious mood, hallucinations, delusions, excessive daytime sleepiness) supports the diagnosis of probable PDD, lack of behavioural symptoms, however, does not exclude the diagnosis.
 - C. None of the group III features present
 - D. None of the group IV features present
-

Possible PDD

- A. Core features: Both must be present
- B. Associated clinical features:
 - Atypical profile of cognitive impairment in one or more domains, such as prominent or receptive-type (fluent) aphasia, or pure storage-failure type amnesia (memory does not improve with cueing or in recognition tasks) with preserved attention
 - Behavioural symptoms may or may not be present

OR

- C. One or more of the group III features present
 - D. None of the group IV features present
-

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and possible PDD. For a diagnosis of either, the presence of core symptoms of (1) diagnosis of parkinsonism, (2) a dementia with an insidious onset and slow progression in the context of established PD, and (3) the absence of features which could suggest other conditions as the cause of mental impairment is required (e.g. evidence for vascular disease on imaging). A diagnosis of probable PDD depends upon the presence

of the core symptoms, as well as a cognitive profile typical for PDD (e.g. dysexecutive, visuospatial dysfunction), and at least one behavioural symptom (e.g. visual hallucinations). Less diagnostic certainty is contained by the diagnosis of possible PDD; this still requires presence of the core features, but the associated cognitive impairment may be, for example, atypical, or the behavioural symptoms may not be present.

Such criteria offer significant advantages in providing a framework for both diagnosis and subsequent management. In addition such criteria enhance scientific enquiry regarding the natural history of PDD, its epidemiology, and help elucidate understanding of the relationship between clinical features and pathology, as well as allow rigorous clinical trials to be conducted. Nevertheless it is important to recognise that these criteria are not fixed, and as new insights are gleaned into the pathophysiology of PDD with the development of effective biomarkers, it is likely that the criteria will continue to evolve.

Parkinson's Disease with Dementia versus Dementia with Lewy Bodies

One continuing area of controversy is the diagnostic separation of PDD from DLB on the basis of the onset of the motor relative to the cognitive symptoms. Both the consensus criteria for DLB [32] and PDD [31] recommend that for a diagnosis of PDD, the extrapyramidal motor features need to be present for at least 12 months before the onset of the dementia, but if the dementia precedes the motor symptoms or occurred within 12 months of the motor features then the diagnosis should be DLB. This one year rule has been applied in the research setting but the arbitrary separation of PDD and DLB on this basis has no strong clinical or pathological basis. While differences do exist between DLB and PDD (table 4), they share similar cognitive and motor profiles and have common neuropsychiatric features. In addition, both PDD and DLB patients respond similarly to treatments such as cholinesterase inhibitors [33] and are both exquisitely sensitive to antipsychotics. Thus unitary approaches and use of terms such as Lewy body dementias (LBDs) which include PDD and DLB have proven useful for researching common neurobiological and genetic processes in these conditions.

Clinical Features

PDD has a recognisable mode of onset, disease progression and displays a distinctive constellation of clinical features; parkinsonism is the initial complaint with the subsequent development over many years of an insidiously progressive cognitive impairment and the manifestation of neuropsychiatric symptoms such as visual hallucinations. Other deleterious non-motor features include sleep behaviour disturbances and autonomic dysfunction. A significant proportion of these symptoms are evident in PD without dementia and elaboration of their occurrence, features,

Table 4. Summary of differences between DLB and PDD

Differences	DLB	PDD
Dementia onset relative to parkinsonism	earlier	later
Executive dysfunction	+++	++
Cognitive fluctuations	+++	++
Psychotic symptoms	+++	++
Levodopa responsiveness	+	++
Parkinsonism	≈25–50% – less tremor	100%
Pathology		
Cortical amyloid load	++	+
Nigral cell loss	+	+++
Alpha-synuclein deposition in striatum	+++	+

management and underlying aetiopathologies are detailed in other chapters within this book. In the present chapter, we will briefly examine their role and association with PDD.

Parkinsonism

The predominant motor phenotype associated with PDD is that of postural instability and gait disturbance (PIGD) [34]. Tremor-dominant patterns, which are often evident earlier in the course of PD, tend to evolve into the PIGD pattern over time [30], and this change often concords with the onset of cognitive difficulties [35], autonomic dysfunction [36] and sleep disorders [37, 38]. With the development of dementia in PD there is an associated rapid deterioration in motor function with increased risk of falls [39]. Reduced responsiveness to levodopa in PDD may reflect the contribution of ‘non-dopaminergic’ lesions, that is, neuropathological changes outside of the dopaminergic-striatal system. Common pathophysiological processes to both the dementia and axial motor symptoms have been proffered and in part may be mediated by dysfunction of the cholinergic system [34].

Cognitive Impairment

Compared to Alzheimer’s disease (AD), those with PDD have disproportionate impairments in attention and executive function [40]. These deficits [41, 42] appear to be most closely associated with the occurrence of visual hallucinations, and attentional dysfunction is the most relevant cognitive predictor for the ability to perform activities of daily living [43].

Regarding memory function, patients with PDD, while impaired compared with similarly aged controls [40] tend to perform better on verbal memory tests than AD patients. In non-demented PD patients it has been suggested that a ‘retrieval deficit’ exists, i.e. free recall is impaired, but cued recall or recognition of material presented

is relatively preserved. While memory deficits are less marked in PDD than AD or DLB, PDD patients do have clear recognition memory deficits [44].

Visuoperceptive and visuospatial skills are also severely affected in PDD [40, 45]; this deficit may be partially attributed to attentional and executive dysfunction. Nevertheless intrinsic pathological changes in the visual system are likely to be important, and there is an inherent linkage between visuoperceptual/visuospatial dysfunction and visual hallucinations in PDD, with patients who experience visual hallucinations performing significantly worse on visual tasks compared with non-hallucinators [45].

Language dysfunction in PDD is less well studied, although patients tend to have reduced verbal fluency and dysarthric speech, with the former being attributed to executive problems and the latter to motor impairment [46].

Perhaps one of the most obvious features of the cognitive dysfunction of PDD, affecting up to 85% of patients [47], is the marked tendency for cognitive function to fluctuate. Fluctuations in cognition can occur in other dementias such as AD and vascular dementia. However in PDD, similar to DLB, they appear qualitatively distinct, where there appears to be an interruption of awareness which is often associated with transient episodes of confusion, communicative difficulties and psychotic symptoms, such as visual hallucinations with delusions [48]. Remission to near-normal cognitive function can then occur. The temporal cycles of these fluctuations can vary in duration in terms of minutes, hours or days, and these fluctuations appear to be independent of clear environmental triggers suggesting that the fluctuations in PDD and DLB are internally driven. Although the precise neurobiological locus is unknown, both cholinergic transmitter changes and thalamocortical circuit dysfunction have been implicated [49, 50].

Neuropsychiatric Symptoms

Visual hallucinations and their basis in PD are discussed in chapter 5. Phenomenologically, there are no differences in visual hallucinations between PD patients with and without dementia, although in the former their occurrence appears much more frequent affecting up to 65% of PDD patients [31], and insight is more likely to be lacking, although patients often have better insight into the unreality of the episode when it is over.

Earlier in the course of disease feelings of presence (i.e. that someone or something is nearby although not actually seen) and passage hallucinations (i.e. a feeling of a shadow of a person or animal passing) are common. However as the hallucinations progress, they tend to become complex and formed, typically of people (often children), animals and body parts that are static, kinetic or indeed the patient is completely immersed in a hallucinatory milieu. The hallucinations can provoke a range of emotional responses from indifference to amusement through to outright fear. In PD visual hallucinations were often initially viewed as a side effect of dopamine replacement therapy [51], with dopaminergic agonists especially implicated.

Auditory hallucinations also occur, but less frequently than visual hallucinations, in about 20% of patients with PDD. Delusional thinking occurs in a minority 20–25% [31]; this contrasts with patients with DLB where delusions are much more common. Delusions are often based around experienced hallucinations and visuoperceptual disturbances, and their content typically includes persecutory, spouse infidelity, and ‘phantom boarder’ themes.

