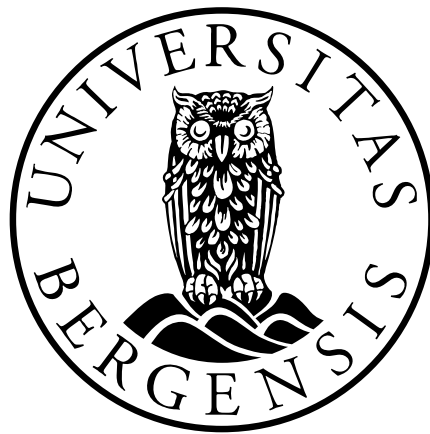# Apathy in Parkinson's disease

A community-based study

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Dissertation for the degree philosophiae doctor (PhD)

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"There can be no transforming of darkness into light and of apathy into movement without emotion."

Carl Gustav Jung

(Swiss psychiatrist, psychologist and founder of the analytic psychology, 1875-1961)

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Scientific environment

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List of papers

Paper I

Pedersen KF, Larsen JP, Aarsland D. Validation of the Unified Parkinson's Disease Rating Scale (UPDRS) section I as a screening and diagnostic instrument for apathy in patients with Parkinson's disease. Parkinsonism Relat Disord. 2008;14(3):183-186. Epub 2007 Sep 21.

Paper II

Pedersen KF, Larsen JP, Alves G, Aarsland D. Prevalence and clinical correlates of apathy in Parkinson's disease: a community-based study. Parkinsonism Relat Disord. 2009;15(4):295-299. Epub 2008 Sep 17.

Paper III

Pedersen KF, Alves G, Aarsland D, Larsen JP. Occurrence and risk factors for apathy in Parkinson's disease: a 4-year prospective longitudinal study. J Neurol Neurosurg Psychiatry. 2009;80(11):1279-1283.

Paper IV

Pedersen KF, Alves G, Bronnick K, Aarsland D, Tysnes OB, Larsen JP. Apathy in drug-naïve patients with incident Parkinson's disease: the Norwegian ParkWest study. J Neurol. 2010;257(2):217-223. Epub 2009 Aug 25.

Abbreviations

AC	Anterior cingulate
ACC	Anterior cingulate cortex
AD	Alzheimer's disease
AES	Apathy Evaluation Scale
AI	Apathy Inventory
AS	Apathy Scale
CBD	Corticobasal degeneration
CNS	Central nervous system
COMT	Catechol-O-methyl transferase
CSF	Cerebrospinal fluid
CT	Computed tomography
CVLT-II	California Verbal Learning Test II
DBS	Deep brain stimulation
DLPFC	Dorsolateral prefrontal cortex
DRS	Dementia Rating Scale (Mattis)
DSM	Diagnostic and Statistical Manual of Mental Disorders
EPA	European Psychiatric Association
GBS	Gottfries-Bråne-Steen scale
GP	General practicner
IQCode	Informant Questionnaire on Cognitive decline in the elderly
LARS	Lille Apathy Rating Scale
LRRK2	Leucine-rich repeat kinase 2

MADRS	Montgomery and Aasberg Depression rating Scale
MAO-B	Monoamine oxidase type B
MD	Medial dorsal nucleus of the thalamus
MDS	Movement disorder society
MHPG	3-methoxy-4-hydroxyphenylglycol (major metabolite of noradrenaline)
MMSE	Mini-Mental State Examination
MRI	Magnetic resonance imaging
MSA	Multiple system atrophy
NA	Nucleus accumbens
NPI	Neuropsychiatric Inventory
OLFC	Lateral orbitofrontal cortex
PD	Parkinson's disease
PDD	Parkinson's disease dementia
PET	Positron emission tomography
PFC	Prefrontal cortex
PIGD	Postural instability and gait disorder
PINK1	Phosphatase and tensin homolog (PTEN)-induced putative kinase 1
PPN	Peduculopontine neuclus
PSP	Progressive supranuclear palsy
RBD	REM sleep behaviour disorder
REM	Rapid eye movement
ROC	Receiver operating characteristic
SNRI	Selective noradrenaline reuptake inhibitor
SPECT	Single photon emission computed tomography
SSRI	Selective serotonin reuptake inhibitor

STN	Subthalamic nucleus
UPDRS	Unified Parkinson's Disease Rating Scale
VOSP	Visual Object and Space Perception Battery
VP	Ventral pallidum
VTA	Ventral tegmental area
5-HT	5-hydroxytryptamine (serotonin)

1. Introduction

Most people are familiar with motivation as an aspect of everyday behaviour. Just think about what drives you to learn? Why did you choose your career? Your partner? Where you would live? Simply put, motivation is WHAT drives you to behave in a certain way or to take a particular action. In modern psychology, the concept of motivation has largely been applied to study learning at school, performance at work, and competition in sport. In recent years, however, pioneers of neuropsychiatry have proposed to define a clinical syndrome of apathy characterized by a lack of motivation. Although disagreement regarding the concept and core features of apathy, most researchers agree that apathy is clearly distinct from depression and can be observed in healthy people as well as in several neurodegenerative disorders and in particular in Alzheimer's disease (AD). The study of apathy is still in its infancy, but several validated apathy rating scales have made it possible to explore the universe of motivational deficits across diagnostic groups.

In recent years, several studies of apathy in patients with Parkinson's disease (PD) have shown that diminished motivation is a common but under-recognised behavioural disorder. However, further studies are needed to gain information about the frequency and clinical correlates of apathy from the time of diagnoses to more advancing stages of PD.

The first part of this thesis gives a brief overview of PD and apathy in general. In the next section we review the current knowledge about apathy in PD. Finally, the main part of this thesis is devoted to our research which intends to describe apathy as a neuropsychiatric disorder in community-based patients with PD across different stages of disease.

2. Parkinson's disease

2.1 Historical background

The English physician James Parkinson (1755-1824) was the first to publish an accurate description of the clinical syndrome that was later to bear his name. In his classical 1817 monograph entitled "An essay on the shaking palsy", Parkinson described the clinical features of six subjects he had seen either as patients or observed on the streets close to his home in Hoxton Square, London.[1] His treatise begins with a succinct summary of the distinctive features of the malady:

"Involuntary tremulous motion, with lessened muscular power,

in parts not in action and even when supported; with a propensity

to bend the trunk forwards and to pass from a walking to a running

pace: the senses and intellects being uninjured."

Although the essence of his description of the disease was remarkably accurate, he did not identify abnormalities in muscle tone or cognition. However, Parkinson recognized several nonmotor features that occurred during the progression of the disorder, such as sleep disturbance, constipation, urinary incontinence, fatigue and delirium. More than half a century later, the French physician Jean-Martin Charcot (1825-1893) added muscular rigidity, micrographia, and sensory changes to the syndrome, and gave credit to Parkinson by referring to the disease as "maladie de Parkinson."

A century passed after the original description by Parkinson before the Russian neuropathologist Constantin Tretiakoff (1892-1958) described degeneration of the substantia nigra associated with PD in his doctoral thesis of 1919.[2] In 1957, Carlsson and colleagues discovered that the hypokinetic syndrome induced by the antipsychotic agent reserpine in experimental animals could be reversed by levodopa, a dopamine precursor that crosses the blood-brain-barrier.[3] Soon thereafter the same group published a theory of dopamine as a neurotransmitter in the brain possibly involved in motor control.[4] A few years later, Ehringer and Hornykiewicz demonstrated markedly decreased dopamine concentrations in the striatum of patients with PD,[5] which led to the first trials of intravenous levodopa showing spectacular improvement of akinesia in patients with PD.[6] In 1967, Cotzias and colleagues presented dramatic effects of large oral doses levodopa in PD patients[7] and two years later levodopa was introduced as a clinically applicable therapy.[8]

While the 1960s were the years of dopamine discovery and the 1970s the decade of efficient treatment of the disease by the introduction of dopamine replacement therapy, the 1980s witnessed motor complications due to chronic levodopa treatment. This led to the rebirth of surgical treatment in the 1990s by introduction of continuous deep brain stimulation (DBS) as a well-documented treatment for carefully selected patients with motor fluctuations and dyskinesias.[9] In recent years, the identification of disease-related genes that cause hereditary forms of PD have led to novel insight into the pathogenesis of PD, that will hopefully offer novel therapeutic options.[10]

2.2 Epidemiology

PD is the second most common neurodegenerative disorder after Alzheimer's disease, affecting approximately 0.3% of the entire population and 1-2% of those older than 60 years in industrialised countries.[11] PD has been shown to be slightly

more predominant in males in some studies.[11, 12] It is estimated that 5 million people worldwide have PD, with an average age at disease onset of approximately 60 years.[13] However, as much as 10% of people with the disease are younger than 45 years of age.[14] The prevalence rate of PD is affected by survival and study methodology (hospital-based surveys versus community-based studies). As a result of these methodological difficulties, crude prevalence rates in PD vary wildly between 10 and 405 per 100,000 inhabitants.[15] Most community-based prevalence studies across Europe, however, found crude prevalence rates between 100 and 200 per 100,000 inhabitants.[16] Incidence calculations are probably a better estimate of the frequency of the disease because they are not affected by mortality. Nevertheless, age-standardized annual incidence rates of PD in population-based studies in European countries and the USA range from 8 to 19 per 100,000 inhabitants,[17] probably due to differences in methods of ascertainment and case definition. Overall risk of PD increases with advancing age and both age-specific incidence and prevalence rise exponentially into the 70s and 80s but then decline in some studies,[11] probably due to poor case ascertainment and low numbers in these age groups. With the aging of the population, it is expected that the number of cases of PD will increase dramatically over the next decades.[18]

2.3 Aetiology

The cause of PD is still unknown, but current knowledge suggests that it is a progressive multisystem degenerative process with several potential causative factors.[19] Several studies have shown a weak, but significant, increased risk of PD in people exposed to pesticides, rural living, farming, and well-water ingestion.[20] In contrast, cigarette smoking and caffeine are associated with decreased risk of PD,[21, 22] and it has been suggested that a premorbid parkinsonian personality may account for this finding.[23] Over the last 12 years, several genes causing monogenic parkinsonian syndromes have been discovered (Table 2.1). Genetic studies found mutations in autosomal dominant genes such as α-synuclein (PARK1) and leucine-rich repeat

kinase 2 (LRRK2), as well as in autosomal recessive genes such as Parkin (PARK2), PINK1 (PARK6) and DJ-1 (PARK7).

Table 2.1 Genetics of PD

Locus/gene	Inheritance	Onset	Pathology	Map position	Gene
PARK1	Dominant	40s	nigral degeneration with Lewy-bodies	4q21	α-synuclein
PARK2	Recessive	20–40	nigral degeneration without Lewy-bodies,	6q25	Parkin
PARK3	Dominant	60s	nigral degeneration with Lewy-bodies, Plaques and tangles in some	2p13	?
PARK4	Dominant	30s	nigral degeneration with Lewy-bodies, vacuoles in neurons of the hippocampus	4q21	α-synuklein triplikations and duplications
PARK5	Dominant	~50	No pathology reported	4p14	ubiquitin C-terminal hydrolase L1
PARK6	Recessive	30–40	No pathology reported	1p35–37	PINK1
PARK7	Recessive	30–40	No pathology reported	1p38	DJ-1
PARK8	Dominant	~60	Variable α-synuclein and tau pathology	12 cen	LRRK2
PARK9	Recessive	20–40	No pathology reported	1p36	ATP13A2
PARK10	Dominant (?)	50–60	No pathology reported	1p32	?
PARK11	Dominant (?)	late	No pathology reported	2q34	?
PARK12	X-linked	late	No pathology reported	Zq21	?
PARK13	Dominant (?)	late	No pathology reported	2p12	HTRA2

PINK = phosphatase and tensin homolog (PTEN)-induced putative kinase; LRRK = leucine-rich repeat kinase. From Gasser.[24]

Although these genetic mutations are relatively rare (< 5% of patients) in sporadic cases of PD with no family history of the condition, they may elucidate possible pathogenetic pathways because of their suggested role in the ubiquitin-proteosome system, in oxidative stress response, and mitochondrial functions.[10] The majority of PD cases are considered to be caused by the interaction of genetic and environmental factors, and susceptibility variants of genes involved in monogenic forms of PD have been identified in sporadic PD in several populations.[25]

2.4 Pathogenesis and pathophysiology

2.4.1 Neuropathology

The loss of dopaminergic, neuromelanin-containing neurons from the pars compacta of the substantia nigra is the pathological hallmark of PD. The resulting loss of neuromelanin from the substantia nigra leads to the depigmentation of this structure observed at post-mortem, but its role in the genesis of PD is unknown. It has been estimated that the clinical signs of PD do not develop until normal striatal dopamine levels are reduced by 80% and total cell loss in the substantia nigra reaches 50% (70% in the ventrolateral tier).[26] This finding implies that the brain has excellent compensatory mechanisms, which consist of a presynaptic increase in the turnover of dopamine in surviving neurones and a postsynaptic increase in dopamine receptor sensitivity. Cell loss in PD is not confined solely to the substantia nigra but also affects the locus coeruleus, dorsal nuclei of the vagus, nucleus basalis of Meynert, raphe nuclei, sympathetic ganglia, hypothalamus and the ventral tegmental area.[27]

The pathological determination of PD also includes the identification of Lewy bodies,[28] which are eosinophilic hyaline inclusions present in the cytoplasm of some remaining neurons in the substantia nigra pars compacta. They can also be found in other catecholaminergic nuclei affected in PD, along with the cerebral cortex, thalamus, brainstem, intermediolateral column of the spinal cord, sympathetic ganglia, and myenteric plexus of the gastrointestinal tract. It was recently discovered that α-synuclein is a major structural component of Lewy bodies.[29] Although the presence of Lewy bodies is an essential feature of PD, it has also been described in other conditions such as multiple system atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), motor neuron disease, pantothenate kinase associated neurodegeneration (PKAN = Hallervorden-Spatz disease), AD, and Down's syndrome.[30] This probably implies that Lewy bodies are a common end-product of neuronal degeneration. Lewy bodies have also been detected in the brains

of about 10% of clinically normal people over 60 years of age. This process is
sometimes referred to as incidental Lewy body disease and might be a
presymptomatic early phase of PD.[31, 32]

In recent years, Braak and colleagues have used synuclein immunostaining
techniques to document a new hypothesis on staging of the neuropathological process
in PD (Figure 2.1).[33, 34] Although their work supports the possibility of
presymptomatic PD in patients with small numbers of Lewy bodies in the brainstem,
it cannot explain the presentation of Lewy body dementia with cognitive dysfunction
appearing before any motor features.[35]