Depression also appears to be a common neuropsychiatric symptom, although epidemiological estimates of prevalence have varied considerably (7% up to 76%) [52], with diagnosis obfuscated by concurrent apathy, bradykinesia, reduced arousal levels, dopaminergic medication side effects and cognitive fluctuations.

Sleep Disturbances

Two major sleep disorders are recognised in PDD: rapid eye movement sleep behaviour disorder and excessive daytime sleepiness; the clinical features and aetiology of these symptoms are described elsewhere (chapter 7).

Autonomic Dysfunction

In both PD and PDD, autonomic dysfunction affects both sympathetic and parasympathetic systems, and the effects are widespread and diverse. Symptoms can include cardiovascular instability leading to orthostatic hypotension and carotid sinus hypersensitivity, and these combined with poor attentional function are likely to contribute to the high frequency of syncope and falls that occur in this population. Other symptoms include urinary retention, constipation and faecal incontinence, erectile dysfunction, and reduced lacrimal, salivary and sweat secretions. These symptoms can significantly affect quality of life and activities of daily living [53].

Aetiologically, alpha-synuclein pathology in PDD is widespread within the autonomic system. This, and the associated acetylcholine deficiency, which impairs effective preganglionic and parasympathetic synaptic neurotransmission, has been speculated as possible cause of the autonomic dysfunction [54]. However clinicians should be aware that other factors may contribute and enhance the autonomic dysfunction including comorbid illnesses, increasing frailty and medication effects (for example, cholinesterase inhibitors and antipsychotics).

Antipsychotic Sensitivity

In DLB severe antipsychotic sensitivity reactions can occur where patients display acute or subacute changes in response to antipsychotic administration with a sudden worsening of parkinsonism, marked rigidity, confusion and alteration in arousal levels. These reactions can occur even when low doses are used and are so profound that they can prove fatal within days or weeks [55].

Similar reactions have been reported in PDD; in one study by Aarsland and colleagues [56] 39% of PDD patients demonstrated antipsychotic sensitivity, and thus

the same caution that is applied to the administration of antipsychotics in DLB should also be applied to PDD.

These effects are thought to be mediated via acute D2 blockade and can occur with both typical and atypical neuroleptic agents. Quetiapine with its low extrapyramidal side effect profile is probably the safest, although an isolated case report for a neuroleptic sensitivity reaction in a DLB patient has been reported [57]. Starting with a very low dose and careful frequent monitoring is probably more important than which specific agent is used.

Beyond this all atypical antipsychotics now include boxed warnings from drug regulatory authorities for increased mortality in older patients with dementia-related psychosis. Additionally, both risperidone and olanzapine have warnings about increased risk of cerebrovascular disease [58, 59]. Overall, while these studies have focussed primarily on AD, it is not unreasonable that clinicians should exercise a high level of caution when prescribing these agents to PDD patients.

Onset, Course, Prognosis and Impact of PDD

The onset of PDD is often unclear, and frequently there is a delay in making the diagnosis of PDD. In some settings routine testing of cognition is not performed, so there may be a lack of awareness or interest in cognitive sequelae, or an unwillingness to label a PD patient as having a 'dementia'. Development of diagnostic criteria for PDD and the recognised longer survival times of PD patients with the associated increased prevalence of PDD will ameliorate these issues of mind set. A diagnostic delineation of PDD from PD is now supported by a simple five point guideline from the movement task force [60]:

- 1 A clear diagnosis of PD according to Queen's Square Brain Bank criteria
- 2 PD develops before the onset of dementia
- 3 There is a global decline in cognitive function (Mini-Mental State score <26)
- 4 Cognitive deficit is sufficient to impair daily life
- 5 Impairment occurs in more than one cognitive domain (e.g. attention, executive, visuoconstructive or memory)

Some thought should be given to the use of appropriate cognitive assessment tools; the Mini-Mental State Examination (MMSE) is often insensitive to the profile of cognitive deficits in PDD. Newer screening tools such as the Montreal Cognitive Assessment may be better [61].

The course of PDD is progressive with no evidence of reversibility. The annual decline in cognitive and motor function scores of PDD patients is about 10% [14], and survival duration from symptom onset (either parkinsonism or dementia) to death has been estimated to be between 5 and 8 years depending upon the population studied [62, 63]; certainly the development of dementia above and beyond the core diagnosis of PD is associated with a twofold increased mortality risk [13]. Plateaus

in deterioration can occur, although on other occasions there can be a precipitous decline in functioning. This is sometimes related to co-morbid insults such as infection, but often the cause for the sudden worsening cannot be established and may be intrinsic to the disease process itself. Predictors of a more rapidly progressing course include PIGD motor phenotype, moderate to severe daytime somnolence, greater neuropsychiatric symptom severity (hallucinations and depressive symptoms), older age, cognitive and attentional fluctuations and the presence of comorbid Alzheimer pathology [14, 64–67].

Associated neuropsychiatric symptoms, such as visual hallucinations, predict subsequent nursing home placement [68]. Quality of life in PDD is also likely to be poor; in a study in DLB patients [69] it was noted that they had lower quality of life scores and used more resources than AD patients with almost a quarter of patients having scores which defined them as being in a state ‘worse than death’; undoubtedly analogies may be drawn to the quality of life of PDD, particularly given the more severe motor impairments which are evident in this condition.

Management of Parkinson’s Disease with Dementia

The management of PDD is complex, given the many symptoms that occur and the problems surrounding early diagnosis. However, recognition and diagnosis of dementia in PD is important because it provides explanation and understanding for patients and carers, allows for future planning, influences management and has major medico-legal implications (advanced care planning, driving, etc.) and can allow access to services, social benefits and financial support.

Non-Pharmacological Treatments

Evidence for the efficacy of specific non-pharmacological interventions in PDD is currently lacking. Visual hallucinations and decreased arousal may be exacerbated by eye disease or environmental issues. Therefore, there it is reasonable cause to assume that cataract removal and better lighting will be helpful. Exercise may help: one recent small study suggested it improved executive function in PD [70].

Pharmacological Management

Some rationalisation of medication may need to occur, for example, reductions in dopaminergic medications early on in the presentation (in the following order: amantadine, direct dopamine agonists, COMT inhibitors and lastly L-dopa). This may avert later antipsychotic use, at least in the short-term [71]. Stopping anticholinergic agents is also an important consideration given the marked cholinergic deficit in PDD. When treatments are added, clinicians need to be aware that some may produce benefits in one domain (e.g. dopaminergic improvements in motor function) but exacerbate symptoms in another (e.g. dopaminergic worsening of psychosis).

Cholinesterase inhibitors have been widely applied in PDD, and their use to treat cognitive impairment is recommended by a number of expert authorities (for example, American Academy of Neurology Practice [72]), and rivastigmine has been licensed by a number of regulatory bodies for treatment of cognitive impairment in PDD. However the evidence base for their efficacy remains relatively limited: a small number of open label studies have shown that galantamine may be beneficial in PDD, but there is only one major RCT using rivastigmine in PDD (EXPRESS study [73]), which demonstrated improved cognition after 24 weeks of treatment, as well as a significant reduction in neuropsychiatric symptoms (including visual hallucinations) and improved activities of daily living.

Overall, cholinesterase inhibitors are tolerated reasonably well in people with PDD, although theoretically there is a potential antagonism with dopamine function in the striatum and some patients report an increase in tremor. In addition, some cardiac safety concerns have been raised; a community study [74] noted that older patients with dementia who are on cholinesterase inhibitors tended to have more hospital visits for bradycardia, were more likely to have a permanent pacemaker inserted, and more likely to have a hip fracture. Nevertheless while these risks were significant, the absolute numbers of these events was relatively small.

Memantine is an N- methyl-D-aspartate (NMDA) receptor antagonist and is purported to have neuroprotective qualities. Two major studies examined the benefits of memantine in PDD and DLB [75, 76]. However, results were not consistent, with Aarsland et al. [75] finding an improvement in global clinical impression scores in PDD (perhaps more than DLB) participants on memantine compared with placebo, whereas Emre et al. [76] noted improvement in global rating scores and neuropsychiatric symptoms in DLB but not PDD.

Antipsychotics have been used to manage psychotic symptoms in PDD, although their use is not without controversy, and the evidence base for their use has mainly been derived from trials which included PD patients with psychosis but no dementia. Olanzapine, risperidone and aripiprazole are associated with exacerbation of motor symptoms and therefore best avoided. Clozapine or quetiapine have been advocated as preferred agents [77]. However clozapine has notable side effects (e.g. agranulocytosis) and needs regular blood monitoring. The efficacy of quetiapine is equivocal; quetiapine does not overtly worsen parkinsonism, but it appears not to have any demonstrable benefits with regard to agitation or psychosis in DLB or PDD patients [78].

Other treatments for cognitive impairment and dementia in PD have been examined, although currently the evidence for the majority is relatively weak (table 5), and there is still a lack of specific disease-modifying treatments.

Aetiology of Parkinson's Disease with Dementia

The causes for cognitive and neuropsychiatric symptoms in PDD are complex, heterogeneous and unclear. However a number of pathological, neurotransmitter, metabolic

Table 5. Examples of alternative pharmacological treatments in PDD

Agent	Treatment use	Comment
Dopaminergic agents	Motor dysfunction Cognitive impairment?	The benefits of dopaminergic agents in treating motor symptoms in PD are beyond question. However whether dopaminergic medications help or hinder cognitive function in PDD is controversial, and this uncertainty is reflected in the lack of understanding how dopamine function is perturbed in PDD. One open label study has suggested L-dopa or pergolide treatment in newly diagnosed PD may help improve cognition for a period [79].
Atomoxetine	Cognitive impairment?	A noradrenaline reuptake inhibitor with some evidence that it may help improve executive function in PD without dementia [80].
Safinamide	Cognitive impairment? Neuroprotective?	An agent with glutamatergic and dopaminergic effects and potentially neuroprotective qualities [81].
Amantadine	Neuroprotective?	An NMDA receptor antagonist which has been associated with reducing cognitive decline and delaying the onset of dementia in PD [82], and glutamate receptors have been suggested as potential targets for the development of novel pharmacological therapies for PD [83].

and perfusion scan correlates have been associated with the occurrence of dementia in PD. We present some of these findings, as well as emerging new evidence, below.

Lewy Body-Related Neuropathology

The predominant feature of pathological disturbance in PDD (and indeed in DLB) is the occurrence of cortical Lewy bodies (LB), which are hyaline cytoplasmic inclusion bodies made up of predominantly aggregated α -synuclein bound together with ubiquitin, heat shock proteins and neurofilaments. These cortical LB lack the classical halo, are smaller and are less morphologically distinct compared with the more classical LB that are found in the substantia nigra associated with the motor manifestations of PD. Other neuropathological features have been described, including dystrophic cellular projections called Lewy neurites which are also alpha-synuclein predominant.

LB load in limbic structures has been reported to be correlated with the severity of dementia [84], and their presence in medial temporal lobe and visual areas has been associated with visual hallucinations [22, 85]. While the association of generalised cortical LB pathology and cognitive impairment in PDD has been reported by some, this is however not a consistent finding [86].

Staging of LB pathology and relationship with the clinical phenotype are also not clear. On the basis of sequential autopsy samples of PD brains, Braak et al. [87] proposed that there was a distinct rostrocaudal pathological progression in PD, where LB initially appeared in glossopharyngeal, vagus and olfactory nuclei and then ascended progressively along the neuroaxis. This pattern corresponds to the development of initial parkinsonism followed by cognitive and neuropsychiatric symptoms which emerge as a consequence of LB cortical involvement. However, this pattern of progression has not been observed consistently [88], and the relationship between the different stages with the development of parkinsonism, cognitive impairment or neuropsychiatric symptoms is lacking [89]. While these data may suggest that cortical LB do not cause the dementia, they are likely to be a marker of the condition. More relevant may be alpha-synuclein aggregates which are not specifically localised to LB. These aggregates are great in number and appear more widely distributed in the brains of patients with PDD and DLB than LB. Their presence in pre-synaptic terminals may impair synaptic function and lead to subsequent neurodegeneration [90].

The presence of co-existent AD pathology in PDD has been confirmed both in postmortem and more recently using amyloid imaging techniques [91]. However, the presence of AD pathology only weakly correlates with the occurrence of dementia in PD, in contrast to LB pathology [92]. Interestingly, as a result of the observation that beta-amyloid in the neocortex is associated with more extensive alpha-synuclein related lesions and higher levels of alpha-synuclein, it has been speculated that there may be a synergistic interaction between LB and AD pathology [93].

Another potential contributor to pathology is vascular disease; limited evidence from imaging of white matter, both structural and diffusion tensor imaging has suggested that white matter hyperintensities are more common in PD patients with poor cognition [94] and white matter integrity is perturbed in the frontal cortex of PD patients [95]. However, not all studies [96] found a relationship in PDD between white matter hyperintensities and cognition. Thus it remains uncertain how vascular disease and its associated lesions interact with the neurodegenerative process in PDD and contribute to the cognitive impairment.

Neurotransmitter System Dysfunction

LB pathology has an established deleterious effects on a wide range of neurotransmitter systems including dopaminergic (nigrostriatal), cholinergic (nucleus basalis of Meynert), noradrenaline (locus coeruleus), and serotonin (raphe nucleus) systems.

Dopaminergic system dysfunction is likely to be greater in PDD than in PD, reflecting a continued attrition of nigrostriatal neurons. Evidence for this comes from the observation of more severe parkinsonism in PDD compared with PD and also from striatal neuroimaging, for example ^{123}I -N-3-fluoropropyl-2-beta-carbomethoxy-3-beta(4-iodophenyl)-notropane (FP-CIT), a dopamine transporter (DAT) single

photon emission tomography (SPECT) ligand, has demonstrated DAT binding at 50% of that compared with PD and DLB [97].

This dopaminergic loss is also likely to have a significant role in the cognitive changes of PDD. A progressive reduction in FP-CIT binding has been associated with cognitive decline in PDD [98] and changes in striatal [18F] fluorodopa uptake, a marker for dopamine synthesis, on Positron emission tomography (PET) has been correlated with impaired cognitive performance [99]. As discussed in the chapter by Williams-Gray and Mason, part of this, particularly the executive dysfunction may be mediated via differences in Catechol-*O*-methyltransferase (COMT) genotype, medication and/or disease stage. In addition to dopamine loss, there are alterations in dopamine receptor densities. Post-synaptic dopamine D2 receptor upregulation in the striatum is a feature of early PD; with disease progression there may be subsequent downregulation [100]. Reduced D2 density, particularly in the temporal lobes has been correlated with cognitive impairment [101], whereas increased thalamic D2 binding appears to be associated with disturbances in consciousness and arousal [102].

Dysfunction in the cholinergic system may be crucial to cognitive impairment in PDD as evidenced by the ability of cholinesterase inhibitors to improve cognitive and neuropsychiatric symptoms in PDD [5]. Other lines of evidence also support this hypothesis: In PDD, there is an extensive, global reduction in choline acetyltransferase, the enzyme responsible for acetylcholine synthesis. Reductions in this enzyme in the temporal lobe are associated with the severity of cognitive impairment [103]. On functional imaging, acetylcholinesterase activity is depressed in PDD compared with PD [104], and the level correlates with severity of executive dysfunction. Conversely, the use of cholinesterase inhibitors in PDD has been associated with increased regional cerebral metabolism [105].

Cholinergic receptor (nicotinic and muscarinic) disturbances have also been reported in PDD [for overview, see Piggott et al. 106], and this relates to the loss of acetylcholine. Their specific role in mental impairment in PDD still remains to be elucidated, although it has been suggested that receptor alteration may modulate arousal and alertness (nicotinic receptors in thalamus and temporal cortex) and visual hallucinations (nicotinic and muscarinic receptors in occipital cortex).

The role of other neurotransmitter systems is less well understood. Serotonergic neuron loss in the raphe nuclei is an early feature of PD and has been speculated to be associated with the frequent depressive symptoms evident in the disease. However whether there is greater loss of serotonin in PDD than PD is not clear [106]. Neuronal loss in the locus coeruleus (noradrenaline) may be more extensive in PDD than PD and correlate with cognitive decline. This has been suggested to contribute to depressive and behavioural symptoms as well as apathy and attentional dysfunction [106].