Figure 2.1 The neuropathological stages of sporadic PD
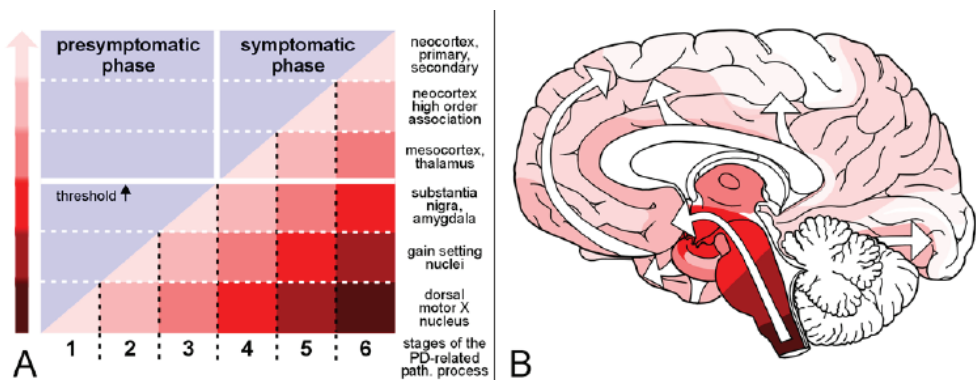
PD presymptomatic and symptomatic phases. A The presymptomatic phase is marked by the appearance of
Lewy neurites/bodies in the brains of asymptomatic persons. In the symptomatic phase, the individual
neuropathological threshold is exceeded (black arrow). The increasing slope and intensity of the coloured areas
below the diagonal indicate the growing severity of the pathology in vulnerable brain regions (right). The
severity of the pathology is indicated by darker degrees of shading in the colored arrow left. B Diagram
showing the ascending pathological process (white arrows). The shading intensity of the colored areas
corresponds to that in A. From Braak et al.[34]

Based on recent findings that nerve cells implanted into the striatum of patients with PD develop PD pathology with loss of dopamine markers and classic Lewy bodies, it has been hypothesised that α-synuclein acts like a prion and that PD may in fact be a prion disorder.[36]

2.4.2 Neurochemistry

In terms of neurochemical changes, the characteristic finding in PD is profound depletion of dopamine predominantly in the nigrostriatal system and to a lesser extent in the mesocortical and mesolimbic pathways.[30] To date, a total of five subtypes of dopamine receptors have been cloned, which are grouped into D1-like (D1 and D5 receptors) and D2-like (D2, D3, and D4 receptors) families.[37] D1 and D2 receptors are mostly localized in the striatum and substantia nigra, D3 receptors are largely expressed in the ventral striatum and nucleus accumbens, D4 receptors are expressed in the frontal cortex, and D5 receptors are mostly localized in the mammilary and pretectal nuclei.[38] In addition to impairment of the dopaminergic neurotransmission, loss of neurones from the locus coeruleus in the brainstem leads to cortical noradrenaline depletion, serotonin (5-hydroxytryptamine; 5-HT) is reduced in the striatum due to raphe nucleus involvement, and loss of cholinergic neurones from the nucleus basalis of Meynert leads to reduced cholinergic innervation of the neocortex and hippocampus.[39] Reduction in the neuropeptides substance P, met-enkephalin, cholecystokinin and somatostatin in the basal ganglia in PD have also been demonstrated, but the functional impact of these changes are unclear.[40]

2.4.3 Pathogenetic mechanisms

Although the cause of neuronal degeneration in PD is unknown, several mechanisms have been proposed: 1) Abnormal protein processing due to dysfunction of the ubiquitin-proteasome system, 2) oxidative stress and free radicals, 3) mitochondrial

dysfunction, 4) apoptosis, 5) excitotoxicity, and 6) inflammation.[41] These mechanisms are not mutually exclusive and may be intimately related, possibly triggered by genetic, environmental, or a complex gene-environmental interaction.

2.4.4 Pathophysiology of basal ganglia

Considerable effort has been made during the last two decades in understanding the functional anatomy of the basal ganglia. The classic model suggests a direct and indirect pathway connecting the striatum and the globus pallidus, with modulatory effects of the dopaminergic neurons on each of these systems (Figure 2.2).

According to this model, the motor symptoms of PD are caused by nigrostriatal dopamine deficiency in the putamen, which results in increased activity in striatopallidal gabaminergic fibres (via enhanced activation by the indirect pathway and decreased inhibition by the direct pathway) and thereby inhibiting the lateral pallidal gabaminergic neurons to the subthalamic nucleus (STN). In this way the glutamatergic STN projection to the pallidum is stimulated, which increases the firing of medial pallidal gabaminergic neurons to the thalamus. This leads to increased inhibition of the thalamocortical pathway that suppresses movement. However, it is now appreciated that the basal ganglia are far more complex than previously understood and are comprised of a complex network of neurons with multiple feedback and feed forward loops rather than the linear pathways portrayed in the classic model.[13]

Figure 2.2 Schematic representation of the classic model of the basal ganglia
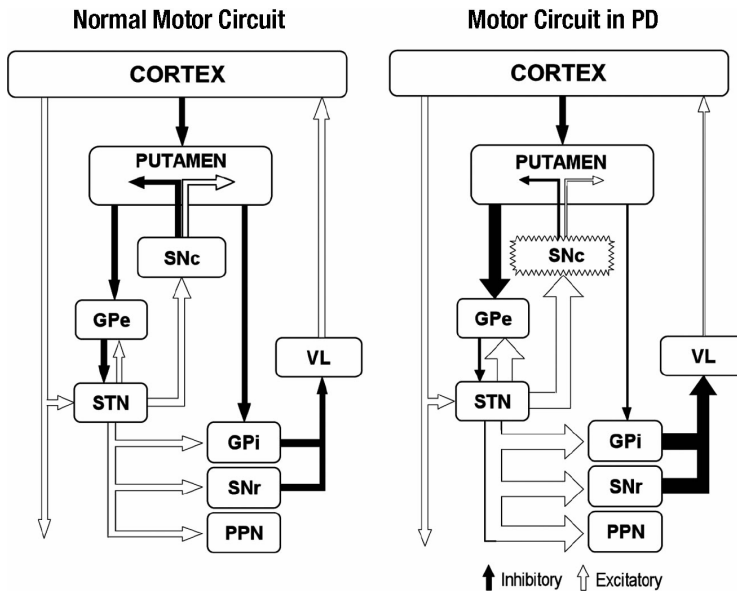
Excitatory fibers are shown in white and inhibitory fibers in black. The model predicts that neuronal firing in the STN and GPi are increased in the parkinsonian state, leading to excessive inhibition of brainstem and thalamocortical neurons with the development of parkinsonian motor features. SNc = substantia nigra pars compacta; GPe = external globus pallidus; STN = subthalamic nucleus; VL = ventral lateral nucleus of the thalamus; Gpi = internal globus pallidus; SNr = substantia nigra pars reticularis; PPN = pedunculopontine nucleus; DA = dopamine. Adapted from Olanow et al.[13]

2.5 Clinical features

2.5.1 Cardinal motor signs

Parkinsonism is a clinical syndrome defined by the presence of a combination of the cardinal motor signs of rest tremor, rigidity, bradykinesia, and postural abnormalities.[42]

Tremor

A 4-6 Hz rest tremor is the most common and easily recognised presenting feature of PD, affecting 60% to 70% of patients at motor onset.[43-45] However, the percentage of patients with tremor at some point during the course of the disease is variable, ranging from 75% to 100%.[44, 46, 47] The typical tremor of PD tends to start unilaterally in the hand, described as supination-pronation ("pill-rolling") tremor, subsequently involving the ipsilateral leg or contralateral arm. Although the tremor on average spreads bilaterally six years after the onset of symptoms,[48] the initially affected side continues to have more tremor than the contralateral side. Rest tremor in patients with PD can also involve the lips, chin and jaw, but head tremor in early disease is atypical and most likely caused by essential tremor or cervical dystonia.[49] Many patients with PD also have tremor when the limb is placed in a position of postural maintance (postural "re-emergent" tremor), which is differentiated from essential tremor in that tremor is often delayed after the patients assumes an outstretched horizontal position.[50] Rest tremor usually disappears at sleep, is reduced during action of the affected limb(s), and worsens by anxiety, emotional excitement and stressful situations. The response of tremor to drug treatment is highly variable.[51]

Rigidity

Rigidity is characterised by unvarying increased resistance throughout the range of passive movement of a limb (flexion, extension or rotation about a joint). The "cogwheel" phenomenon is a particular type of rigidity in some patients with PD, thought to be caused by tremor superimposed on increased tone.[52] However, many will instead have "lead-pipe" rigidity, where the tonic resistance is smooth throughout the entire range of passive motion. The flexed posture resulting in flexed neck and trunk posture, as well as flexed elbows and knees, are often associated with rigidity, although generally occurs late in the disease.[49] Patients may experience rigidity as stiffness associated with vague aching and discomfort of a limb, especially

in the shoulder where rigidity initially may be misdiagnosed as arthritis, bursitis or rotator cuff injury.[53, 54] Rigidity often begins unilaterally, typically on the same side as the rest tremor if present, and eventually progresses to the contralateral side and remains asymmetric throughout the disease.[48] The frequency of rigidity in patients with PD has only been reported in a few series, with values ranging from 89% to 99%.[55]

Bradykinesia

Bradykinesia means slowness of movement and is one of the most disabling motor symptoms of PD. It is eventually seen in all patients and is considered a requirement for diagnosis of PD in many published diagnostic criteria. Patients with bradykinesia have difficulties with planning, initiating and maintaining movement in addition to performing sequential and simultaneous tasks.[56] Patients often have a difficult time describing symptoms of bradykinesia, often using "weakness", "incoordination", and "tiredness" to describe their decreased ability to initiate voluntary movement. Bradykinesia may be clinically manifested as decreased eye blinking, micrographia, decreased finger dexterity, shuffling steps, difficulty arising from chair, and hypophonia, among others. Freezing (motor blocks) is a form of akinesia that is poorly understood and contributes to gait difficulty in PD. It usually does not occur until more advanced stages of PD and typically manifests as a sudden and transient (usually <10 seconds) inability to move, most commonly during walking.[49] Like tremor and rigidity, bradykinesia often presents unilaterally, progresses slowly to the contralateral side of the body, and remains asymmetric throughout the disease.[57]

Postural abnormalities

Postural abnormalities in PD refer to changes in posture as well as gait problems with imbalance. The bent posture with flexion in the neck, trunk, and arms is probably due

to rigidity and muscle spasm. The typical parkinsonian gait is slow, small stepped, and shuffling. Postural imbalance is caused by impairment of centrally mediated postural reflexes, which are important to make rapid postural corrections. Falls are common in late PD and are a major cause of morbidity. They may be caused by either postural imbalance or a displaced centre of gravity due to flexed posture.

2.5.2 Other motor abnormalities

PD patients may also exhibit a number of secondary motor symptoms, which are mostly variants of one or more of the cardinal signs. Hypomimi, or loss of facial expression, is most likely caused by a combination of both bradykinesia and rigidity. Bulbar dysfunction manifested by dysartri, hypophonia, dysphagia and sialorrhoea are frequently observed in patients with PD and are thought to be related to orofacial-laryngeal bradykineasia and rigidity.[58] Some PD patients develop restrictive or obstructive respiratory disturbances due to rigidity in the neck and chest wall.[59] Respiration may also be compromised by levodopa related respiratory dyskinesia.[60] Respiratory problems in patients with PD are associated with substantial morbidity and mortality.[49] A number of oculomotor abnormalities have been described in PD patients, such as decreased blink rate, positive glabellar reflex, and upgaze limitation, among others.[61]

2.5.3 Nonmotor features

While PD has traditionally been considered a motor system disorder, it is now widely recognized that nonmotor symptoms of PD are common, occur across all stages of PD, are underreported, and are a key determinant of reduced functioning and quality of life.[62] In a hospital-based cross-sectional study of 99 nondemented patients with PD, only 12% of the sample had no anxiety, depression, fatigue, sleep disturbance, or sensory symptoms after seven years of disease duration.[63] Nonmotor symptoms of PD

occur both in early and advanced stages, and some symptoms such as olfactory
deficit, constipation, rapid-eye movement (REM) sleep behaviour disorder (RBD),
and depression might even precede the onset of motor symptoms by several years.[64]
A recent hospital-based study of 101 PD patients demonstrated that during routine
office visits, neurologists failed to identify the presence of anxiety, depression and
fatigue in over 50% of cases, and sleep disturbance in over 40% of patients.[65]
Numerous studies have shown that nonmotor symptoms significantly impair quality
of life and may precipitate hospitalisation in patients with PD.[66] The spectrum of
nonmotor manifestations of PD is broad, as shown in Table 2.2. This section will
focus on cognitive deficits and depressive disorders, whereas apathy in PD will be
discussed in detail in chapter 4.

Table 2.2 Nonmotor features of Parkinson's disease

Neuropsychiatric dysfunction
  Mood disorders
  Apathy and anhedonia
  Frontal executive dysfunction
  Dementia and psychosis
Sleep disorders
  Sleep fragmentation and insomnia
  RBD
  PLMS/RLS
  Excessive daytime somnolence
Autonomic dysfunction
  Orthostatic hypotension
  Urogenital dysfunction
  Constipation
Sensory symptoms and pain
  Olfactory dysfunction
  Abnormal sensations
  Pain

RBD, rapid eye movement sleep behaviour disorder; PLMS, periodic
limb movements in sleep; RLS, restless legs syndrome.

From Poewe.[67]

Cognitive impairment and dementia

Cognitive impairment is commonly associated with PD. The frequency of cognitive dysfunction in patients with PD without clinical evidence of dementia was reported to be 36% at the time of PD diagnosis.[68] At a mean of 3.5 years follow-up, 10% of the incident PD cohort had developed dementia and further 57% showed evidence of cognitive impairment.[69] A recent study has demonstrated a twofold increase in the proportion with cognitive impairment in patients with early untreated PD compared to matched controls.[70] Executive functions, memory, visuospatial skills, attention, and mental processing speed are the most frequently encountered domains of cognitive dysfunction in non-demented patients with PD.[71-73] With increasing disease duration of PD, the severity and range of cognitive deficits typically increase. However, core language functions are likely to remain intact for the most part of the disease process.[74] Prevalence studies of dementia in PD vary depending on the age, disease duration, and population surveyed.[75] The point prevalence of PD dementia (PDD) has been estimated to approximately 30%, which accounts for 3-4% of dementia in the general population.[75] However, it is likely that this is an underestimate of the true frequency, as highlighted by two recent longitudinal studies with 12 and 20 years of duration[76, 77] reporting over 80% of PD patients with dementia. A six-fold increased risk of developing dementia in PD compared to non-PD subjects has been demonstrated.[78] Risk factors for PDD include advanced age,[79] mild cognitive impairment[69] and severity of parkinsonism, particularly axial symptoms like postural instability and speech problems.[80, 81] New consensus criteria for a clinical diagnosis of PDD have recently been proposed.[74]

Depressive disorders

Depression is one of the most common neuropsychiatric disorders in PD patients with significantly higher prevalence rates than in age-matched controls and patients with other chronic diseases.[82, 83] About 20% of patients report depressive symptoms

preceding the motor onset of PD, and depressed patients have a two-three fold increased risk of developing PD compared to non-depressed control subjects.[83, 84] The prevalence of depression has varied widely between different studies depending on the definitions, assessment instruments, and the population studied.[85] In a recent systematic review of prevalence studies in PD, the weighted prevalence of major depression, minor depression and dysthymia was 17%, 22% and 13%, respectively.[86] In the general population these numbers were lower, whereas higher prevalence rates were found in hospital outpatient and inpatient settings. For example, Tandberg and colleagues reported that 7.7% of patients with PD in the community met the criteria for major depressive disorder[82] according to criteria of the Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, Revised (DSM-III-R).[87] Despite their high prevalence, depressive disorders are frequently undiagnosed in PD.[65] One important reason is the potential overlap between some core features of depression with motor symptoms of PD. For example, bradykinesia and facial masking resemble the psychomotor slowing, decreased initiative, and restricted affect seen in major depression or apathy.[88] In addition, several cognitive, vegetative, and somatic symptoms of major depression are commonly seen in patients with PD who do not have depression.[89] Based on these challenging aspects of recognition of depressive symptoms in PD, provisional diagnostic criteria for depression in PD have recently been recommended.[90] The clinical profile of depressive disorders associated with PD generally resemble those of non-PD major depression, although anxiety, dysphoria, and irritability may be more prominently present in patients with PD, whereas self-blame tendencies, feelings of guilt, and suicidality are less prevalent.[91] Major depression, in contrast to minor (dysthymic) depression, has been significantly related to deficits in executive functions and the akinetic-rigid variant of PD, and predicts a faster cognitive and physical decline.[92] To date, right-sided onset of motor symptoms is the only disease-specific marker of depression found in PD.[93]

2.6 Diagnosis and differential diagnosis

Although PD is the major cause of parkinsonism, the earliest symptoms are often subtle and this can lead to misdiagnosis.[94] Strict diagnostic criteria have been shown to increase the accuracy of a pathology diagnosis of PD.[95] Associated features such as asymmetry of motor onset, presence of resting tremor, and good response to dopamine medication therapy may help to distinguish PD from other parkinsonian disorders (Table 2.3).

Table 2.3 Differential diagnosis in parkinsonian disorders

Type of parkinsonism	Subtype/cause
Parkinson's disease[a]	• Idiopathic • Familial

Symptomatic parkinsonism	• Drug-induced
	  ○ Neuroleptics, antidepressants, lithium
	  ○ Antiemetics
	  ○ Antihypertensive agents, antiarrhythmics
	• Vascular disease
	• Intoxication (MPTP, rotenone, others)
	• Traumatic
	• Post-infectious
	• Neoplasm
	• Normal pressure hydrocephalus

Parkinsonism due to other neurodegenerative disorders	• Atypical parkinsonism
	  ○ Multiple system atrophy (MSA)[a]
	  ○ Progressive supranuclear palsy (PSP)[b]
	  ○ Corticobasal degeneration (CBD)[b]
	• Dementia with Lewy bodies (DLB)[a]
	• Alzheimer's disease[b]
	• Others

[a] synucleinopathy; [b] tauopathy

From Alves et al.[96]

Early occurrence of gait dysfunction, severe dysautonomia, hallucinations, dementia, or supranuclear gaze palsy are uncommon and suggestive of parkinsonism due to other neurodegenerative disorders. Structural brain imaging, using computed

tomography (CT) and magnetic resonance imaging (MRI), is mainly used to exclude secondary causes of parkinsonism, but may also be helpful in distinguishing between PD and atypical parkinsonian syndromes like MSA and PSP. Functional brain imaging, using dopamine-ligands in single-photon emission computed tomography (SPECT) and positron emission tomography (PET), can be helpful to establish the clinical diagnosis of PD in uncertain cases but is not reliable when distinguishing PD from atypical forms of parkinsonism.

2.7 Treatment

At present, no preventive or curative treatment for PD is available, and thus pharmacotherapy may only provide symptomatic effects on motor and, to a less extent, nonmotor symptoms in PD. Although most treatment strategies focus on pharmacologic agents, exercise and lifestyle changes, as well as speech therapy may be helpful in some patients. Guidelines for the management of PD are produced on a regular basis.[97-99] In the following the major pharmacologic and surgical treatment modalities for PD will be addressed.

MAO-B inhibitors

Selegiline is an irreversible inhibitor of monoamine oxidase type B (MAO-B), which reduces the breakdown of dopamine in the striatum. Although selegiline has been shown to delay disease progression in PD,[100, 101] which may indicate neuroprotective properties, the results are not yet conclusive.[102] Selegiline can be used as initial monotherapy in PD or as adjuvant therapy once motor complications have developed on levodopa. Of notice, because selegiline is metabolised to amphetamine derivates, it may cause insomnia, nightmares and hallucinations. Recently, a new second generation irreversible MAO-B inhibitor, rasagiline, has been suggested to induce neuroprotective effects similar to those of selegiline.[103] Rasagiline does not

metabolise to amphetamine derivates, reducing the side-effects experienced with selegiline. Indication for treatment with rasagiline in PD is the same as for selegiline. There are currently no comparative studies of rasagiline and selegiline..

Levodopa

Forty years after its introduction, levodopa remains the most efficacious drug for symptomatic treatment of PD.[104] Levodopa is a precursor of dopamine that crosses the blood-brain barrier and is decarboxylated to dopamine in the presynaptic terminal by dopaminergic neurons. To reduce the peripheral metabolism of levodopa, which causes nausea, and increase the availability of levodopa in the brain, it is usually administered with a peripheral dopa decarboxylase inhibitor such as carbidopa or benserazide. Levodopa provides rapid and effective relief of bradykinesia and rigidity with associated pain, and improves tremor in many patients. However, long-term levodopa therapy is associated with more frequent development of motor fluctuations and dyskinesias compared to other dopaminergic drugs. In addition, symptoms such as postural instability, speech disturbance and sialorrhea may not be improved due to non-dopaminergic mechanisms of PD. Levodopa is usually the preferred treatment of early PD with onset over age 70 years, as these patients are less prone to develop serious long-term motor complications due to a rather short life-expectancy.

Dopamine agonists

Dopamine agonists act directly on postsynaptic dopamine receptors without the need for oxidative metabolism.[105] Furthermore, most dopamine agonists have significantly longer half-lives than levodopa and thus provide more continuous dopaminergic receptor stimulation. The pulsatile dopamine receptor stimulation caused by non-continuous delivery of levodopa has been hypothesized as a critical factor for the development of dyskinesis.[106] Indeed, several controlled trials have shown that initial

therapy with dopamine agonists is associated with less rapid development of motor fluctuations and dyskinesias compared to initial treatment with levodopa.[107] Dopamine agonists are broadly divided into ergot and non-ergot agonists, which all act on D2-like dopamine receptors. However, different dopamine agonists have selective subspecificities within the D2-family (D2, D3, and D4 receptors) and this may offer the potential of specific clinical profiles and different adverse reactions accociated with specific types of receptor stimulation. It is now current practice to initiate non-ergot dopamine agonists (pramipexole, ropinorole, and rotigotine) instead of ergot-derived agonists to avoid serosal reactons and cardic valvulopathy (pergolide and carbegoline). To avoid common side-effects such as nausea, vomiting, ortostatic hypotension, and daytime sleepiness, doses are generally increased very slowly. Dopamine agonists are usually preferred as initial monotherapy in patients with younger age,[108] but may also be given as adjuncts to levodopa in later disease.

COMT inhibitors

Catechol-O-methyltransferase (COMT) is the main enzyme responsible for the metabolism of levodopa after dopa decarboxylase inhibition. Entacapone is a reversible peripheral COMT inhibitor that increases serum half-life of levodopa by inhibiting its conversion into 3-O-methyldopa, thereby prolonging its duration of action. When administered in combination with levodopa, entacapone reduces *off*-time and increases *on*-time which allows a reduction in levodopa dose.[109] Entacapone is approved for adjunctive therapy in patients with motor fluctuations. A triple combination tablet containing entacapone/levodopa/carbidopa is currently available and may improve compliance which is known to be a problem in PD. COMT inhibitors cause dopaminergic side-effects (nausea, vomiting, and dyskinesias) along with diarrhoea and yellow discolouration of urine.

Other medical management and responses

Amantidine and anticholinergic drugs have limited symptomatic effect and may cause significant adverse effects such as confusion and hallucinations, especially in older patients and those with dementia. These drugs are no longer recommended for routine use in PD in Norway. Of notice, placebo-associated responses could lead to an initial 20% improvement in motor scores.[14] This improvement is hypothesized to be mediated through mesolimbic dopaminergic pathways.[110, 111]

Surgical treatment

Functional neurosurgery may be appropriate for a small number of PD patients with severe motor complications (motor fluctuations and/or dyskinesias) or disabling tremor that cannot be managed by medical therapy. DBS has now largely replaced lesional therapy because the effect of electrical stimulation is adjustable and reversible. During the last decade, DBS of the STN has become the gold standard neurosurgical treatment for motor complications in PD. Younger age, shorter disease duration, and a positive response to levodopa (levodopa challenge response) predict a favourable outcome.[112] Patients should not have severe cognitive, behavioural, or psychiatric problems such as depression, or other medical conditions that would increase the risk of surgery. Multiple studies have reported substantial long-term benefits of DBS STN regarding motor function and motor complications.[113, 114] However, progression of PD and worsening of axial symptoms as well as development of dementia did occur.[113] Recent reports suggest that DBS of the pedunculopontine nucleus (PPN) could improve drug-resistant gait freezing and postural instability in advanced PD, especially when combined with DBS of the STN.[115] However, further studies in more patients are needed to fully explore the benefit of PPN as a new target for STN.

2.8 Prognosis and complications

Although PD is still an incurable chronic progressive disease, quality of life and functional capacity is usually substantially improved in the first period after symptomatic therapy is introduced. Some studies in early PD suggest that on average five years after initiation of drug therapy, severity of motor impairment and disability return to pre-treatment levels.[116, 117] With the progression of the disease higher doses of dopaminergic treatment are necessary to maintain motor function. Eventually, many patients develop long-term motor and psychiatric side-effects. The Sydney Multicentre Study of PD[118] recently found no differences in the Hoehn and Yahr staging in their patients after 15 years of treatment when compared to data from the classic pre-levodopa study by Hoehn and Yahr.[119] The authors concluded that modern treatment does not lead to significant long-term benefit in patients with PD. Noteworthy, there is remarkable interindividual variation in the progression of PD. Prospective longitudinal studies suggest that especially higher age at motor onset,[120, 121] and to a lesser degree a postural instability and gait disorder (PIGD) motor subtype, lack of rest tremor, more severe functional impairment, and cognitive dysfunction [122-124] are risk factors for more severe functional decline in PD. In contrast, cigarette smoking, coffe and tea consumption, and pesticide exposure appear not to impact the rate of motor progression in patients with PD.[125-127]

Progressive disease, postural instability, and freezing are common risk factors for falls and hip fractures in patients with PD.[128, 129] Prominent hallucinations seems largely responsible for nursing home placement, [130, 131] and the risk for dementia is up to 6 times higher in patients with PD than in healthy people.[78] Despite modern treatment, life expectancy is still decreased in PD relative to control subjects. In a recent comprehensive review, mortality hazard ratios ranged between 1.5 and 2.7 in several European countries, Australia and the USA.[11] Dementia seems to be the highest risk factor for shortened life.[132] The cause of death in patients with PD are often related to immobility and fatal infections.[133]

3. Apathy

3.1 Historical perspective

The word apathy stems from the Greek *apatheia* derived from *apathes,* "*a*" (without) + "*pathos*" (passion), and was originally coined by the Greek Stoic philosophers more than 2000 years ago to refer to the condition of being free from emotions and passions. The Stoics considered *apatheia* the only human lifestyle leading to a virtuous and happy life, whereas states of extreme emotions - such as fear, pain, desire and pleasure - would incline humans towards irrational behaviours.[134] The great humanists of the Renaissance used the term apathy in its ancient meaning, but by the early 19th century the term apathy was used to describe loss of normal psychological function, for example "apathie affective" and "apathie intellectuelle."[134] During the last 20 years, the work of Robert Marin has served as a major stimulus to research interest in apathy. Marin proposed a specific set of diagnostic criteria and validated ad hoc scales,[135, 136] which are still by many considered gold standard.

3.2 Challenges in defining and assessing apathy

3.2.1 Different concepts of apathy

In the early 1990s, Marin proposed to define apathy as a primary lack of motivation that manifests itself as reduced goal-directed behaviour (e.g. lack of initiative, productivity and effort), reduced goal-directed cognition (e.g. lack of intellectual interest and curiosity), and reduced emotional concomitants of goal-directed behaviour (e.g. flattened affect and lack of emotional response to positive or negative events).[135] He defined motivation as the direction, intensity and persistence of goal-directed activity. Marin also considered apathy to be a distinct neuropsychiatric

syndrome if the primary lack of motivation was not attributable to diminished level of consciousness, cognitive impairment or emotional distress.

Because apathy frequently occurs in patients with dementia or depression, Sergio Starkstein proposed to broaden Marin's criteria to include patients with apathy in the context of depression, dementia, or other neurodegenerative diseases.[137] Recently, Starkstein and Leentjens proposed to include a time criterion to ascertain the persisting nature of apathy, i.e. the symptoms had to be present for at least 4 weeks during most of the day.[134]

Donald Stuss and colleagues argued that the definition and assessment of motivation is problematic, and suggested to define apathy as an absence of responsiveness to stimuli as demonstrated by a lack of self-initiated action. They considered employing syndromal criteria for apathy to be potentially limiting, and suggested instead to divide apathy into separable types or states that differ in both functional disturbances underlying the clinical presentation and neural substrates of involvement.[138]

Recently, Levy and Dubois criticized lack of motivation to be an obscure psychological concept, and suggested to define apathy as an observable behavioural syndrome consisting of a quantitative reduction of voluntary (or goal-directed) behaviours. They considered apathy to be related to disruption of emotional-affective, cognitive, and auto-activation processes in the prefrontal cortex-basal ganglia circuits.[139]

Modern conceptualizations of apathy include various dimensions of apathy (Table 3.1). Although disagreements as to whether disorders of motivation[135] or of initiative

and self-generated voluntary and purposeful behaviour [138, 139] are core features, most conceptualizations consider apathy a neuropsychiatric syndrome which includes most of these dimensions.

Table 3.1 Concepts of apathy

Author	Concept
Marin et al.[136]	Disorder of motivation with cognitive, sensory, motor and affective subtypes
Cummings et al.[140]	Disorder of interest or motivation; including lack of emotion, lack of initiation, lack of enthusiasm
Stuss et al.[138]	Disorder of initiative, manifesting lack of self-initiated action, which may be affective, behavioural or cognitive and includes ''social apathy'' – a disorder of sense of self and of social awareness
Robert et al.[141]	Disorder of motivation with emotional blunting, lack of initiative, lack of interest
Sockeel et al.[142]	Disorder of intellectual curiosity, action initiation, emotion and self-awareness
Levy and Dubois[139]	Disorder of voluntary and goal-directed behaviours; with three subtypes of disrupted ''signal'' processing: – emotional-affective, cognitive and auto-activation
Starkstein and Leentjens[134]	Disorder of motivation with diminished goal-directed behaviour and cognition

From Robert et al.[143]

3.2.2 Apathy is not depression

Apathy has traditionally been viewed as a feature of depression due to overlapping symptoms such as diminished interest, psychomotor retardation and concentration difficulties. In fact, the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV)[144] allows the diagnosis of primary major depression in the absence of depressed mood provided that markedly diminished interest or pleasure is

accompanied by four other common symptoms. The category of minor depression has recently been shown to include a relatively large proportion of individuals with apathy rather than a "true" affective disorder in PD patients, indicating that minor depression should be diagnosed using the DSM-IV criteria only when sad mood is present.[145] While apathetic patients are emotionally indifferent, dysphoric feelings (sadness, guilt, and pessimistic thoughts) are typical for depression. Thus, depressed mood is a key distinguishing feature between apathy and depression. Despite the overlapping phenomenology between these two syndromes, several studies have shown that apathy in various diagnostic groups can be distinguished from depression in the sense that some patients have apathy but not depression, and vice versa.[146] The potential neuroanatomical differences underlying these two distinct syndromes have yet to be determined. Interestingly, in a volumetric MRI-based study of the prefrontal cortex in 84 elderly subjects with or without major depression, the depressed group had smaller orbitofrontal gray matter volumes compared to the age-matched normal comparison group, whereas apathy was associated with decreased gray matter volume in the right anterior cingulate gyrus.[147]

3.2.3 Relation to cognitive decline and dementia

Mental slowing and poor concentration may be part of both apathy and cognitive decline or dementia. In fact, several studies have shown that apathy is associated with executive dysfunction and dementia in various diagnostic groups.[146] However, whether cognitive deficits are necessary to produce apathy, or if apathy causes cognitive impairment, has not been specifically examined. As is the case with depression,[148] some would argue that apathy should be included as part of a dysexecutive syndrome.[149]

3.3 Diagnostic criteria

Recently, a task force including members of the Association Française de Psychiatrie Biologique, the European Psychiatric Association (EPA), the European Alzheimer's Disease Consortium and experts from Europe, Australia and North America has formulated new criteria regarding apathy in dementia and neuropsychiatry (Table 3.2).