More work is needed to clarify the aetiological place of alterations in neurotransmitter systems in PDD; it may in fact be the balance between different systems which is important in dementia [107]. For example, patients with LBD and visual

hallucinations show a pattern of decreased cholinergic function, but a relative preservation of monoaminergic function [108].

Metabolic and Perfusion Impairments

Reductions in brain glucose metabolism, as measured using ^{18}F -fluorodeoxyglucose (FDG) PET imaging, and in perfusion measured with SPECT, have been found in PD patients with both cognitive impairment and with dementia. Deficits appear global and widespread, affecting parietal, frontal and occipital cortices [109, 110].

Principal component analyses with FDG PET to identify areas of the brain which co-vary in function, have found salient metabolic networks that are disrupted in PDD [111]. One of these covariance networks, the so-called 'PD-related cognitive pattern' which includes prefrontal, midline frontal, precuneus and inferior parietal regions is associated with cognitive impairment in PD, and reduced activity in this network is longitudinally associated with declining cognitive function. Perfusion and metabolism deficits in distributed brain areas including frontal [112], parietal [113] and temporal cortex [114] have also been associated with visual hallucinations, although there is a lack of consensus on precisely which brain areas are involved.

Emerging New Evidence

New lines of enquiry regarding the molecular basis of PD have been opened up (see for example the discussion by Olanow and McNaught [115]) and by extension are likely to be highly relevant to understanding the pathological basis of PDD.

In particular, there is an increasing recognition that in PD there is an inherent dysfunction of cellular protein clearing processes such as the autophagy and lysosomal clearance system and ubiquitin-proteasome system, which results in the accumulation of toxic intracellular proteins that undermine neuronal function and ultimately lead to neuronal cell death. It has been suggested that compensatory cellular strategies to deal with toxic protein accumulations result in so-called aggresomes of which LB are one type; thus, LB may represent a protective stress response rather than being pathogenic in themselves [116]. Intriguingly, known genetic mutations in PD such as PARKIN, PARK1, LRRK2 [115], as well as glucocerebrosidase mutations [117] have been associated with dysfunction in cellular protein degradation, providing further support for the importance of these cellular systems in the aetiology of PD. Mitochondrial dysfunction may be another important and possibly related player. A number of gene mutations which cause familial PD such as PARKIN and PINK1 appear to have a role in the maintenance of normal mitochondrial function. It has been speculated that, in part, PD may be caused by impaired energy production [for discussion, see 86].

Finally and controversially PD has been suggested to be a prion-like disease. Support for this comes from the observation of Lewy pathology in foetal neurons grafted into the brains of PD patients, suggesting a spread of alpha-synuclein from

the host brain tissue to the grafts [118]. At the molecular level, alpha-synuclein can be transmitted via endocytosis to neighbouring neurons and neuronal precursor cells, forming Lewy-like inclusions [119].

Conclusions

There is increasing recognition of the inevitability of dementia developing in PD. Thus, there is a pressing need to be able to diagnose the condition better and to explain mechanistically how the condition arises at a micro- and macro-structural level. Treatments are available, which partially ameliorate some of the symptoms in PDD, but further work is needed to develop disease-modifying agents. However, the first and essential step has been taken in that we now know the 'shaking palsy' to be not just a motor disorder but something much more.

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Somatoform Disorders in Parkinson's Disease and Dementia with Lewy Bodies Evidence Underlying Psychotic Traits

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Abstract

Somatoform disorders have only recently been described in Parkinson's disease (PD) and dementia with Lewy bodies (DLB). Of 1,210 patients with neurodegenerative diseases referred to our institutions from 1999, 488 were diagnosed with PD, 415 with Alzheimer's disease, 162 with DLB, 48 with progressive supranuclear palsy, 48 with multiple system atrophy, and 49 with frontotemporal dementia. Rates of somatoform disorder were considerably higher in DLB (18%) and PD (7.5%) than in any other group (0–2%). Somatoform disorders in PD and DLB were characterized by motor and non-motor patterns with bizarre presentations, and were often accompanied by catatonic signs (41%). In 77%, they preceded PD motor signs by 6–120 months, and in 86%, they were recurrent at follow-up. In 91%, there was preceding or concomitant hypochondriasis. Global cognitive decline was greater in PD with somatoform disorder than without ($p < 0.001$), comparable to that observed in the DLB group. The phenomenology suggests a blurred boundary between somatoform disorder and psychosis (somatic delusions). The presence of somatoform disorder may identify a subgroup of PD patients with distinctive clinical symptoms, including catatonic features and a poor cognitive outcome.

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Depression, apathy, and impulse control disorder with its variants, including L-dopa dysregulation syndrome, have a defined status among psychiatric complications of Parkinson's disease (PD), and are discussed in detail in earlier chapters [1]. New evidence suggests that the spectrum of psychiatric symptoms in PD and related diseases may include yet inadequately described disorders.

A recent survey in 20,140 patients hospitalized in Sweden for PD found that prior hospitalization for schizophrenia, mood disorders, neuroticism and depression increased the risk for the development of subsequent PD. Even taking into account the possible effect of neuroleptic exposure, the study suggests that the relation of mental disorders with parkinsonism is more complex than commonly believed [2]. Psychosis in PD is studied far less often than depression, apathy or impulse control disorder. In many studies, psychosis is used as a synonym for hallucinations, with the latter being considered a core element of dementia with Lewy bodies (DLB) and, less consistently, PD with dementia [3].

In recent years, we have focused our attention on the broad spectrum of somatoform disorders in PD and DLB patients, ranging from the DSM IV-TR somatoform disorder category [4] with its variants to related disorders characterized by bizarre and delusional somatic complaints.

Several observations have attracted our interest in somatoform disorder in PD and DLB: (1) somatoform disorder might precede the onset of neurodegenerative disorders [5, 6]. (2) Conversion type somatoform disorders are described anecdotally in patients who develop PD [5, 7–9]. (3) Alexithymia (inability to distinguish feelings from sensation of emotional arousal) is increased in PD [10]. (4) Babinski's definition of hysteria (= somatoform disorder) was that it consists of an 'illness that could be induced by suggestion and abolished by persuasion' [11]. Suggestibility is also a feature in PD, as shown by the magnitude of the placebo effect, which may induce a reduction in motor symptom severity up to 30% [12], confounding pharmacological studies. (5) Historically, a variety of motor or non-motor features different from the well-known postural, gait and motor symptoms have been reported in untreated PD patients. These features consist of abnormal bizarre gymnastic postures, 'poses gymniques', or of somatic complaints or unclassified gait abnormalities, which were categorized as overlapping with hysteria or catatonia. Some of these features were attributed to patients affected by parkinsonism due to encephalitis lethargica, but in others encephalitis was excluded as a cause [13].

A Prospective Cohort Study in Somatoform Disorder in Lewy Body Disease

In order to clarify the relevance of somatoform disorder in parkinsonism, we designed a prospective cohort study comparing patients with somatoform disorder preceding or concomitant with the onset of motor PD symptoms with randomly selected PD patients without somatoform disorder. Similarly, we compared DLB patients with somatoform disorder with those without somatoform disorder. These groups were followed up clinically and with different laboratory assessments for at least 4 years in order to understand whether the presence of somatoform disorder affected motor and cognitive outcomes, and we report some of the findings [14] here and give updates of our more recent cohort data.

Prior to our study, somatoform disorder had been described as a prodromal symptom of Alzheimer's disease in two studies performed in a resident population of nuns [6, 14]. Elderly subjects who presented with somatoform disorder (described as hysteria in these papers) in the course of their life, were shown to be more prone than others to develop dementia with advancing age.

At the time of the publication of our study [15], a review described somatoform disorders among the non-motor psychiatric manifestations of parkinsonism and PD [16], and a study based on a neuropsychiatry scale reported a 40% prevalence of somatizations in PD [17].