Table 3.2 Apathy proposed criteria

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 patient's previous level of functioning and which is not consistent with his age or culture. These changes in motivation may be reported by the patient himself or by the observations of others.

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

Domain B1 : Loss of, or diminished, goal-directed behaviour as evidenced by at least one of the following:

- Loss of self-initiated behaviour (for example: starting conversation, doing basic tasks of day-to-day living, seeking social activities, communicating choices)
- Loss of environment-stimulated behaviour (for example: responding to conversation, participating in social activities)

Domain B2 : Loss of, or diminished, goal-directed cognitive activity as evidenced by at least one of the following:

- Loss of spontaneous ideas and curiosity for routine and new events (i.e., challenging tasks, recent news, social opportunities, personal/family and social affairs).
- Loss of environment-stimulated ideas and curiosity for routine and new events (i.e., in the persons residence, neighbourhood or community)

Domain B3 : Loss of, or diminished, emotion as evidenced by at least one of the following:

- Loss of spontaneous emotion, observed or self-reported (for example, subjective feeling of weak or absent emotions, or observation by others of a blunted affect)
- Loss of emotional responsiveness to positive or negative stimuli or events (for example, 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).

From Robert et al.[143]

The task force chaired by Philippe Robert discussed an advanced draft at a consensus meeting held during the EPA conference in April 7th 2008, and a final agreement

concerning operational definitions and hierarchy of the criteria was reached.[143] This is the first formal consensus on diagnostic criteria for apathy in neuropsychiatric disorders. According to this consensus report, apathy is defined as a disorder of motivation that persists over time with the following requirements: 1)The core feature of apathy, diminished motivation, must be present for at least four weeks; 2) two of the three dimensions of apathy (reduced goal-directed behaviour, cognitive activity, and emotions) must be present; 3) functional impairment attributable to apathy should be identifiable; and 4) exclusion criteria regarding symptoms and states that mimic apathy are specified. Importantly, the task force has attempted to formulate the criteria in such a way that they may be applied to disorders beyond dementia and neuropsychiatric disorders.

3.4 Differential diagnosis

In clinical practice and research, several neuropsychiatric syndrome definitions that share one or more symptoms with the apathy syndrome, are still regularly used. The nosological position of these syndromes in relation to the concept of apathy, however, still remains uncertain.[134] In addition to depression and dementia, as previously mentioned, these syndromes include abulia, akinetic syndromes, despair and demoralisation.

Abulia

The term abulia, stemming from the Greek "a" (without) + "boule" (will), has been defined as a lack of will or motivation or an inability to decide.[150] Marin reserved this diagnosis for "patients who are awake but otherwise severely impaired in their ability to communicate and to initiate and self-regulate purposeful behavior", and considered abulia to be a more severe form of apathy.[150] Bhatia and Marsden defined abulia as "apathy with loss of initiative and of spontaneous thought and emotional responses",

and described this syndrome in relation to basal ganglia lesions.[151] More recently, a consensus report by British neurologists and psychiatrists included eight typical features of abulia,[152] and acknowledged that in clinical practice the terms apathy and abulia were often used interchangeably.

Akinetic syndromes

Several akinetic syndromes have been described.[134] Starkstein reported a severe loss of drive and motivation, known as *psychic akinesia*, in patients with bilateral ischaemic lesions to the globus pallidus.[153] These patients display no goal-directed activity, but may perform most of their daily activity if they are strongly stimulated. Laplane and Dubois described a similar basal ganglia related syndrome labelled *auto-activation deficit*,[154] and defined this condition as "a deficit in spontaneous activation of mental processing, observed in behavioural, cognitve, or affective domains, which can be totally reversed by external stimulation that activates normal patterns of response". Starkstein argued that it is almost impossible to separate abulia from the auto-activation deficit because the concept of these two syndromes are poorly defined.[134] Habib used the term *athymhormia*, from the Greek "a" (without) + "thumos" (mood) + "horme" (impulse), to define a syndrome characterized by "a striking reduction in spontaneous motion and speech, with subadjacent mental emptiness and, maybe the crucial point, an apperent flatness or at least poor expressiveness of affect."[155] He further stressed that patients with athymhormia are not depressed, and suggested that this syndrome was caused by disruption at the emotional-limbic level. Cummings have described patients with *akinetic mutism* as profoundly apathetic: they typically have their eyes open, do not speak spontaneously, answer questions in monosyllables if at all, move little, are incontinent, eat and drink only if fed, display no emotion even when experiencing pain and are indifferent to their dire circumstances.[156] Recently, Marin and Wilkoscz defined akinetic mutism as total absence of spontaneous behaviour and speech occurring in the presence of preserved visual tracking.[157] They also considered

apathy, abulia and akinetic mutism as disorders of motivation that lie one a continuum, with apathy the least severe and akinetic mutism the most severe manifestation of diminished motivation.

Despair and demoralisation

These psychological states occur primarily in normal individuals in response to the experience of overwhelming stress or severe changes in their social environment.[150, 158] Although despair and demoralisation share with apathy the symptom of loss of motivation, apathy denotes a lack of concern or emotional distress, whereas despair and demoralisation are considered dysphoric, unpleasant states characterized by pessimistic or hopeless orientation toward the future.[150, 158]

3.5 Common conditions associated with apathy

Based on clinical experience and scientific research, apathy and more severe disorders of diminished motivation have been reported in numerous medical, neurological and psychiatric disorders, as well as secondary to drug abuse and institutionalization (Table 3.3). There is no evidence that damage to any one structure, neural pathway or region of the brain is uniquely responsible for producing apathy.[159] Nevertheless, damage or dysfunction or abnormal connectivity within specific frontal-subcortical circuits leads to an increased probability of the occurrence of apathy,[159, 160] see next section.

Table 3.3 Conditions associated with apathy, abulia, and akinetic mutism

Neurological disorders*	Medical disorders
Frontal lobe	Apathetic hyperthyroidism
Frontotemporal dementia	Hypothyroidism
Anterior cerebral artery infarction	Pseudohypoparathyroidism
Tumor	Lyme disease
Hydrocephalus	Chronic fatigue syndrome
Trauma	Testosterone deficiency
Right hemisphere	Debilitating medical conditions, for example,
Right middle cerebral artery infarction	malignancy, congestive heart failure, renal or heart
Cerebral white matter	failure
Ischemic white matter disease	*Drug induced*
Multiple sclerosis	Neuroleptics, especially "typical" neuroleptics
Binswanger's encephalopathy	Selective serotonin reuptake inhibitors
HIV	Marijuana dependence
Basal ganglia	Amphetamine or cocaine withdrawal
Parkinson's disease	*Socioenvironmental (lack of reward, loss of*
Huntington's disease	*incentive, lack of perceived control)*
Progressive supranuclear palsy	Role change
Carbon monoxide poisoning	Institutionalism
Diencephalon	
Degeneration or infarction of thalamus	
Wernicke-Korsakoff disease	*Akinetic mutism results from bilateral dysfunction of
Amygdala	the cortico-striatal-pallidal-thalamic circuit, which
Kluver-Bucy syndrome	consists of anterior cingulum, nucleus accumbens,
Multifocal disease	ventral pallidum, and mediodorsal nucleus of
Alzheimer's disease (apathy may be	thalamus. When improving or less severe, such cases
mediated by damage to the	present as abulia or apathy. Etiology may be vascular,
prefrontal cortex, the parietal	trauma, tumor, degeneration, or toxin (eg, carbon
cortex, and the amygdala)	monoxide poisoning).

From Marin et al.[157]

3.6 Neurobiology of apathy

Present knowledge about the neurobiology of apathy derives from an understanding of the neural basis of motivation.[161] Some of this research has been carried out in humans, but the majority of knowledge about the connectivity, neurochemistry, and physiology of the neural systems involved in motivated behaviour is derived from experimental studies in animals.[160-162]

3.6.1 Neurocircuitry

Kalivas and colleagues have presented an elegant model describing four distinct neural subcircuits that are believed to provide the neural basis of motivation.[160, 162, 163]

Subcircuit number 1

Components: the ventral tegmental area (VTA), nucleus accumbens (NA), and the ventral pallidum (VP). Function: provides a "motivational working memory" that allows the prioritization of motivational valencies across the temporal domain.

Subcircuit number 2

Components: the VP, medial dorsal nucleus of the thalamus (MD), prefrontal cortex (PFC), NA, and the VTA. Function: provides the cognitive colouring of motivation.

Subcircuit number 3

Components: the VP, PPN, and the VTA. Function: integration of arousal into motivation.

Subcicuit number 4

Components: the VTA, amygdala, and the NA. Function: integration of "reward memory" (ie, incentive value) into motivational response.

These four subcircuits constitute the motivational circuitry (Figure 3.1) responsible for "translating motivation into action, receiving and integrating information about the organism's past and present, and transforming it to cognitive, autonomic, and motor outcomes that hopefully will lead to goal attainment."[160]

Figure 3.1 The motivational circuitry
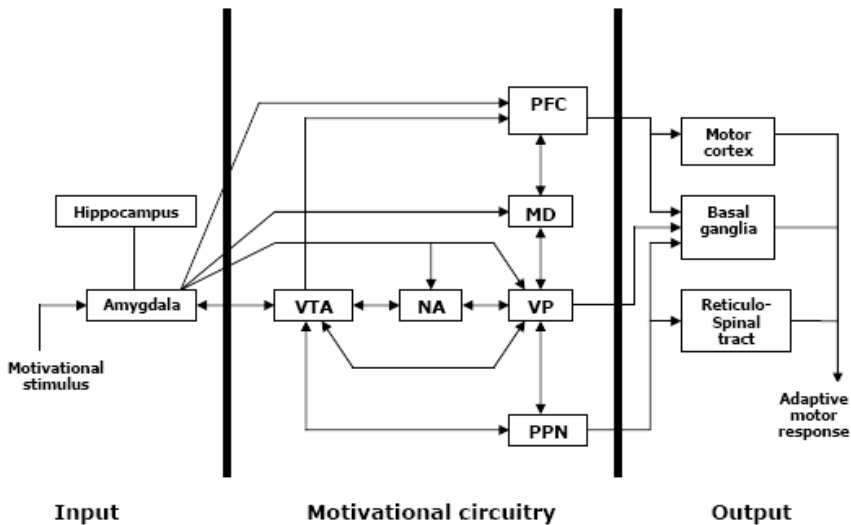
The motivational circuitry responsible for translating motivationally relevant environmental stimuli into adaptive responses. The circuit lies partly in classic limbic structures, such as the amygdala and hippocampus, and transmits to classic motor output systems, such as the motor cortex, basal ganglia, and the reticulospinal tract. PFC = prefrontal cortex. MD = mediodorsal thalamus. VTA = ventral tegmental area. NA = nucleus accumbens. VP = ventral pallidum. PPN = pedunculopontine motor region. Adapted from Kalivas et al.[162]

Limbic input from amygdala and hippocampus modifies information in the motivational circuitry on the basis of the current environment.[157] Experimental studies have also shown that the anterior cingulate (AC) plays an essential role in motivational aspects of decision making.[157] The AC, NA, VP, and MD comprise an

"affective" striato-thalamo-cortical circuit (Figure 3.2) thought to mediate motivation.[161, 162]

Figure 3.2 Striato-thalamo-cortical circuits and their interactions with limbic structures
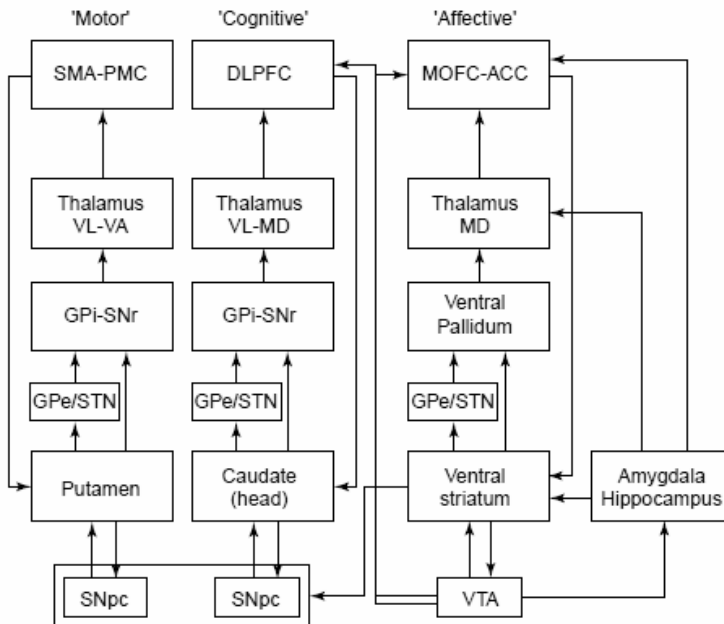
The amygdala and other limbic structures involved with motivational and emotional processes, provide input via the ventral striatum, thalamus and cortex. These offer many direct and indirect opportunities for the emotional and motivational processses to influence the activity of other circuits including those concerned with cognition and motor function. Abbreviations: ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; Pe, globus pallidus external section; GPi, globus pallidus internal segment; MD, mediodorsal; MOFC, medial orbitofrontal cortex; PMC, premotor cortex; SMA, supplementary motor area; SNpc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus; VA, ventroanterior; VL, ventrolateral; VM, ventromedial; VTA, ventral tegmental area. From Pluck and Brown.[159]

Disruption of this circuit - also known as the anterior cingulate circuit - produces akinetic mutism, abulia, or apathy depending on the structure damaged and the severity of the dysfunction.[164] Cummings has described an anterior cingulate syndrome [156] where patients are profoundly apathetic, i.e. present with symptoms of akinetic mutism caused by bilateral anterior cingulate injury. In contrast, unilateral lesions produce transient akinetic mutism.

The dorsolateral prefrontal circuit, which is part of the nonmotor frontal-subcortical circuitry (Figure 3.3), subserves executive function and is responsible for integrating motivationally relevant information into cognitive and behavioural responses.[165] A strong correlation between apathy and executive dysfunction has been reported across various diagnostic groups.[146, 166] Finally, apathy may present as an accompanying symptom associated with personality changes caused by lesions of the lateral orbitofrontal circuit.[156]

The current state of the motivational circuitry determines the behavioural response via projections to motor cortex, basal ganglia, and brain stem (Figure 3.1). Traditionally, motor output systems operate via motor cortex and basal ganglia. However, recent research has suggested that motivational output has access to autonomic and locomotor centers of the brain stem via the PPN,[167] which in turn sends projections to the reticulospinal tract. Stimulation of the PPN results in autonomic behaviours such as fight or flight and stereotypic rhythmic displays.[160]

Figure 3.3 The nonmotor frontal-subcortical circuitry
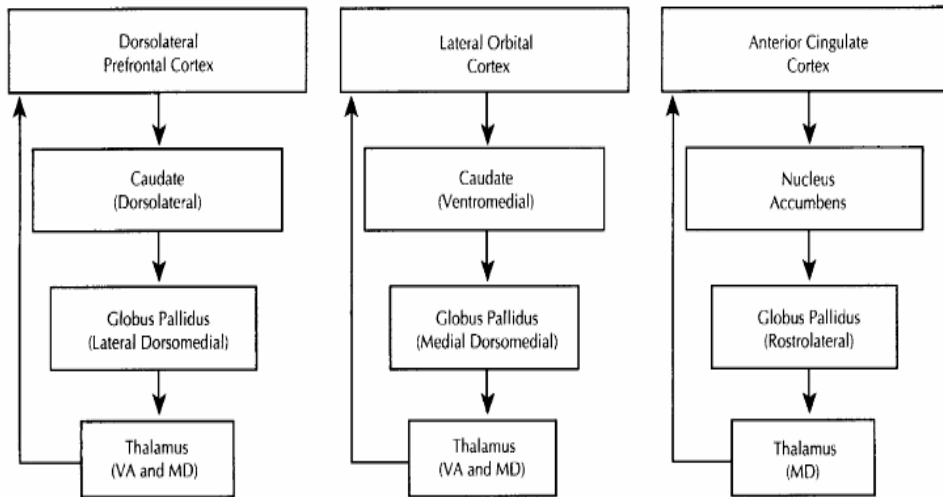
Organization of the three frontal-subcortical circuits in which lesions produce alterations of cognition and emotion. VA indicates ventral anterior; MD, medial dorsal. The indirect circuits and connections of the substantia nigra and the subthalamic nucleus are not shown. From Cummings.[156]

3.6.2 Neurochemistry

The chemical coding within the motivational circuitry is complex and not fully established. However, knowledge of the major elements is helpful to an understanding of clinical disorders of motivation.

The substantia nigra is the principal source of striatal dopamine and the VTA is the major source of dopamine within the mesocortical and mesolimbic systems.[168, 169] Modulation of dopamine activity regulates changes in arousal, motivation, sensorimotor integration, and locomotor response.[160] The dorsal striatum (putamen and caudate nucleus) is less sensitive to dopamine than the ventral striatum (primarily nucleus accumbens) and is involved in sensorimotor integration and the generation of

stereotypic behaviours.[160] The ventral striatum, however, is essential in mediating the communication between neural systems involved in motivation, emotion, and locomotor response that is necessary for generation of complex flexible behaviours.[160] Subcortical dopamine activity in the NA and VTA is partly regulated via excitatory amino acids from the medial PFC, amygdala and hippocampus (Figure 3.4).[160, 170] Dysfunction within these structures appears to decrease the threshold necessary for dopamine activation under stressful conditions, leading to excessive arousal and increased spontaneous motor behaviour.[160]

Figure 3.4 Neural circuitry mediating the activiation of

goal-directed behaviour
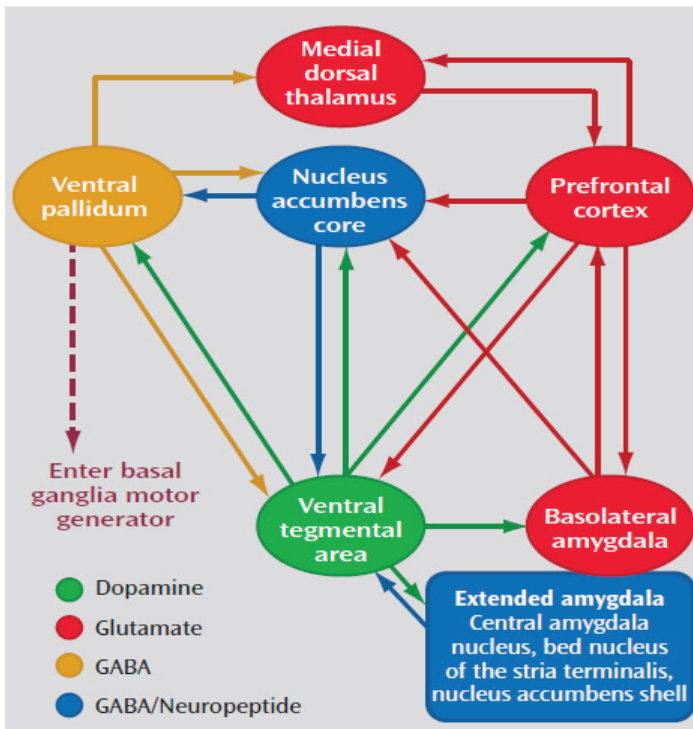
From Kalivas and Volkow.[170]

The mesencephalic locomotor region (primarily the nucleus basalis of Meynert and the PPN) appears to modulate the motivational circuitry via cholinergic projections to the limbic system, extrapyramidal system, thalamus, tectum (dorsal portion of the midbrain composed of the paired superior and inferior colliculi), and cortical regions.[171] These ascending projections regulate dopamine efflux from the nigrostriatal neurons, and thereby influence motor behaviour.[171] Therapeutic benefit of cholinesterase inhibitors for treating apathy in demented patients supports the modulatory effect of cholinergic systems on motivated behaviour.[163]

The modulatory role of serotonin (5-HT) on motivation is extremely complex because receptor subclasses vary significantly with respect to their effect on cholinergic and dopamine activity.[172] Serotoninergic fibers originating in the raphe nuclei of the midbrain project to almost all brain areas, including mesolimbic structures and cortex.[173] It has been suggested that serotonin may increase motivation via 5-HT3 receptors that enhance mesolimbic dopamine activity in the VTA and NA.[163] In contrast, selective serotonin reuptake inhibitors (SSRIs) have been reported to induce apathy in different patient groups.[174, 175] Long-term SSRI therapy causes prolonged and excessive serotonin in the synapse and is proposed to decrease dopamine transmission in the frontal lobe,[176] which may eventually lead to diminished motivation and apathy.[175]

3.7 Evaluation and treatment of apathy

Evaluation

During routine office visits, primary care physicians and neurologists are less likely to recognize apathy than depression or cognitive impairment. There are several possible explanations for this.[177] First, apathetic patients may be unaware of their own behavioural changes, i.e. lack insight, and are therefore unlikely to be motivated to

report this problem to the physician. Second, disorders of emotion (positive symptoms) are generally more emphasized by physicians than disorders of motivation (negative symptoms). Finally, recognition of behavioural symptoms is affected by the time constraint of the medical office visit and the fact that non-psychiatric physicians are preoccupied with primary medical problems. Despite this relative lack of attention, apathy is increasingly recognized as a common behavioural syndrome in neurological and psychiatric disorders.[134] Because apathy has been associated with a number of adverse outcomes – including reduced functional level, poor illness outcome, diminshed insight into one's own behavioural deficits, caregiver distress and chronicity – and is potentially treatable,[146] it is important that physicians understand how to diagnose, treat, and measure the severity of diminshed motivation.

The evaluation of apathy should include a detailed history (information from the medical record, personell involved in the patient's care, the medication record, family and if possible the patient), clinical examination and neuroimaging to determine the presence of potential causes, such as medications (e.g. neuroleptics, SSRIs, beta-blockers) or underlying medical or neurological disorders (e.g. thyroid dysfunction, testosterone deficiency, cerebrovascular disorders, chronic subdural hematoma, cerebral tumor, parkinsonism, hydrocephalus, delirium, and malaise of chronic illness).[178] It is important to include a general mental status examination to reveal possible cognitive deficits, which usually require more detailed cognitive testing (i.e. neuropsychological evaluation) to determine the type and severity of such. Assessment of emotion is especially important to diagnose an underlying depressive disorder. Finally, laboratory examination should be undertaken to confirm suspicion of other conditions based on the history and clinical examination (blood and cerebrovascular fluid analysis, urinanalysis/urine toxicology). If apathy is present, validated apathy rating scales [179] should be used to measure the severity of symptoms and to monitor responses to treatment over time.

Treatment

Identification of a reversible cause of diminished motivation (e.g. severe hypothyroidism, Lyme disease, high-potency typical neuroleptics) is important because reversing or arresting the underlying condition may prove sufficient to eliminate or significantly reduce the severity of apathetic symptoms.

If the underlying cause of diminshed motivation cannot be fully reversed (e.g. neurodegenerative diseases, head trauma), pharmacotherapy should be considered. Although little empirical research has been conducted on potential pharmacologic treatments for apathy,[180] agents that potentiate dopamine release and/or delay dopamine reuptake in the CNS are considered the most effective treatment for apathy.[178, 180] Dopamine agonists, methylphenidate, and atypical antipsychotics have all been been demonstrated to reduce apathy in several patient populations.[180] In addition, acetylcholinesterase inhibitors have been reported to reduce apathy in patients with dementia and subjects with traumativ brain injury.[180] Patients with mixed apathy and depression need special attention. SSRIs have been associated with apathy in some patients with depression,[174, 175] and frontal lobe dysfunction due to alteration of serotonin has been suggested as a possible underlying mechanism. In these patients, reducing SSRI-dosage or switching to an selective noradrenaline reuptake inhibitor (SNRI) should be considered.[161, 181] When apathy is a residual feature following successful relief of dysphoric and vegetative symptoms of major depression, stimulant therapy with dopamine agonists or methyphenidate should be initiated.[177, 182] Multimodal integration of socioenvironmental and psychological therapies may be benefical to some patients with apathy, and is described in detail elsewhere.[178, 180] It is especially important to educate caregivers about the symptoms of apathy because family members often mistakenly interpret this behaviour as a lack of caring and withdrawal from them.[183] Finally, ethical considerations regarding management of patients with apathy should always be addressed.[184]

4. Apathy in Parkinson's disease

4.1 Apathy rating scales in Parkinson's disease

The Movement Disorder Society (MDS) recently commissioned a task force to identify and assess the clinimetric properties of scales that have either been validated or used in patients with PD.[179] Four rating scales specifically designed to assess apathy were identified. These include the Apathy Evaluation Scale (AES),[136] the Apathy Scale (AS),[185] the Apathy Inventory (AI),[141] and the Lille Apathy Rating Scale (LARS).[142] In addition, item 4 (motivation/initiative) of the Unified Parkinson's Disease Rating Scale (UPDRS)[186] and item 7 (apathy) of the Neuropsychiatric Inventory (NPI)[140] were included because of its wide use in PD. The scales and items were classified according to the total number of required criteria (Table 4.1).

Table 4.1 Classification of apathy scales used in Parkinson's disease

Scale	Used in PD	Used in PD beyond original developers	Successful clinimetric testing in PD	Classification
AES	X	X	0	Suggested
AS	X	X	X	Recommended
AI	X	0	0	Listed
LARS	X	0	X	Suggested
UPDRS item 4	X	X	X	Recommended*
NPI section 7	X	X	0	Suggested

* As a single item construct, item 4 of the UPDRS cannot be considered a "scale" and is only advised for crude screening purposes. Adapted from Leentjens et al.[179]

The AES was developed by Marin and colleagues to assess behavioural, cognitive, and emotional domains of apathy. It consists of 18 items that are scored on a four-point Likert scale (range 1-4), with higher scores indicating more severe apathy. This scale has patient-rated, informant-rated, and clinician-rated versions. The AES has shown good internal consistency in PD patients, but information on the validity is not available.

The AS is an abridged and modified version of AES that was specifically designed for patients with PD. It consists of 14 items that are phrased as questions to the patient, and the answers are scored on a four-point Likert scale (range 0-3). A caregiver rated version is also available. The AS has shown good face validity, internal consistency, and interrater and test-retest reliability in PD patients. In a sample of 12 PD patients, this scale showed acceptable sensitivity and 100% specificity when validated against clinical judgement of apathy.

The AI was designed for global assessment of apathy, and consists of three items regarding change in certain behaviours (i.e. emotional blunting, lack of initiative, and loss of interest). In case of a positive answer, the change is estimated on a 12-point Likert scale. Both patient-rated and informant-based versions exist. If the response to the item is yes, two additional questions estimate the frequency and severity of the symptom. This scale showed good internal consistency, interrater and test-retest reliability in 12 PD patients, but needs better validation to be recommended for use in PD.

The Lille Apathy Rating Scale (LARS) was recently developed and designed to specifically assess apathy in PD patients with or without dementia. It consists of 33 items divided into nine domains, and is administered to the patient or an informant as

a structured interview. The first three questions are scored on a five-point Likert scale (range 0-4), whereas the remaining items are answered yes or no. The total score ranges between -36 and +36 points, with positive scores indicating more severe apathy. This scale showed good internal consistency, adequate interrater and test-retest reliability, and good sensitivity and specificity when validated against clinical judgement of apathy.

Item 4 (motivation/initiative) of the UPDRS is scored on a five-point Likert scale (range 0-4), with increasing scores indicating more severe loss of motivation and/or initiative. This item does not include emotional concomitants of apathy. The psychometric properties of this item showed moderate interrater reliability, fair test-retest reliability, and acceptable sensitivity and specificity when a cutoff ≥ 2 was applied with regard to the diagnosis of apathy based on proposed diagnostic criteria.[187]

The NPI is an informant-based structured interview developed to assess different behavioural disturbances, including apathy, in patients with dementia and other neurodegenerative disorders. Item 7 includes four screening questions regarding core symptoms of apathy. In case of a positive answer, eight additional questions regarding different domains of apathy and the total frequency and severity of these symptoms are assessed. This item has not been specifically validated in PD patients, but has shown good interrater agreement in a small sample of PD patients from the community.[188]

The MDS task force stressed that the validity of apathy scales in PD is limited because of the lack of consensus on diagnostic criteria.[179] Several unsolved issues that require further research were addressed, including confounding influence of

depressive symptomatology and cognitive decline on the performance of apathy rating scales, the reliability of answers in patient-rated verus informant-rated instruments, and assessment of apathy in different phases of motor fluctuations (*on* versus *off* states).

4.2 Epidemiology

Several studies of apathy in PD have been reported, with frequency rates ranging from 16.5% to 70%, depending upon the instruments used for assessment and by whom, different cut-off scores, and the selection of the samples examined (Table 6.2). In addition, frequency rates are affected by overlapping symptoms with mood disorders and variable degree of cognitive impairment in the study population. Most samples were not community-based, but rather consisted of hospital-based samples recruited from outpatient neurological clinics, implying a considerable risk of selection bias.