Definition: Somatoform Disorder

The definition of somatoform disorder in DSM-IV-TR [4] relates to a general category including seven, partly disparate disorders: (1) somatization disorder, (2) somatic body dysmorphic disorder, (3) delusional disorder somatic type, (4) undifferentiated somatoform disorder, (5) conversion disorder, (6) pain disorder, and (7) hypochondriasis. Each has a different frequency in the general population, varying from 0.2–2% for somatization or conversion disorder to 3–13% for hypochondriasis. Despite this heterogeneity, the core entity defined by DSM-IV-TR somatoform disorder is a somatoform complaint that is incongruent with rules of anatomy and physiology in the absence of any specific evidence of organic illness in medical and laboratory assessments.

Prevalence of Somatoform Disorder in Patients with Neurodegenerative Disorders

In the 10 years from 1999, 1,572 new patients were evaluated in our Movement Disorder and Memory Clinic. Over at least 2 years of follow-up, 943 patients were classified under neurodegenerative disorders. Four hundred and eighty-eight were diagnosed with PD (or genetic parkinsonism), 415 with Alzheimer's disease, 162 with DLB, 48 with progressive supranuclear palsy, 48 with multiple systems atrophy, and 49 with frontotemporal dementia. Seventy-four patients received a diagnosis of concomitant somatoform disorder. Among them, 9 patients were affected by psychogenic movement disorders or catatonia, 7 patients were affected by Alzheimer's disease, and one had progressive supranuclear palsy.

A significant proportion of patients with somatoform disorder were affected by Lewy body disease; 29 PD patients had somatoform disorder at the time of PD diagnosis, and in 7 somatoform disorder symptoms had been observed in the 6 preceding years. Definite somatoform disorder was also found in 29 DLB patients, and in the majority (93%) of these hospital notes gave a history of incongruent somatoform complaints. All were reported by caregivers and general practitioners to have had

hypochondriasis. Somatoform disorder had preceded DLB by 12 years in one patient, and by 6–2 years in the other 14 patients, with the remainder having somatoform disorder in parallel with their diagnosis of DLB.

Follow-Up of Patients with Lewy Body Disease and Somatoform Disorder

In our 9-year longitudinal study, MMSE and ‘frontal’ battery test scores decreased significantly in PD patients with somatoform disorder, compared with patients without somatoform disorder. However, the progression of decline was similar in all DLB patients regardless of whether they had somatoform disorder or not. At the end of the 9-year follow-up period, all patients with PD-somatoform disorder, DLB-somatoform disorder and DLB without somatoform disorder were institutionalized, whereas none of the PD patients without somatoform disorder required institutional care.

Clinical Phenomenology and Overlap of Psychotic Symptoms

We identified three characteristic features in PD-somatoform disorder patients:

First, a temporal pattern of occurrence or recurrences of somatoform disorder was observed in all patients, with somatoform disorder episodes appearing in clusters lasting from 2 weeks to 3 months; only in 2 patients did the disorder last longer than a year. These episodes had characteristics of DSM-IV-TR somatization disorder, or of conversion disorder, or of intense somatic type delusional disorder often with bizarre or Cotard type contents, indicating the need for further classification, and of catatonia.

Second, in 73% of patients there was denial of the diagnosis of parkinsonism and occurrence of marked side effects with initial dopaminergic drug exposure. Adverse responses included intolerable gastric pain, nausea, burping and retching despite concomitant treatment with H₂ antagonists, ondansetron or granisetron, domperidone, globus pharyngeus after ingesting pills, but not food or liquids, confusion, sensation of empty headedness, dizziness with normal orthostatic blood pressure, hypersomnolence or insomnia.

Third, a clear history of hypochondria occurred in 92% of subjects. The essential feature was preoccupation and centrality of concerns about disease, doctor shopping, frustration and anger in the doctor-patient relationship, which was consistently reported by relatives and general practitioners in 91% patients and corroborated by hospital records documenting several admissions for minor disorders in 82% patients.

Somatoform disorder symptoms could be motor or non-motor. Yet in all patients apart from examples of simple motor and non-motor patterns, including hemiparesis, paraparesis, anesthesia, hypoesthesia, with classic conversion signs including

distractibility and Hoover sign (consisting of absent pressure on contralateral talon when attempting to lift, lying in bed, the pseudo-paretic lower limb), the outstanding symptoms often presented with bizarre patterns.

Conclusions

We identified symptoms of somatoform disorder in a clinically significant proportion of PD patients (7.5% in the updated cohort data) and in an even higher percentage of DLB patients (19%).

Symptoms observed in our patients included those described under the different subgroupings of DSM-IV-TR: typical of conversion disorders (like bent knee and tiptoeing, posturing, hemiparesis or paraparesis, psychogenic movement disorders), of somatization disorders (like unexplained and multi-localized pain, anesthesia, hypesthesia), and bizarre somatoform delusions (bizarre delusions of progressive deformation of body parts). These were observed concomitantly with the onset of PD motor signs or during PD progression, and were recurrent during the course of PD. During recurrences, somatoform symptoms appeared with different patterns. Hypochondria, listed by DSM-IV-TR among somatoform disorders, was also a consistent presentation in the medical history of the majority of patients (91%), leading to hospitalization years before motor PD symptoms had appeared. When PD was diagnosed, denial and resistance to the PD diagnosis was consistently observed in patients with hypochondriasis. While counterintuitive, this feature may be construed taking into account psychodynamic hypotheses of manipulative anger [18].

In 41% of PD and DLB patients with somatoform disorder, catatonic symptoms were observed including negativism, immobility, abnormal posturing, waxy flexibility and stereotypies. This frequency suggests that catatonia should be sought specifically in addition to the more global search for the wider variety of somatoform disorder symptoms.

Neurobiological hypotheses suggest that somatoform disorder and catatonia in general are different grades of expression of a same pathological entity, resulting from the dysfunction of frontal lobes-basal ganglia-thalamus interactions [19]. Our study confirms that somatoform disorder and catatonia can appear as a continuum, at least in the group of patients affected by PD or DLB.

Somatoform disorder can appear in parkinsonism with catatonia and somatic delusions, Cotard or Ganser syndrome, which are properly classified as psychotic symptoms. We suggest that the boundary between somatoform disorder and psychosis is blurred in PD and DLB patients. The blurring and overlap between somatoform and psychotic disorders further underlines the need to improve categorization and understanding of types of psychotic symptoms in PD and DLB. The consensus criteria for DLB include delusions among the supportive elements needed for the diagnosis. Our

previous report [15] suggests that somatic delusions play a dominant role in these diseases and should be sought for in order to support the diagnosis.

The second conclusion briefly presented here is that presence of somatoform disorder is a prognostic predictor for the development of dementia of the DLB type in patients with PD. The progression of PD motor symptoms was similar in PD patients with somatoform disorder without somatization, while the progression of cognitive test scores was different. Somatoform disorder predicted a decline in executive function, and a faster progression to subcortical-frontal dementia. Once a patient with somatoform disorder developed objective PD signs, the progression to dementia or institutionalization could be reliably predicted. Somatoform disorder may precede the occurrence of clinical and imaging evidence of PD by years, but once PD signs have developed the pattern of progression is more similar to DLB than the progression observed in PD without somatoform disorder.

It could be argued that the need for institutionalization could be due to repeat requests for medical care, one of the presenting features of somatoform disorder. However, in our survey recurrences of somatoform disorder diminished as dementia scores increased; thus, it is more likely that the need for institutionalization was due to the presence of psychosis and dementia.

For comparison, our studies included several groups of patients recruited in the same setting and affected by Alzheimer's disease, frontotemporal dementia and progressive supranuclear palsy. The comparison with these patients showed that somatoform disorder, or the evidence of prior hospitalization for somatoform disorder, was significantly lower in patients with these diseases than in PD or DLB patients.

We could not confirm the results of a previous cohort study showing that somatoform disorder predicted the occurrence of dementia of the Alzheimer type [6, 14]. However, when data for the prior study were collected, recognition of DLB or dementia associated with synucleinopathy was infrequent, and it might be argued that categorization of dementias into Alzheimer's disease was, at the time, excessive.