Table 4.2 Frequency of apathy in Parkinson's disease

Study	Sample	N	Apathy	Instrument (cut-off)	Depression	Dementia	Mean MMSE score	Control group
Starkstein [185]	Hospital	50	42%	AS (≥ 14)	56%	None	25.4 - 28.7	No
Levy [189]	Hospital	40	32.5%	NPI (≥ 1)	55%	Unknown	27.9	Other degenerative brain diseases
Aarsland [188]	Community	139	16.5%	NPI (≥ 1)	38%	36 – 42%	25.2	No
Isella [190]	Hospital	30	70% (43%)*	AS (>14) (AS >16)*	60%	None (excluded)	Unknown	Healthy
Pluck [191]	Hospital	45	38%	AES (>38)	43%	7%	27.8	Osteoarthritis
Kirsch-Darrow [192]	Hospital	80	51%	AS (≥14)	26%	Unknown	Unknown	Dystonia
Dujardin [193]	Hospital	159	32%	LARS (≥ -16)	25%	24.5%	Unknown	Healthy
Aarsland [194]	International multicentre	537	54% (38%)*	NPI (≥ 1) (NPI ≥ 4)*	58% (21%)*	100%	19.3	No
Kulisevsky [195]	Hospital	1351	48% (16%)*	NPI (≥ 1) (NPI ≥ 4)*	69% (30%)*	None (excluded)	Unknown	No

MMSE = Mini-Mental State Examination; AS = Apathy Scale (self-rated); AES = Apathy Evaluation Scale (clinician-rated); NPI = Neuropsychiatric Inventory (apathy item); LARS = Lille Apathy Rating Scale (clinician-rated); UPDRSI4 = Unified Parkinson's Disease rating Scale item 4 (motivation/initiative). *After adjusting cut-off score.

4.3 Relation to demographic, clinical and biochemical characteristics

Although apathy is frequently reported in PD patients with depression,[185, 188] several studies have shown that apathy may occur in the absence of depression.[190, 192] Kirsch-Darrow and colleagues evaluated 80 subjects with PD and 20 subjects with dystonia, and found that half of the PD group had apathy compared with 20% of the dystonia group.[192] Interestingly, almost 30% in the PD group in contrast to none in the dystonia group had apathy in the absence of depression. The authors concluded that

apathy is a core feature of PD that can present independently of depression. However, the relationship between apathy and cognition was not examined. Other studies have demonstrated that apathy is associated with cognitive impairment in PD, especially executive dysfunction.[185, 188, 191, 193, 196] Starkstein and colleagues reported that PD patients with apathy showed more deficits in tasks of verbal memory and time-dependent tasks,[185] whereas others have shown that apathy is mainly determined by decreased global cognition.[193] Pluck and Brown found significantly higher levels of apathy in patients with PD compared to equally disabled osteoarthritic patients, suggesting that apathy in PD is more likely a consequence of neurodegeneration than psychological reaction or adaption to disability.[191] Morover, apathy has been rated one of the most distressing behavioural features by caregivers of demented patients with PD.[194] By contrast, age, education level, motor severity, levodopa dose, and PD duration are less likely to be associated with apathy. Although testosterone deficiency has been linked to apathy in male patients with PD,[197] the role of testosterone in the pathophysiology of apathy in these patients is still controversial.[198]

4.4 The biological basis of apathy in Parkinson's disease

The etiopathogenesis of apathy in PD is not clear. Mayeux and colleagues found a correlation between the cerebrospinal fluid (CSF) concentration of 3-methoxy-4-hydroxyphenylglycol (MHPG), the major metabolite of noradrenaline, and cognitive measures of bradyphrenia,[199] which suggests that bradyphrenia (which is similar to the concept of apathy) in PD may be related to dysfunction of catecholaminergic pathways and the locus ceruleus.[185] A positive influence of levodopa treatment on self-reported motivation in PD patients with motor fluctuations has been described,[200] indicating that apathy in PD is at least partly a dopamine-dependent syndrome. The cholinergic systems may also have an important modulatory effect upon motivation in PD patients, based on the therapeutic benefit of cholinesterase inhibitors for treating apathetic behaviour in some PD patients with cognitive impairment and dementia.[201-203] No MRI changes have been shown to correlate with apathy in PD

patients,[190] but in a recent study apathy was reported to be inversely correlated with a marker of both dopamine and noradrenaline transporter ($[^{11}C]$RTI-32 binding) in the ventral striatum (Remy 2005).[204] Together, these data show that the neurobiology of apathy in PD is complex and probably involves several different neurotransmitter systems which are involved in the signalling between frontal and subcortical areas.

4.5 Treatment strategies

General strategies

The first step is to address other differential diagnosis and exclude reversible medical, pharmacological, or psychosocial causes of apathy.[182] Because neuroleptic drugs and SSRIs may cause apathy,[163] clinicians should consider whether these drugs can be eliminated or given in lower doses. It is important to know that sensory deprivation caused by hearing and sight loss, as well as solitary life with low stimulus environment, are likely to render the patient apathetic.[178] Apathy have a significant negative impact on family functioning because family members often mistakenly interpret this behaviour as deliberate or insensitive. Non-pharmacological interventions include educating patients and caregivers about the symptoms of apathy, limiting patient's responsibility for medication administration, simplification of tasks in patients with associated executive dysfunction, occupational therapy to explore deficits and maximize functioning, and establish structured environments and day programs to maintain a satisfactory activity level.[178, 183]

Pharmacologic treatment

The clinical management of apathy is still in its infancy.[177] Pharmacologic treatment of apathy regardless of the underlying etiology remains anectdotal and have only been tested in open trials or reported as case studies. In general, depressed patients with prominent apathetic features may benefit from a more stimulating

antidepressant, such as bupropion.[182, 205] In contrast, SSRIs do not seem to improve apathy, and may even lead to worsening of apathetic features.[174] At present, dopamine receptor agonists are regarded as the most effective treatment for apathy in neurological disorders.[177] In PD, levodopa has shown some positive but incomplete effect in patients with motor fluctuations.[200] If apathy persists when motor symptoms are adequately treated, higher doses of the dopaminergic medications or introduction of a dopamine agonists should be considered.[177] A recent meta-analysis of seven randomized controlled trials suggested that pramipexole, a potent dopamine D2 agonist with preference for D3 receptors, had a beneficial effect on mood and motivational symptoms in PD patients who did not have major depressive disorder.[206] However, the clinical value of pramipexole in the treatment of apathetic syndromes requires further investigation. In non-PD patients, older subjects with apathy may benefit from psychostimulants such as methylphenidate and dextroamphetamine.[207] To date, methylphenidate has only been described to be beneficial in a single case report of an older patient with PD.[208] Placebo-controlled studies with cholinesterase inhibitors have shown promising results on behavioural syndromes, including apathy, in PD with cognitive impairment and dementia.[201-203]

Effects of deep brain stimulation (DBS) on apathy

Several studies have reported changes in mood and apathy after DBS surgery in PD. In a comprehensive review of apathy following STN DBS surgery,[209] four studies reported increased apathy score from pre-surgery to post-surgery, two reports did not find any change, and one report of reduction in acute apathy when stimulators were switched from *off* to *on*. None of these reports found a significant reduction in mean apathy scores over time, leading to the conclusion that apathy is not improved by STN DBS surgery.

4.6 Course and prognosis

No studies have examined the longitudinal course of apathy in PD. Because the risk of developing dementia is up to six-fold higher in PD than in non-PD subjects,[78] and the cumulative prevalence of dementia increases with age and duration of PD,[210] higher frequency rates of apathy are expected in more advanced stages of PD compared with early disease.

5. Aims of the thesis

The primary objectives of this thesis were to describe and achieve a better understanding of apathy as a neuropsychiatric disorder in community-based patients with PD across different stages of disease. To obtain this information we:

- validated the motivation/initiative item of UPDRS part I as a screening and diagnostic instrument for apathy in patients with PD (paper I).
- examined the prevalence and clinical correlates of apathy in a large population-based sample of patients with PD, and explored whether apathy may present as a primary behavioural disturbance independent from depression and cognitive impairment, or the direct physiologic effects of psychotropic medication (paper II).
- investigated the occurrence and risk for apathy with emphasis on motor, depressive and cognitive symptoms in a longitudinal cohort of patients with PD over 4 years (paper III).
- examined the frequency and clinical correlates of apathy in an incidence cohort of patients with untreated PD (paper IV).

6. METHODS

6.1 Patient selection and follow-up

In paper I-III, patients were recruited from a population-based prevalence study of PD conducted in Rogaland County, Western Norway between September 1992 and May 1993.[211] In an attempt to achieve complete case ascertainment in the study area comprising 220,000 inhabitants from nine municipalities, all available health care sources were used, including an extensive search of all potential candidates in hospital files and information gathered from general practioners (GPs), nursing homes, district nurses, health workers and the Rogaland Parkinson's Disease Society. About 400 candidates were interviewed and examined by a neurologist with special interest in movement disorders at two consecutive visits held within 1 month in the study period, of whom 245 fulfilled a diagnosis of PD according to published diagnostic criteria.[212] The crude prevalence rate was 110.9 per 100,000 inhabitants on January 1, 1993. Of the 245 patients initially diagnosed with PD according to published criteria, three patients died before the examination program was completed, two refused to participate, sufficient data was missing in one, and seven were rediagnosed as not having PD. Thus, 232 patients were included in the prevalence study of apathy in paper II. These patients were followed prospectively and the survivors were invited to participate in a follow-up study in 1997 and 2001. A total of 139 were eligible for examination in 1997, and in 2001 we included 79 patients to participate in a 4-year longitudinal study of apathy (paper III). Fifty-eight patients at 8-years follow-up in 2001 were eligible for validation of the UPDRS apathy item in paper I.

The Norwegian ParkWest study is a multicentre population-based prospective longitudinal cohort study of the incidence, neurobiology and prognosis of PD in

Western and Southern Norway.[12] The study area is constituted by the four counties of Sogn and Fjordane, Hordaland, Rogaland and Aust-Agder, comprising a total population of more than one million inhabitants. All neurological services in the study area participated in the project to include all cases with incident PD during a 22 months period between November 2004 and August 2006. Multiple case finding strategies were employd: 1) Hand-screening of all referral letters to the participating study centres to identify symptoms possibly representing incident parkinsonism, 2) notification about the study to all other hospital departments and 3) GPs in the study area, including those consulting nursing homes, geriatric care centres and other institutions for persons of older age, 4) electronic screening of inpatient and outpatient hospital databases for patients being diagnosed with incident PD during the inclusion period and for three months after to capture delays in coding, and 5) an electronic population screening by linkage to GPs electronic medical record systems. Of totally 603 subjects screened, 265 fulfilled strict diagnostic research criteria of PD[55] after an average of 28 months prospective follow-up. The crude incidence rate was 13.7 per 100,000 person years.[12] A cohort of 212 subjects consented in long-term study participation, 201 of whom were ever drug-naïve and therefore eligible for inclusion in paper IV. None of the 201 patients had a history of markedly cognitive decline preceding motor symptoms or in the first year of the disease.

6.2 Control subjects (paper IV)

Paper IV also included 201 control subjects recruited from friends and spouses of patients with PD, or unrelated persons from social clubs for the elderly, in the study area between November 2004 and April 2007. To be included, control individuals had to be free from parkinsonism but other movement disorders besides parkinsonism, neurological disorders, or major medical or psychiatric disorders were not considered to be exclusion criteria. A subgroup of 171 subjects who provided the best possible match to age and sex distribution and years of education was included for group comparisons.

6.3 Diagnosis of PD

In order to achieve high sensitivity and specificity in case ascertainment, a new diagnostic classification was used to diagnose PD at different levels of clinical confidence in paper I-III:[212]

Clinical definite PD

The patient presents with resting tremor and at least two of the following signs: bradykinesia, rigidity, or postural abnormality. Additional mandatory features are unilateral onset and asymmetrical development, as well as good to excellent response to dopaminergic agents. Neither atypical signs and symptoms nor significant changes on CT or MRI other than mild diffuse cortical atrophy or mild hypertensive periventricular foci are accepted.

Clinical probable PD

The patient must present at least two of the four cardinal signs, but one of the following atypical features is allowed: early mild dementia or clinically relevant autonomic failure, symmetrical disease presentation, only moderate response to dopaminergic treatment, atypical signs or symptoms indicating another parkinsonian disorder, or significant brain changes on CT or MRI.

Clinical possible PD

The patient must present at least two of the four cardinal signs and response to dopaminergic agents should be at least moderate. Mild to moderate dementia and autonomic failure may be allowed. Other atypical signs or symptoms indicating

another parkinsonian disorder, or significant brain changes on CT or MRI, are not accepted.

In paper IV, we applied recently proposed criteria by Gelb and colleagues to diagnose PD at three levels of confidence:[55]

Table 1. Grouping of Clinical Features According to Diagnostic Utility

Group A features: characteristic of Parkinson disease
- Resting tremor
- Bradykinesia
- Rigidity
- Asymmetric onset

Group B features: suggestive of alternative diagnoses
- Features unusual early in the clinical course
  - Prominent postural instability in the first 3 years after symptom onset
  - Freezing phenomena in the first 3 years
  - Hallucinations unrelated to medications in the first 3 years
  - Dementia preceding motor symptoms or in the first year
- Supranuclear gaze palsy (other than restriction of upward gaze) or slowing of vertical saccades
- Severe, symptomatic dysautonomia unrelated to medications
- Documentation of a condition known to produce parkinsonism and plausibly connected to the patient's symptoms (such as suitably located focal brain lesions or neuroleptic use within the past 6 months)

Table 2. Proposed Diagnostic Criteria for Parkinson Disease

Criteria for POSSIBLE diagnosis of Parkinson disease:

At least 2 of the 4 features in Group A* are present; at least 1 of these is tremor or bradykinesia

and

Either   None of the features in Group B* is present

Or   Symptoms have been present for less than 3 years, and none of the features in Group B* is present to date

and

Either   Substantial and sustained response to levodopa or a dopamine agonist has been documented

Or   Patient has not had an adequate trial of levodopa or dopamine agonist

Criteria for PROBABLE diagnosis of Parkinson disease:

At least 3 of the 4 features in Group A* are present

and

None of the features in Group B* is present (note: symptom duration of at least 3 years is necessary to meet this requirement)

and

Substantial and sustained response to levodopa or a dopamine agonist has been documented

Criteria for DEFINITE diagnosis of Parkinson disease:

All criteria for POSSIBLE Parkinson disease are met

and

Histopathologic confirmation of the diagnosis is obtained at autopsy (see Table 3)

Table 3. Proposed Criteria for Histopathologic Confirmation of Parkinson Disease

Substantial nerve cell depletion with accompanying gliosis in the substantia nigra

At least 1 Lewy body in the substantia nigra or in the locus ceruleus (note: it may be necessary to examine up to 4 nonoverlapping sections in each of these areas before concluding that Lewy bodies are absent)

No pathologic evidence for other diseases that produce parkinsonism (eg, progressive supranuclear palsy, multiple system atrophy, cortical-basal ganglionic degeneration) (note: in excluding other diseases that produce parkinsonism, published consensus criteria should be used when available[65])

6.3 Clinical assessment tools

6.3.1 Assessment of parkinsonism and disability

Several established clinical instruments have been developed to measure the severity and progression of motor symptoms and disability in PD:

The UPDRS is the most widely known rating tool in PD.[186] It was developed in 1987 by an international group of movement disorder specialists, and has been shown to be both reliable and valid in measuring the longitudinal course of the disease. The UPDRS evaluates four components: Mentation, behaviour, and mood (part I), activities of daily living (part II), motor examination (part III), and complications of therapy (part IV). Each item in part I-III is scored on a five-point Likert scale (0 indicates normal functioning and 4 indicates maximal severity). Recently, the UPDRS has undergone major revisions to better capture the nonmotor problems experienced by patients with PD.[213]

Another widely used assessment instrument in PD is the Hoehn and Yahr staging scale.[119] This scale was introduced in 1967 and intends to measure the development of the disease, including impairment and disability of movement, balance and gait. Stages of disease progression range from 0 (no signs of PD) to 5 (parkinsonian symptoms on both sides and not able to walk). Nonmotor problems are not evaluated by the scale.