The low frequency of somatoform disorder in patients with frontotemporal dementia and progressive supranuclear palsy was surprising, as frontotemporal dementia and progressive supranuclear palsy are undoubtedly examples of frontal lobe dementia. This finding suggests that further investigations may be needed on the anatomical pattern of frontal lobe dysfunction and pathway disruption in these three disorders. Neuropsychological tests showed that, at onset, progressive supranuclear palsy and frontotemporal dementia patients had worse scores than PD patients presenting with somatoform disorder. We hypothesize that, in order to express somatization disorder, the frontal lobe should be dysfunctional but partly preserved, while a severe loss of frontal lobe function may abolish the ability of somatization. This hypothesis is consistent with observations that patients who presented with somatization disorders did so before or concomitantly with PD onset or in the following 2 or 3 years, while this clinical pattern disappeared due to dementia in the long-term follow-up.

A recent neuroimaging study showed that focal hypoactivity in precuneus and supramarginal gyri, when concomitant with hyperactivation of orbitofrontal areas, is linked with the expression of unconscious somatizations [20]. This recent discovery relocates the focus of imaging studies on somatoform disorder and forecasts innovative approaches to these disorders. Parietal areas, including precuneus and supramarginal gyrus, are in fact considered essential in providing integration of internal and extra-personal (visual or sensory polymodal) space. In DLB and PD with dementia patients, imaging studies show specific hypoactivity of parieto-occipital areas [20]. Therefore, the recent study [21] supports the hypothesis suggesting that somatoform disorder should be present and frequent in these diseases.

The prevalence of somatoform disorder matches the prevalence of impulse control disorder (8% in PD) as reported in the literature [4].

In summary, we suggest that somatoform disorder manifestations identify an important subgroup of PD patients with distinctive clinical features and clinical course in terms of cognitive decline. Further studies of PD-somatoform disorder patients may be useful to link non-motor elements of psychiatric behaviors and cognition in PD with the neural networks that could explain their relationship.

Somatoform disorder is not frequent enough to be considered as a PD pre-motor sign (as REM sleep behavior disorder, loss of olfaction, constipation), but its linkage with PD-dementia suggests that it may be a useful tool to study PD-dementia, and that somatoform disorder might be considered as a potential non-motor precursor of PD-dementia and might be added to the supportive features of DLB for consensus-based diagnoses.

Finally, our study indicates the need for further independent epidemiological assessments to confirm the frequencies, as regional service and cultural factors will modify the expression of somatoform disorders in PD and DLB populations.

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Drug-Induced Parkinsonism and Abnormal Involuntary Movements

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Abstract

Motor side effects emerging from the use of neuroleptics have been recognised since their first use in the 1950s. There is however an increasing awareness that other drug classes (in particular other psychotropic drugs and calcium channel blockers) are also implicated in the genesis of parkinsonism and other abnormal involuntary movements. Second-generation antipsychotics have a reduced propensity to lead to these side effects but may still cause problems in high-risk groups like people with dementia. Treatments for the various movement problems (parkinsonism, dyskinesia and dystonias) vary dependent upon the symptoms that predominate, given the differential balance between dopaminergic and cholinergic dysfunction between these three side effect clusters. Though stopping or switching the offending drug is always the first option, newer drugs for the treatment of Alzheimer's disease whose effects are upon cholinergic transmission are showing some promise as an adjunct to treatments for motor side effects.

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From their launch in the 1950s, it was widely recognised that the beneficial effects of antipsychotic drugs were being severely hampered by their propensity to create movement disorders in patients. This led to research (led principally by the pharmaceutical industry) into the biological basis of these side effects with a view to creating new, equally efficacious drugs for psychosis, which were less likely to cause motor side effects. These 'atypical' or 'second-generation' antipsychotics have had a major impact on the management of psychosis over the last 20 years.

Iatrogenic parkinsonism and other abnormal involuntary movements can undoubtedly be severely disabling for patients. These side effects have an indirect impact on compliance thereby reducing the efficacy of the offending drug, as well as more broadly on quality of life. Moreover, the injudicious use of treatments for these iatrogenic movement disorders can in themselves have deleterious effects on the patient's mental state.

The clinical features of these side effects will be discussed, which will be followed by a review of what is currently known regarding the biological basis of these symptoms.

This will lead to a description of the drugs most commonly associated with the generation of movement disorders and the patient groups most at risk. Finally, a concluding comment is made upon treatment options.

Clinical Features of Iatrogenic Movement Disorders

Parkinsonism

The motor symptoms of parkinsonism are characterised by four cardinal features namely tremor, bradykinesia, postural instability and hypertonicity. Dystonias also commonly arise in Parkinson's disease but will be discussed separately below.

The tremor is characteristically at a frequency of approximately 4–6 Hz and can affect any voluntary muscle group in the body. It is most clearly observable though in the fingers and hands leading to the characteristic pill rolling tremor. The tremor can be improved by activity which helps to differentiate it from benign essential tremor which is made worse upon activation.

Bradykinesia (literally slow movement) also can have an impact on all muscle groups. It is particularly observable when it affects the muscles of facial expression giving rise to the characteristic 'mask-like facies' and truncal muscles leading to decreased arm swing, stooping and festinant gait.

Postural instability leads to impaired balance and falls. It tends to occur more frequently in elderly patients, and therefore it is a particular problem when using antipsychotic drugs in this patient group.

Hypertonicity of skeletal muscles can be very problematic for patients, and when superimposed on tremor gives rise to the characteristic cogwheel rigidity noted in clinical examination. Without tremor, the hypertonicity may give rise (if severe) to 'lead pipe rigidity'.

Iatrogenic parkinsonism can be distinguished from idiopathic parkinsonism, as the former tends to cause symmetrical motor symptoms (though up to one third of patients with drug-induced parkinsonism have been reported to have unilateral symptoms [1, 2]), has a subacute onset and is often associated with dyskinesia and akathisia. Drug-induced parkinsonism is also associated with the so-called 'rabbit syndrome' which is a low-frequency, high-amplitude jaw tremor [3, 4]. This is an important distinction to make as correct diagnosis will avoid the use of inappropriate dopaminergic therapy. It is also worth considering that whilst neuroleptic drugs are most likely to cause this side effect, they may also be caused by other classes of drugs (table 1).

Dyskinesia

Dyskinetic movements are distinguished from the tremor seen in Parkinson's disease because they are irregular in rhythm. These side effects may emerge suddenly (acute dyskinesia) or after chronic exposure to antipsychotics (chronic or tardive

Table 1. Drugs associated with the development of parkinsonian symptoms (updated from Van Gelder [53])

Class	Commonly associated	Occasionally associated	Rarely associated
Phenothiazines	chlorpromazine, promethazine, levopromazine, triflupromazine, thioridazine, trifluoperazine, prochlorperazine, perphenazine, fluphenazine, mesoridazine, piperazine, acetophenazine, trimeprazine, thiethylperazine		
Butyrophenones	haloperidol, droperidol, triperidol		
Diphenylbutyl-piperidine	pimozide		
Indolines	molindone		
Substituted benzamides	metoclopramide, cisapride, sulpiride, clebopride, veralipride, alizapride, remoxipride, tiapride, veralipride	domperidone	
Dibenzazepine	loxapine		
Thioxanthenes	flupentixol, chlorprothixene, thiothixine		
Atypicals	risperidone, olanzapine	clozapine, quetiapine	
Ca ²⁺ channel blockers	flunarizine, cinnarizine	verapamil, diltiazem, nifedipine	
Anti-hypertensives		amlodipine, amiodarone	captopril
Anti-arrhythmics			aprimidine
Anticonvulsants		valproic acid	phenytoin
Antidepressants		citalopram, fluoxetine, paroxetine, sertraline, bupropion	nefazodone, phenelzine

Table 1. Continued

Class	Commonly associated	Occasionally associated	Rarely associated
Analgesics and anti-inflammatories		meperidine	fentanyl, bupivacaine, flurbiprofen, naproxen, gold, procaine, sufentanil, sulindac
Anti-infectives		amphotericin B	cephaloridine, chloroquine
Chemotherapy		cytosine arabinoside, cyclophosphamide	
Immunosuppresants		cyclosporine	
Anaesthetic agents			isoflurane, halothane
Other neuropsychiatrics		disulfiram, lithium, methyl dopa	
Cholinergic agents			bethanecol, tacrine, propiverine
Other			papaverine, pentoxifylline, estrogen and other oral contraceptives

dyskinesia). It is important to distinguish parkinsonian tremor from dyskinesia as the treatments vary, with (for instance) anticholinergic treatments being likely to make dyskinetic symptoms worse.