The Schwab and England scale is commonly used to assess disability in PD patients.[214] It assesses speed and independency in performing activities of daily living, and ranges from 100% (completely independent, essentially normal) to 0% (bedridden, vegetative dysfunction).

In paper III, total UPDRS motor score (range 0-108) was divided into six motor domains (speech, facial expression, tremor, rigidity, bradykinesia, and axial impairment) based on the cardinal clinical manifestations of PD.[81] These six motor domains were grouped into two subscores that represented predominantly dopaminergic (subscore A: tremor, rigidity, bradykinesia, and facial expression; range 0-88) and nondopaminergic (subscore B: speech and axial impairment; range 0-20) deficiencies.[81]

6.4.2 Assessment of apathy

Several scales have been designed to assess apathy and have been validated or used in studies with PD patients,[179] see section 4.1. Two different scales were applied in this thesis.

The AS is a 14-item abridged and modified version of the AES developed by Marin and colleagues in 1991. It was specifically developed for patients with PD, because the AES was considered too demanding. Questions are answered on a four-point Likert scale (0 = a lot, 1 = some, 2 = slightly, and 4 = not at all) and apathy scores range from 0 to 42, with higher scores indicating more severe apathy. The reliability and validity of the original, patient-based version of AS has been established,[185] but a caregiver-rated version is available as well. An international committee with extensive expertise in the area of mood and motivational symptoms in PD have recently assessed the clinimetric properties of the AS. This scale was recommended to screen and to assess the severity of apathy in PD patients.[179] In paper I, the AS was used to generate diagnosis of apathy by means of a specific scheme suggested by Starkstein and colleagues.[215, 216] Briefly, apathy was diagnosed whenever patients had poor or no motivation (a score of ≥ 2 on item 7), interest (a score of ≥ 2 on item 1 or 2), effort (a score of ≥ 2 on item 4 or 9), and had feelings of indifference or lack of emotions most or all of the time (a score of ≥ 2 on item 10 or 13). This diagnostic

scheme has recently showed high sensitivity and specificity for clinically diagnosed apathy in a large series of PD patients.[217]

The NPI was designed to assess psychopathology in dementia and other neurodegenerative disorders. It includes an apathy subsection where the informant is asked four screening questions regarding loss of interest, lack of motivation, poor engagement and indifference. A positive endorsement of any of those items triggers a subset of eight subquestions to explore the symptoms and severity of apathy. Frequency is rated on a 1 to 4 scale, and severity on a 1 to 3 scale. In study III, subjects were considered apathetic if they had a composite apathy score (severity multiplied by frequency) of ≥ 4, as recently recommended in PDD.[218] In study IV, however, patients with possible dementia were excluded. Therefore, a different approach was applied to diagnose subjects (patients with PD and control individuals) with apathy. A diagnosis of apathy was considered if subjects had an NPI apathy score of ≥ 1. We also checked that all these subjects fulfilled the recently proposed consensus criteria for apathy.[143] For this purpose, we verified that the NPI apathy subquestions included at least one symptom in at least two of the three apathy domains: (1) diminished goal-directed behaviour (Does the patient seem less spontaneous and less active than usual? Is the patient less likely to initiate a conversation? Does the patient contribute less to household chores (not due to motor severity)? Does the patient show any other signs that he/she doesn't care about doing new things?); (2) diminished goal-directed cognitive activity (Does the patient seem less interested in the activities and plans of others? Has the patient lost interest in friends and family members?); and (3) diminished emotion (Is the patient less affectionate or lacking in emotions when compared to his/her usual self? Is the patient less enthusiastic about his/her usual interests?). High interrater reliability of the NPI apathy subsection has been demonstrated in PD.[188] A later version of the NPI[219] was also used to measure emotional distress experienced by the caregiver

engendered by the apathetic behaviour (level of distress: not at all = 1, minimal = 2, moderate = 3, severe = 4, very severe or extreme distress = 5).

6.4.3 Assessment of depression

Severity of depressive symptoms was assessed using the MADRS.[220] This 10-item scale is based on a clinical interview of the patient, where the observer decides the score on each item on a seven-point scale (ranging from 0 to 6 points). The items are rated with regards on the state of the patient over the past week. This rating scale covers all the DSM-IV criteria of a major depressive episode, except psychomotor retardation/agitation and neurovegetative symptoms such as hypersomnia and increased appetite. It was originally designed to measure change in severity of depressive symptoms during antidepressant clinical trials, and has been shown to be sensitive, reliable and valid as a measure instrument of depression. Leentjens and colleagues found the MADRS to be an adequate instrument for measuring depressive symptoms and for diagnosing a major depressive disorder in PD.[221] In study II and III, major depression was diagnosed by administering a semistructured interview according to the DSM-III-R.

6.4.4 Assessment of cognitive impairment and dementia

The MMSE is one of the most widely used clinical instruments for quickly detecting cognitive impairment.[222] It consists of 30 items assessing orientation, short-term memory (retention), attention, short-term memory (recall), and language. The MMSE can be used to screen for cognitive impairment and assess its severity at a given time point, monitor the course of cognitive changes over time, and to document the response to treatment. It provides a total score indicating the cognitive function of a subject. Although the MMSE has been shown to be both a reliable and valid measure

of cognitive impairment, it is relatively insensitive to executive dysfunction[218] and is influenced by the effects of age and level of education.[223]

In paper II, dementia was diagnosed according to DSM-III-R criteria based on a semistructured interview with the caregiver and scores on the MMSE, Gottfries-Bråne-Steen (GBS) scale,[224] and item 1 (intellectual impairment) of UPDRS part I. The GBS rates severity of dementia and provides a profile of the symptoms of dementia by estimating motor, intellectual, emotional, and other characteristic features of dementia in four subscales. Each item is scored on a clearly defined seven-point scale (0 indicates normal functioning and 6 indicates maximal severity). The rating is based on observation of the patient and an interview with the patient and a caregiver. The UPDRS intellectual impairment item rates memory, orientation, problem solving, function at home, and personal care. The scores ranges from 0 (no impairment) to 4 (severe impairment).

A more extensive cognitive assessment battery was performed to diagnose dementia in paper III, including the MMSE, Mattis Dementia Rating Scale (Mattis DRS),[225] and selected neuropsychological tests that were thought to be independent of motor abilities. The Mattis DRS is a widely used dementia screening instrument that is divided into five subscales measuring attention, initiation, construction, conceptualization, and memory. Scores range from 0 (maximal severity) to 144 (normal cognitive function). The scale has been shown to robustly and accurately distinguish between cortical and subcortical dementia profiles.[226] Three neuropsychological tests were included. The multiple choice version of the Benton Visual Retention Test[227] consists of 15 items presented for 10 seconds, where subjects are supposed to recognize one or more designs that they have seen before. This test assesses short-time visual memory. The Judgement of Line Orientation Test[228] consists of 30 items, each showing a different pair of angled lines to be

matched with display cards, and was designed to assess visual/spatial abilities. The Stroop test[229] was used to assess selective attention/executive functions. We used a version which consists of three cards: subjects name the colour of coloured patches (1st card), read printed words (2nd card), and read printed colour names in which the ink used for printing is a colour different from the colour designed by the printed name (3rd card). Both the time needed to complete each card and the number of errors was recorded. For MMSE and MDRS, age- and education-based cut-off scores were used. Dementia was diagnosed according DSM-III-R criteria based on the clinical interview, cognitive rating scales, and neuropsychological tests.

In early PD, cognitive dysfunction may be subtle and therefore not assessable by common clinical rating instruments. To detect early cognitive changes in paper IV, a battery of neuropsychological tests not or only minimally affected by motor performance was chosen to assess four cognitive domains in PD. Verbal memory was evaluated using the California Verbal Learning Test II (CVLT-II),[230] which consists of 16 words which were read five times, and after each time the patient was asked to recall as many words as possible. Total immediate recall (sum of trials 1–5), short-delay, and long-delay free recall (after 20 minutes) scores were included in the analyses. Attention and executive functions were assessed with the semantic verbal fluency[231] and interference part of the Stroop test.[232] In the semantic verbal fluency test patients are asked to generate as many names of animals as possible within 1 minute. The interference part of the Stroop test is performed by asking the patient to tell the colour of the word (3rd card). Psychomotor speed was examined using the sum of words produced during the colour (1st card) and the word (2nd card) conditions from the Stroop test. Visuospatial abilities were assessed using the Silhouettes and Cube subtests from the Visual Object and Space Perception Battery (VOSP).[233] In the Silhouette test, the subject is asked to identify the outline of 30 objects which are rotated through varying degrees from the lateral axis. The cube tests consist of 10 representations of a three dimensional arrangement of square bricks, and the subject

is asked to count the number of bricks. Dementia associated with PD was diagnosed using recently proposed consensus criteria as a guide,[74] based on neuropsychological tesing, MMSE, and the Informant Questionnaire on Cognitive decline in the elderly (IQCode).[234] The IQCode is a standardized measure with proven psychometric properties, and a cut-off which was based on the sample closest in composition to our PD population was chosen.[70]

6.4.5 Statistical analysis

In paper I, the Spearman correlation coefficient was used to calculate the association between different measures of apathy and depressive symptoms. A receiver operating characteristic (ROC) curve was employed to analyse sensitivity and specificity for the UPDRS apathy item, and to select an optimal cut-off score for identifying apathy.

In paper II-IV, Mann-Whitney tests were used for comparisons of medians for continuous variables and differences in proportions of categorical variables were analyzed by χ^2 tests or Fisher's exact tests where an expected cell frequency was less than five. When comparing more than two groups, Kruskal-Wallis tests were used for continuous variables and linear-by-linear association tests for categorical variables. Binary logistic regression analyses with forward stepping (likelihood ratio method) were applied to assess variables that were independent correlates of apathy. In paper II, effect size estimates were applied to measure which factors contributed most strongly to the presence of apathy. Finally, in paper IV we used Wilcoxon signed rank tests to compare differences between paired groups over time.

7. Results

Paper I

We examined the validity of the motivation/initiative item of the UPDRS part I as a screening and diagnostic measure for apathy in PD, and found that a cut-off score of 2 was adequate to screen for apathy with questionable diagnostic quality, whereas a cut-off score of 4 had high diagnostic accuracy at the cost of unacceptable low sensitivity.

Paper II

Apathy was diagnosed in 38% of 232 patients with PD. In 11% of the total sample apathy coexisted with depression and dementia, whereas 10% had apathy and depression without dementia, 6.5% apathy and dementia without depression, and 9% were apathetic without dementia or depression (data missing in 1.5% patients). Apathy was significantly associated with higher depression scores, lower cognitive functioning, and more severe motor symptoms. When excluding patients with depression, dementia, cognitive impairment with no dementia (population-based age- and education-corrected norms for the MMSE), and those using psychotropic medication, 5% of the 232 patients remained apathetic.

Paper III

Of the 79 patients with PD examined in 1997 and 2001, 29 patients (36.7%) had never apathy, 11 (13.9%) had persistent apathy, and further 39 (49.4%) developed apathy during follow-up. At follow-up, patients with apathy were more frequently depressed and demented than never-apathetic patients. Dementia at baseline and a

more rapid decline in speech and axial impairment during follow-up were independent risk factors for incident apathy.

Paper IV

Apathy was diagnosed in 22.9% of 175 nondemented, drug-naïve patients with incident PD, of whom 37.5% had significant depressive symptoms, whereas none of the 165 matched control subjects were apathetic. Apathy was significantly associated with male gender, higher depression scores and more severe motor symptoms, but was not associated with greater cognitive impairment. When excluding patients with significant depressive symptoms, apathy remained significantly associated with motor severity. Approximately 50% of the caregivers of patients with apathy reported the apathetic behaviour to be at least moderately distressing.

8. Discussion

8.1 Methodological considerations

Epidemiological research seeks to provide information about the distribution and size of disease problems, and their associated risk factors in the general population. In particular, epidemiological data may help to identify aetiological factors in the pathogenesis of diseases and to provide data essential for identifying at risk-groups and planning of services for the prevention, control and treatment of disease. The quality of epidemiological research depends on several methodological aspects which are necessary to obtain reliable and reproducible data.

The diagnosis of PD is still based on disease history and clinical examination, as no exact test is currently available to provide a definite diagnosis. In addition, PD is characterized by considerable clinical heterogeneity and symptoms may overlap with both symptomatic parkinsonism (e.g. drug-induced, vascular disease, post-infectious) and parkinsonism caused by other neurodegenerative disorders (e.g. MSA, PSP, dementia with Lewy bodies) in early stages. Therefore, the use of careful diagnostic criteria is essential to provide high sensitivity and specificity for the diagnosis of PD. Studies from several brain banks in the early 1990s reported poor precision of the clinical diagnosis of PD.[235, 236] Even though patients were diagnosed by neurologists, only 76% had Lewy bodies in the brain at autopsy. In an effort to achieve both high sensitivity and specificity, we applied a new diagnostic classification in paper I-III to diagnose patients with PD at different levels of confidence.[211, 212] Furthermore, patients were reevaluated after four and eight years to possibly revise the clinical diagnosis of PD in those who had developed atypical signs and symptoms during the course of disease. As a result, less than 3% were rediagnosed as not suffering from PD during follow-up. Of the 22 patients who have been autopsied so far, all fulfilled

neuropathological criteria of PD.[237] In paper IV, which is part of the Norwegian ParkWest study,[12] patients were diagnosed according to widely acknowledged criteria of PD[55] after an average of 28 months prospective follow-up. Like the diagnostic criteria used in paper I-III, the new criteria differentiated three levels of diagnostic confidence.

An unfavourable trend in epidemiological studies is to include patients based on retrospective review of medical records, which are likely to represent information from highly selected subpopulations with more advanced disease. In addition, cohort studies often include selected groups, such as PD patients treated at highly specialized movement disorder clinics, who may not be representative for the disease population in a specific geographic area. To achieve a high degree of case ascertainment in Rogaland County, patients in paper I-III were recruited through search in hospital files and information gathered from the local branch of the Norwegian Parkinson's disease Society, GPs, nursinghomes, district nurses, and health workers in the study area. In paper IV, multiple sources of case ascertainment were used to establish a representative cohort of patients with incident PD from the four counties of Sogn and Fjordane, Hordaland, Rogaland and Aust-Agder. The following strategies were employed for case identification: 1) Screening of all referral letters to the participating study centres for symptoms possibly representing incident parkinsonism, 2) notification of all other hospital departments and all GPs in the study area, 3) electronic screening of inpatient and outpatient hospital databases for patients being diagnosed with PD for the first time during the screening period and for 3 months after to capture delays in coding, and 4) an electronic population screening of 43,716 individuals by linkage to GPs' electronic medical record systems dated back to 1 year before study start.

The assessment of all participants included semistructured interviews on demographic variables, medical history and medication. Standardized and validated instruments for assessment of parkinsonism and disability, depression, cognitive impairment and dementia were applied by trained and experienced staff at each study visit. These are thoroughly described in the methodology chapter of this thesis. However, the assessment of apathy needs further discussion. To date, none of the apathy rating instruments currently available have been validated against recently proposed consensus criteria for the clinical diagnosis of apathy in neuropsychiatric disorders.[143] Due to the lack of validated tools for assessment of apathy at baseline in the prevalence study of PD in Rogaland County, we attempted to validate the UPDRS apathy item against a specific diagnostic scheme[215, 216] in patients from the same study at 8-years follow-up. We found that the optimal cut-off score for a diagnosis of apathy was ≥ 2 (paper I), which we further applied to examine the prevalence and clinical correlates of apathy at baseline (paper II). In Paper III, apathy was diagnosed by using a composite NPI apathy subscore of ≥ 4, which has recently been recommended in PDD.[218] This is reasonable, given that more than 60% of patients were demented at follow-up. In Paper IV, subjects with possible dementia were excluded and apathy diagnosed whenever participants had an NPI apathy subscore of ≥ 1 and fulfilled the apathy domain section of the recently proposed consensus criteria for apathy. A major limitation of this thesis is the use of different apathy rating instruments and cut-off scores rather than a structured psychiatric interview to diagnose apathy. Consequently, it is possible that subjects with apathy might have been left undetected, or vice versa, that some participants were wrongly diagnosed with apathy. However, the fact that our classifications of apathy were strongly associated with depression and cognitive dysfunction, as shown in most other studies of apathy in PD,[179] strengthen our findings as reliable.

Finally, the use of adequate statistical methods is important to produce reliable data. In paper I, we applied a ROC curve to select an optimal cut-off score for identifying

apathy. In paper II-IV, we used binary logistic regression models for correlated data. These allowed the assessment of several variables to identify independent correlates of apathy.

8.2 Findings

8.2.1 Validity of the UPDRS apathy item in PD

The UPDRS was originally developed as a core assessment tool to evaluate change in PD signs and symptoms over time. Although this instrument mainly focuses on motor aspects of PD (part II-IV), part I consists of four items assessing intellectual impairment, thought disorder, depression, and motivation/initiative, which is meant to be used as a screening for dementia, psychosis, depression, and apathy, respectively. The motivation/intitative item is rated on a five-point Likert scale and scores include the following: 0 = Normal, 1 = less assertive than usual; more passive, 2 = loss of initiative or disinterest in elective (nonroutine) activities, 3 = loss of initiative or disinterest in day-to-day (routine) activities, and 4 = withdrawn; complete loss of motivation.

Although the motivation/initiative item has previously been applied as an assessment tool to diagnose apathy in patients with PD,[238, 239] the validity of this item was unknown. Therefore, in our first study (paper I) we aimed to examine its properties as a screening and diagnostic instrument for apathy in a cohort of patients with moderate to advanced PD who were given the AS as part of a follow-up examination in an ongoing prospective longitudinal study of PD in Rogaland County, Western Norway. To provide a gold standard for the diagnosis of apathy, we applied a specific diagnostic scheme[215, 216] which converted AS core items into a version of currently proposed criteria.[137] The main finding was that a cut-off score of ≥ 2 on the motivation/initiative item was adequate for apathy screening at the cost of

questionable diagnostic accuracy, whereas a cut-off score of ≥ 4 had high diagnostic quality with poor sensitivity. Based on our finding, we suggested to use a cut-off score of ≥ 2 as a screening tool, and then apply AS-derived or other criteria for a more accurate diagnosis. Methodological limitations of this study include the lack of a gold standard of established diagnostic criteria and validated ad-hoc scales for apathy, a relatively high proportion of patients with missing data due to severe dementia or refusal to participate, which could have biased the frequency of apathy to a lower rate, and the recruitment of patients after 8-years follow-up, which may have led to a sample of more severe cases. At the time of submission of our study, Starkstein and Merello conducted a validation study of the UPDRS part I using similar methods.[187] Their patients were younger (mean age 65.9 vs. 74.2 years), had shorter duration of illness (mean duration 5.9 vs. 9.3 years), were not biased toward more severe cases (Hoehn-Yahr stage ≥ III: 53% vs. 67%), but were generally similar regarding global cognitive functions (mean MMSE score 24.4 vs. 23.0). As in our study, they concluded that a motivation/initiative cut-off of 2 is adequate for screening, but not for diagnostic purposes in PD. These findings have recently been supported by Gallagher and colleagues using another apathy rating scale,[240] whereas Kirsch-Darrow and colleagues suggested caution when screening for apathy with the motivation/initiative item due to its poor sensitivity in relation to an AS cut-off score of ≥ 14.[241] Although the majority of validity studies supported our finding, it is necessary to re-examine the operating characteristics of the AS and motivation/initiative item with newly proposed consensus criteria for apathy as a guide. Of notice, the AS-derived diagnostic scheme has recently been validated in PD patients against the opinion of an experienced neuropsychiatrist blind to psychiatric findings. In this study,[217] Starkstein and colleagues reported high sensitivity (82%) and specificity (92%) for clinically diagnosed apathy.

8.2.2 Frequency of apathy in early versus late PD

Prevalence rates of apathy in PD vary widely across studies, ranging from 16.5% to 70%. Possible reasons for this variation include the selection of the population studied and the way the diagnosis is established. For example, the lowest prevalence is reported in a follow-up study of 139 community-based patients from Rogaland County, Western Norway.[188] These patients were on average 74 years old, and the mean duration of PD was nearly 13 years with 64% of the population in Hoehn and Yahr stage III or above. Fifty patients, 36% of the sample, met the DSM-III-R criteria for dementia. Using an NPI subscore of ≥ 1, Aarsland and colleagues found that 16.5% of the patients were apathetic and 38% depressed. In contrast, the highest prevalence rate is reported in a hospital-based study of 30 patients from Italy.[190] The mean age of the sample was 65 years, mean disease duration 5 years, and the mean UPDRS motor score was 32. Patients with severe dementia were excluded. When applying the self-rated AS with a cut-off score of > 14, 70% of the patients appeared apathetic. After adjusting the cut-off score to > 16, the prevalence declined to 43%. Eighteen patients, 60% of the sample, were depressed according to the Geriatric Depression Rating Scale.[242]

To explore changes in the frequency of apathy in early versus late PD, we examined two different population-based samples using the diagnostic procedures described in the methodology chapter of this thesis. In Paper IV, we examined 175 nondemented, drug-naïve patients with newly diagnosed PD and 165 matched control subjects from the Norwegian ParkWest study. Apathy was found in 23% of the PD patients, of whom 37.5% had significant depressive symptoms, whereas none of the control subjects were apathetic. In paper II and III, patients were derived from the prevalence study of PD in Rogaland County. At baseline, apathy was diagnosed in 38% of the 232 patients (paper II). Patients were on average 73.5 years old, mean duration of disease 9 years, and the mean UPDRS motor score was 28.5. Twenty-one patients, 9% of the population, were apathetic without dementia or depression. After excluding

patients with cognitive impairment without dementia and those using psychotropic medication, only 5% remained with "pure" apathy. At 8-years follow-up, or a mean disease duration of 17 years, 79 patients were available for examination (paper IV). The mean UPDRS motor score ranged from 51 to 61 in those who had developed and those with persistent apathy during the last 4 years, respectively. We found that 63% of the sample were apathetic, of whom 32% were depressed and 88% demented. These observations demonstrate that apathy increases with the duration and progression of PD, especially as patients get demented. Obviously, major limitations are collection of data from two different populations, long time intervals between study visits, and different diagnostic procedures of apathy. Therefore, caution must be taken when interpreting our findings.

8.2.3 Clinical correlates of apathy in PD

In contrast to varying results regarding the frequency of apathy in PD, studies of clinical correlates have been relatively concurrent. Most studies report an association of apathy with depression and more severe cognitive symptoms or dementia. In paper II, we replicated these findings in a large community-based study of apathy in PD, showing that apathy was associated with higher depression scores and lower cognitive functioning. Further analysis showed that the MADRS dysphoric/apathy factor primarily contributed to the dependency between apathy and MADRS scores. Similar findings have been reported by others (ref).[193, 243, 244] Furthermore, apathy coexisted with depression in 21 % and with dementia in 17.5% of the total sample. Only 9% with neither depression nor dementia had apathy. Because apathy may be a residual symptom of a depressive episode or side-effect of antidepressant or antipsychotic drugs, we further excluded those using psychotropic medication. Five percent remained apathetic, which indicates that apathy rarely presents as an independent syndrome in patients with mild to moderate PD. This finding has been supported by two other studies.[193, 217] Dujardin and colleagues found a strong association between depression, dementia and apathy in PD patients with varying

degrees of disease severity.[193] Recently, Starkstein and colleagues examined patients with mostly mild to moderate PD, and reported that 83% of those with apathy had comorbid depression and 56% had dementia.[217] In contrast, when examining a large multicentre-based population of untreated, nondemented patients with newly diagnosed PD, we found significant association between apathy and higher depression scores but not greater cognitive impairment (paper IV). Apathy was diagnosed in 23% patients with PD, of whom only 37.5% had significant depressive symptoms. All together, these findings suggest that the proportion of PD patients with an isolated syndrome of apathy is higher in early versus late PD, probably reflecting different profiles of neurotransmitter changes.

Previous studies have not reported any differences between PD patients with or without apathy regarding demographic variables, duration of illness, and motor severity, suggesting that apathy may not be simply related to progression of disease. In paper II and IV, however, we reported a significant association between apathy and severity of motor symptoms, indicating a common underlying pathophysiological mechanism. One hypothesis is that apathy in PD patients is a marker of more severe dopaminergic dysfunction in both nigrostriatal and mesolimbic pathways, and loss of direct dopaminergic projections from the brainstem ventral tegmental area to motor basal ganglia connections is a possible explanation. However, further studies are needed to explore this hypothesis. In paper IV, we also found a significant association between apathy and male gender. Low testosterone levels in elderly men with PD have been linked to symptoms of apathy,[197] but the role of testosterone in the pathophysiology of apathy is still controversial.[198] An alternative, although speculative, explanation could simply be that female caregivers are more prone to report behavioural deficits than male caregivers are. Finally, in the same study apathy contributed to considerable distress among 50% of the caregivers, which underscores the importance of educating family members about the symptoms of apathy in early PD.

8.2.4 Longitudinal course and risk factors of apathy in PD

Previous studies of apathy in PD have only been cross-sectional. However, there is a need for studies exploring the development of apathy in PD over time, and several important questions need to be answered: What is the longitudinal incidence and prevalence of apathy in PD? Which demographic and clinical variables are related to apathy over time and across different stages of PD? Is apathy a persistent problem over time in patients with PD? Is persistent apathy a risk factor for more severe motor symptoms, depression or cognitive dysfunction in PD? What factors predict incident apathy in PD? In paper III, we followed a cohort of patients with PD over four years, and found that 37% never had apathy, 14% had persistent apathy, and further 49% developed apathy during follow-up. Patients with apathy were more frequently depressed and demented at follow-up compared to never-apathetic patients. Persistent apathy was not associated with incident depression or dementia at follow-up. However, low statistical power due to relatively few patients with incident apathy (n = 11) may perhaps explain this finding, and further studies including more patients are needed to fully examine this question. Nevertheless, we found that dementia at baseline and a more rapid decline in speech and axial impairment during follow-up contributed significantly to the risk of incident apathy. This finding indicates that progression of motor signs predominantly mediated by non-dopaminergic systems may be a useful preclinical marker for incident apathy in PD. Further research in larger groups of patients with early PD and with more frequent evaluations over time is necessary to identify factors that may predict apathy at an earlier stage of the disease.

8.3 Implications for clinical practice and future research

Apathy has long been living in the shadow of depression and dementia. In fact, some would argue that apathy is a mood disorder or part of a dysexecutive syndrome. However, recent consensus criteria for apathy now consider it to be an independent

neuropsychiatric syndrome characterized by loss of or diminished motivation.[143] The results of the present thesis confirm previous studies showing that apathy is both common and may exist independently of significant depressive symptoms or severe cognitive dysfunction in PD. One of the most important findings in our research is that in early untreated PD the majority of patients have apathy without comorbid depression or severe cognitive problems. The significant association between apathy and more severe motor symptoms in these patients, highlights the need for further studies exploring the effect of dopaminergic medications, especially dopamine agonists with high affinity to D3 receptors that are largely expressed in the nucleus accumbens and ventral striatum, on the symptoms of apathy. However, large randomized placebo-controlled studies are needed for this purpose. Another important finding in the present thesis is that a more rapid decline in progression of speech problems and axial symptoms were associated with incident apathy in patients with moderate to advanced PD. Given the considerable clinical heterogeneity in PD, identification of certain motor subtypes of the disease may serve as prognostic indicators of patients at risk of developing apathy. Last, but not least, there is a need for valid and reliable assessment tools to evaluate apathy in PD and other neurodegenerative disorders. Existing apathy scales commonly used in PD patients should be validated against newly proposed consensus criteria to assess sensitivity and specificity among patients with or without apathy. The confounding influence of depressive symptomatology, cognitive decline and motor fluctuations (*on* versus *off* states) on the performance of apathy rating scales, as well as reliability of patient-rated versus caregiver-rated instruments should also be evaluated.

9. Conclusions

The aims of this thesis were to describe and achieve a better understanding of apathy as a neuropsychiatric disturbance in community-based patients with PD from the time of diagnosis to more advancing stages.

We have shown that the UPDRS part I is an adequate screening instrument for apathy in patients with PD, using proposed diagnostic criteria for apathy as a guide. However, in clinical practice more sophisticated apathy rating scales are recommended for diagnostic accuracy.

The occurrence and clinical correlates of apathy in early versus more advanced stages of PD were examined in two different community-based cohorts. We found that the frequency of apathy increased from 23% in early untreated PD, to 38% in patients with a mean disease duration of nine years, and that after 17 years of PD 63% had developed apathy. Unfortunately, due to different assessment tools the severity of apathy symptoms was not examined. However, the frequency of comorbid depression and especially severe cognitive dysfunction and dementia increased during progression of PD. Also, apathy was significantly associated with motor severity in both early untreated PD and in those with a mean disease duration of nine years, implying a common underlying pathophysiological mechanism. Somewhat unexpectedly, we observed a significant association between apathy and male gender in patients with early PD. Possible explanations for this finding are low testosterone levels in elderly men and the use of caregiver-rated assessment tools. In the same cohort, apathy contributed to considerable distress in more than 50% of the caregivers of those with apathy.

In a prospective longitudinal cohort study of more advanced cases of PD, we showed that apathy was a persistent behavioural problem with high incidence and prevalence over time. We found that dementia and a more rapid decline in speech and axial impairment, features predominantly associated with dysfunction in non-dopaminergic pathways, were independent risk factors for incident apathy.

In summary, apathy is a common neuropsychiatric disturbance at all stages of PD, contributes to considerable caregiver distress in early disease, and is mostly associated with motor severity, depression and cognitive dysfunction. Rapid progression of speech problems and axial impairment may be a useful preclinical marker for incident apathy in PD. Although our findings indicate that dopaminergic dysfunction may explain the occurrence of apathy in the early stages of PD, whereas non-dopaminergic deficits are mostly responsible for apathy in more advanced stages, future studies should explore this hypothesis by using validated apathy rating instruments, functional brain imaging and biologically relevant biomarkers.

10. References

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