Chorea (which is Greek for 'dance' as in *choreography*) is a particular subtype of dyskinetic movement that is both irregular and non-repetitive. It can appear that the choreic movements travel from muscle group to muscle group causing the characteristic dance-like presentation.

Dystonia

There are many different aetiologies to dystonias which include both genetic and iatrogenic causes. Iatrogenic dystonias can be either acute or chronic and may or may not be related to other features of parkinsonism. Acute dystonic reactions include the

oculogyric crisis, where muscles of the eye and neck contract violently very soon after administration of a dopamine-blocking drug, though a wide range of other drugs have also been associated with this condition. Chronic dystonias can be particularly disfiguring and stigmatising especially when they affect shoulder, neck (torticollis) and facial muscles including eye lids (blepharospasm).

Biological Basis of Iatrogenic Movement Disorders

The biological basis of the movement disorders is complex. However, those listed above as secondary to medication are characterised by the action of drugs on central nuclei and in particular pathways and nuclei associated with the basal ganglia, a functional unit located at the base of the forebrain.

The basal ganglia have principal connections to the cortices and thalamus. Although involved in multiple functions including cognition and emotional function, it is their role in the control of involuntary movements that is relevant to this chapter. The other functions, though, are clinically important and discussed elsewhere in this book. At rest, the structures of the basal ganglia can be considered to provide a tonic inhibition of motor activity. This inhibition is released through conscious activity via an increased release of dopamine from (in particular) the substantia nigra, thereby allowing voluntary control of motor activity in the necessary area.

The basal ganglia's key nuclei with regard to movement disorders are the striatum (caudate, putamen and globus pallidus), substantia nigra and the subthalamic nucleus. In Parkinson's disease, α -synucleinopathy leads to neurodegeneration of the melanin-pigmented dopaminergic neurones of the substantia nigra pars compacta. When activity in the pathways between the substantia nigra and striatum drop by 80%, parkinsonism will develop [5]. It follows that the treatment of Parkinson's disease is principally through dopamine replacement. Drugs, therefore, that inhibit dopaminergic receptors in the basal ganglia are associated with parkinsonian symptoms. As there is usually functional reserve in this system, people with reduced albeit asymptomatic reductions in dopaminergic function of the basal ganglia will be more sensitive to the effects of dopamine receptor blockers.

There are several centrally expressed subtypes of dopamine receptors. These include the D2 receptors that were originally considered important in the symptoms observed in schizophrenia and other psychotic disorders through their presence and possible dysfunction in the dopaminergic mesolimbic (positive symptoms) and mesocortical (negative symptoms) pathways. The dopaminergic hypothesis of schizophrenia was developed from the accidental discovery of effective dopamine receptor blocking drugs and subsequently motivated drug development in the 1950s and 1960s to generate new dopamine antagonists. However, early antipsychotics (e.g. chlorpromazine) lacked specificity for this receptor, affecting other dopamine receptors, as well as serotonergic, histaminergic and noradrenergic receptors, and led to multiple

side effects. The desired blockade of mesolimbic dopaminergic pathways led to concurrent inhibition of D2 receptors in the substantia nigra resulting in parkinsonism.

Cholinergic interneurons within the basal ganglia balance the dopaminergic activity here. Accordingly, in Parkinson's disease, when the equilibrium is upset through degeneration of dopaminergic neurones, there is a relative predominance of cholinergic activity. The genesis of the abnormal movements in Parkinson's disease can therefore be considered as both a deficiency of dopaminergic activity as well as a relative increase in cholinergic activity. Accordingly, as well as dopamine augmentation as a therapy for Parkinson's disease, anticholinergic medication may also be of some benefit to help reset the equilibrium.

However, cholinergic pathways elsewhere are involved in cognition, vigilance and emotional modulation and degenerate in Parkinson's disease – while anticholinergic medication may therefore be associated with an improvement in movements, it is at the expense of deterioration in cognition in this disease, as well as in patients with psychosis, where anticholinergic medication may additionally mediate confusion and psychotic symptoms.

As the neurotransmitter basis of parkinsonism is due to dopamine deficiency or iatrogenic blockade with a resultant excess of cholinergic activity in the basal ganglia, dyskinesias may be due to dopaminergic hypersensitivity and cholinergic hypofunction. It has also been proposed that tardive dyskinesia may emerge due to free radical damage of relevant basal ganglia neurones. Long-term antipsychotic use is associated with the genesis of free radicals emerging from increased catecholamine metabolism [6]. Mitigating such oxidative damage to susceptible neurones has formed the basis of anti-oxidant treatments for tardive dyskinesia.

While parkinsonian side effects emerge from pathology and drug interactions in the substantia nigra, dyskinesic symptoms may be more closely associated with problems in the striatum – in particular with the caudate nucleus.

Whilst dystonias may emerge as part of a general parkinsonian reaction to medication, they may also arise acutely without other cardinal features of parkinsonism. Patients who developed an oculogyric crisis often do so after only a matter of hours after ingesting the medication responsible. Whilst associated with juvenile parkinsonism, there are also suggestions that acute dystonia may be related to abnormalities in the putamen, thalamus, substantia nigra or globus pallidus. Research into myoclonus and other dystonias has tended to focus on lesions of the pallidum within the basal ganglia. However, it is most likely that the vast majority of patients who develop acute dystonic reactions after ingesting medications known to cause these problems have no pathology in any of these or other brain nuclei.

In summary, lesions in any of the structures of the basal ganglia may be associated with the development of parkinsonism, dyskinesias or dystonias. Parkinsonism tends to be associated with problems of the substantia nigra, dyskinesia with the caudate, and dystonias with the globus pallidus (although there is no complete specificity). Furthermore, any of these symptom clusters can be caused by acute and chronic

exposure to anti-dopaminergic drugs, but dyskinesias are also associated with cholinergic hypofunction which has important implications for treatment.

Drugs Associated with Parkinsonism and Other Abnormal Involuntary Movements

There are numerous drugs and drug classes that are associated with the development of parkinsonism (table 1) and other abnormal involuntary movements. Drug-induced parkinsonism is often not recognised, especially in the non-psychiatric patient [7]. The side effect often develops within 1 month of the start of treatment, with 60% of patients developing it by this time point and 90% within 3 months [8]. The potency of antipsychotics is defined by their ability to block the D2 receptors. Therefore, high-potency neuroleptics tend to have a greater propensity to cause extra-pyramidal side effects. However, some high-potency neuroleptics that also have anticholinergic properties are associated with fewer motor side effects. Atypical antipsychotics tend to have broader pharmacodynamic effects, and it is thought that their activity at 5HT_{2a} receptors mediate efficacy with less need for blocking of the D2 receptors in the mesolimbic pathways and therefore in the substantia nigra.

The evidence surrounding iatrogenic dystonias is less well developed. Conventional neuroleptics are clearly implicated as are (from case reports) calcium channel blockers. Additionally, there are several case reports noting an association with olanzapine, carbamazepine, lithium, imipramine, gabapentin and ziprasidone. Other dystonias (e.g. cervical dystonia) are less clearly associated with iatrogenic causes.

High-Risk Groups (for Drug-Induced Movement Disorders)

Iatrogenic parkinsonism is common in the elderly [9] with rates as high as 2.7% from community samples, with idiopathic parkinsonism being present in another 3% [10]. Moreover, the presence of cognitive impairment, female gender and HIV disease have all been cited as increasing the risk of developing parkinsonism.

Certain types of drugs (table 1), after prolonged exposure and high doses, have also been associated with increasing the risk of iatrogenic parkinsonism.

The interaction between dementia, neuroleptic medication and parkinsonism is well established. The risk of postural instability and falls has been of concern [11] and has motivated national public health strategies to reduce the use of neuroleptics in people with dementia [12]. Patients with Parkinson's disease dementia and Lewy body dementia are particularly prone to autonomic instability [13–15], because of pre-existing α -synucleinopathy affecting dopaminergic pathways and autonomic nuclei in the brain stem. Patients with Alzheimer's dementia are also at greater risk of parkinsonism and are also (perhaps through different mechanisms) more prone to orthostatic hypotension [13]. In vascular dementia, white matter lesion (WML)

volume has been associated with falls in a well-controlled prospective study [16], though it was not clear from this study whether parkinsonism mediated this association. Moreover, WML burden in idiopathic Parkinson's disease is associated with more motor symptoms [for review see 17].

It is known that smokers are less likely to develop Parkinson's disease. Despite the fact that smokers with schizophrenia tend to receive more antipsychotic medication than non-smokers [18], there is consistent evidence that the former are less likely to develop parkinsonism [19]. This is in conflict with the observation that parkinsonism is treated with anticholinergic drugs, and may be due to the fact that chronic exposure to nicotine leads to receptor desensitisation and upregulation of some ($\alpha_4\beta_2$) but not other (α_7) nicotinic receptors [for review see 20]. While this may drive dependence on nicotine in smokers, it may also result in a functional reduction in cholinergic activity in the basal ganglia, helping to reduce the risk of parkinsonism. This hypothesis would predict that smoking leads to increased rates of dyskinesia associated with hypofunction of cholinergic activity. This has in fact been demonstrated [21, 22], especially with regard to patients on conventional neuroleptics as compared with clozapine [22]. Despite earlier reports of a reduced risk of dystonias in smokers [23], later evidence suggests that blepharospasm is not associated with smoking status [24, 25], though it may be associated with coffee consumption [25] and anxiety [24]. Other dystonias have been less well characterised in this regard, but there may be a protective effect of smoking [23].

Management

The first step in managing drug-induced abnormal involuntary movements is to recognise the syndrome and that one of the patient's medications may be its cause. If the culprit can be identified (see table 1), then the next logical step is to discontinue this drug, and if necessary replace it with another drug with similar efficacy but a reduced propensity to cause the same side effect. The advent of atypical antipsychotics with evidence of reduced abnormal movements in controlled trials [26], including in the elderly [27, 28], led to a dramatic change away from conventional neuroleptics. If symptoms do persist, idiopathic parkinsonism may actually cause the observed movement disorder. Tardive dyskinesia may be more resilient to change, with a reduced likelihood of improvement despite discontinuation of the offending therapy. This suggests that it may be related to eventual structural damage to the basal ganglia after chronic exposure.

In cases where there is not a clear relationship between drug exposure and parkinsonism, single-photon emission tomography with ^{123}I Iodine labelled ^{123}I -N-w-fluoropropyl-2 β -carbomethoxy-3 β -(4-iodophenyl)nortropane will be conclusive, as this dopamine transporter scan will be normal in patients with iatrogenic parkinsonism compared with the reduced uptake of tracer in the putamen of patients with idiopathic parkinsonism [29].

In Alzheimer's disease, the use of antipsychotics to manage behavioural symptoms remains commonplace, despite the association with mortality especially with conventional (5-fold increase in risk) compared with atypical (double the risk) neuroleptics [30]. A more precise diagnosis of psychotic symptoms may lead to a more judicious use of antipsychotics, although other drug classes may also be useful: SSRIs for depression associated with dementia have proved disappointing [e.g. 31], but have proved valuable for agitation [32]. Trazodone is indicated for agitation [32] and insomnia [33]. Memantine would appear to have a particular propensity to manage symptoms of agitation [34]. The cholinesterase inhibitors appear to have benefit for broadly defined neuropsychiatric symptoms, including psychotic phenomena [e.g. 35, 36]. Many psychotic symptoms in Alzheimer's disease and Lewy body dementia respond to treatment with cholinesterase inhibitors, with empirical evidence for the use of rivastigmine to treat hallucinations in Alzheimer's disease [37] and Lewy body dementia [38, 39]. There is a genetic linkage between delusions in Alzheimer's dementia with haplotypic variation in the α_7 nicotinic receptor gene [40]. This supports the hypothesis that psychotic symptoms in dementia are a manifestation of the well-documented cholinergic deficits in the disease.

Where switching is either not possible or fails to manage the symptoms effectively, various pharmacological interventions have been tested.

For parkinsonism, the use of anticholinergic drugs like benztropine may be efficacious [41], although use should be limited to short-term, especially in the elderly where there is a clear risk of iatrogenic confusion and worsening psychosis [42]. Moreover, though their use for idiopathic Parkinson's disease is well supported [42], their use for iatrogenic parkinsonism is not. Anticholinergics are useful also in dystonic symptoms but should be avoided in dyskinesia as they are likely to make symptoms worse.

Trials of drugs for the management of persistent dyskinesia have largely been disappointing. Acetylcholinesterase inhibitors, despite hypothetically addressing the hypocholinergic function in dyskinesia, have shown little benefit in small studies of donepezil [43, 44] and galanthamine [45], despite an earlier promising Cochrane Review [46]. However, recent evidence from a small study suggested that donepezil did reduce the frequency of falls in patients with idiopathic Parkinson's disease [47]. As tardive dyskinesia may be a consequence of synaptotoxic and eventually neurotoxic oxidative stress due to chronic neuroleptic use [6], anti-oxidant strategies may ameliorate symptoms. A recent Cochrane review noted that although far from conclusive, vitamin E tended to reduce the severity of established tardive dyskinesia and merited further study [48].

For cervical dystonia (torticollis) and other dystonias, patients can initially be offered physiotherapy or occupational therapy. Failing these conservative interventions, pharmacotherapy, botulinum toxin or surgery can be undertaken. While the evidence for the use of botulinum in primary cervical dystonia is robust, its efficacy in secondary (iatrogenic) dystonia is less certain [49, 50]. Drug treatments include

anticholinergic, dopaminergic, antidopaminergic and benzodiazepine therapies, though these are less well studied than local injection of botulinum [51, 52]. Of various drug classes, gradually uptitrated anticholinergics are the most likely to show benefit [52].

Conclusions

Iatrogenic parkinsonism and other abnormal involuntary movements have detrimental effects on compliance and thereby the efficacy of the drugs concerned. They are also associated with reduced quality of life and can be extremely disabling and stigmatising. Recognising that they may arise in other drug classes apart from neuroleptics is crucial.

The advent of new antipsychotics with a reduced propensity to parkinsonian side effects has caused a reduced acceptance of such side effects by patients and clinicians. However, where switching to an atypical antipsychotic is not possible or acceptable, low and carefully monitored use of anticholinergic medication may be helpful for parkinsonism and dystonias, but harmful for dyskinesias.

Chronic or tardive dyskinesia would appear to be secondary to neurodegeneration perhaps secondary to oxidative damage to key basal ganglia nuclei, and has proven to be more resistant to switching therapies. Prevention through avoidance of drugs linked to their genesis and (perhaps) prophylaxis with vitamin E may be indicated.

The evidence supporting the use of pharmacotherapy for dystonias is patchy; there is a robust evidence for the use of botulinum toxin for primary dystonia, and the evidence for this intervention for secondary dystonia is less complete.

In conclusion, early recognition and monitoring of patients for abnormal movements and a much lower threshold for what is acceptable as a side effect to psychotropic and other medications will improve the patient's prognosis.

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24 Biological Child Psychiatry

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Psychiatric symptoms are common in the neurological and geriatric care of patients with Parkinson's disease. This book assembles short reviews from experts in the field to chart the various psychiatric syndromes known in Parkinson's disease, their presentation, etiology and management. Presented are special topics on epidemiology of psychiatric symptoms, affective disorders and apathy, early cognitive impairment through to dementia, visuoperceptual dysfunction, psychotic disorders, sleep disturbances, impulse disorders and sexual problems. Further, rarely discussed issues, such as the relationship between somatoform disorders and parkinsonism are reviewed.

This publication is essential reading for old age psychiatrists, gerontologists and neurologists who work with patients suffering from Parkinson's disease. In addition, health practitioners who deal with senior patients, as well as scientists who need a quick update on the progress in this important clinical field will find this volume a helpful reference.