Impulse Control Disorders in Parkinson's disease

by

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I just know that she is made of smoke
But I've lost my way
She knows that I am broke
But that I must play

Temptation
Temptation, yeah
Temptation
I can't resist

Tom Waits, 1987

Table of Contents

Scientific environment

This PhD project was carried out at The Norwegian Centre for Movement Disorders (NKB), Stavanger University Hospital.

My main supervisor has been Kenn Freddy Pedersen, PhD, who is a senior researcher at NKB and neurologist at the Department of Neurology, Stavanger University Hospital. Professor Guido Alves, director of NKB and Professor at Department of Science and Technology, University of Stavanger, and Professor Kolbjørn Brønnick, at the Faculty of Health Sciences, University of Stavanger have been co-supervisors. Jodi Maple-Grødem, senior researcher at NKB and associate Professor at Centre for Organelle Research, University of Stavanger supervised, paper II in this thesis.

Professor Ole-Bjørn Tysnes at the Department of Neurology, Haukeland University Hospital and Department of Clinical Medicine, University of Bergen, contributed to all papers in this thesis.

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Paper III was carried out in collaboration with Anders Bjørnestad, PhD, at NKB and Department of Neurology, Stavanger University Hospital.

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Aleksander H. Erga

Abstract

Background Parkinson's disease (PD) is a common neurodegenerative disorder, affecting 1% of the population aged over 60. PD is characterized by the presence of several motor symptoms, which often are accompanied by a range of neuropsychiatric and non-motor symptoms. Impulse control disorders (ICDs) include a range of behavioral disorders, frequently occurring as a complication of PD. However, the epidemiology and risk profile for developing ICDs in patients with PD has not been fully examined.

Objectives The overall aim of this thesis was to describe the epidemiology, genetic risk and long-term trajectory of ICDs in PD.

Methods All papers of this thesis are based on the Norwegian ParkWest study, a prospective, population-based, multicentre, longitudinal cohort study of patients with newly diagnosed PD. In this study, 212 patients were followed prospectively by experienced movement disorders specialists. A large cohort of non-PD subjects was included as a control group. Assessment of ICDs was first introduced five years after baseline assessment. Associated features and risk factors of ICDs were explored in both cross-sectional and longitudinal analyses. Associated genetic polymorphisms were explored based on already gathered whole-exome sequencing data from the Norwegian ParkWest study.

Results At study start, patients with PD had about 3-fold increased odds of having any ICD and more than 7-fold increased odds of multiple ICDs compared with matched normal controls. Patients treated with dopamine agonist, but not other dopaminergic drugs, had even higher odds of having an ICD compared with controls. ICD status in patients was independently associated with dopamine agonist treatment and depressive symptoms. In additional analyses on the PD cohort, we did not find any association between ICD status and presence of psychotic symptoms.

Presence of ICDs in patients with PD at study start was associated with 11 single-nucleotide polymorphisms across nine genes. In addition to already identified polymorphisms, we found a novel polymorphism in the *DRD1*-gene.

A 4-year prospective follow-up study of this cohort showed that 47% of patients reported any ICD and that 23% incident cases of ICDs emerged during the study period. Patients with PD had more than 4-fold increased odds of having ICDs compared with well-matched controls during follow-up. However, ICDs resolved in nearly 30% of patients. ICD status in patients was independently associated with dopamine agonist use and younger age, but not with greater cognitive decline over time.

Conclusions ICDs are more common in patients with PD than normal controls and associated with dopamine agonist use, depressive symptoms and younger age, but not with psychotic symptoms or greater cognitive decline over time. ICDs have been associated with polymorphisms across dopaminergic, serotonergic, glutamatergic and opioid transmitter pathways in patients with PD. In the present study, we identified one novel polymorphism in the dopamine receptor D1-gene. These findings underscore the importance of continued clinical assessments of ICDs in PD patients over time, and suggest that genetic screening tests may be a viable method of identifying patients at risk of ICDs if exposed to dopamine agonists.

List of publications

I. Erga AH, Alves G, Larsen JP, Tysnes OB, Pedersen KF. Impulsive and Compulsive Behaviors in Parkinson's Disease: The Norwegian ParkWest Study. J Parkinsons Dis. 2017;7(1):183-91

II. Erga AH, Dalen I, Ushakova A, Chung J, Charalampos T, Alves G, Pedersen KF, Maple-Grødem J. Dopaminergic and Opioid Pathways Associated with Impulse Control Disorders in Parkinson's Disease. Front Neurol. 2018;9

III. Erga AH, Bjornestad A, Tysnes OB, Alves G, Pedersen KF. Is psychosis associated with impulse control disorders in Parkinson's disease? Parkinsonism & Relat Disord. 2018;53:110-11

IV. Erga, AH, Alves, G, Tysnes, OB, Pedersen KF. Evolution of impulsive compulsive behaviours and cognition in Parkinson's disease. Submitted.

List of abbreviations

CE	Compulsive eating
CI	Confidence interval
CS	Compulsive shopping
CSB	Compulsive sexual behavior
CVLT-II	California Verbal Learning Test II
DA	Dopamine agonist
DDS	Dopamine dysregulation syndrome
DRT	Dopamine replacement therapy
DRD1-3	Dopamine receptor D1-3 - genes
DSM	Diagnostic and Statistical Manual of Mental Disorders
DWAS	Dopamine agonist withdrawal syndrome
GD	Gambling disorder
H&Y	Hoehn and Yahr
ICB	Impulsive and compulsive behaviors
ICD	Impulse control disorders
ICD-11	International Classification of Disease, 11th revision
LB	Lewy bodies
LED	Levodopa equivalent dosage
LD	Levodopa
MADRS	Montgomery and Aasberg Depression Rating Scale

MCI	Mild Cognitive Impairment
MIDI	Minnesota Impulse Disorders Interview
MMSE	Mini-Mental State Examination
MDS	Movement Disorders Society
NC	Normal controls
NPI	Neuropsychiatric Inventory
OR	Odds ratio
PD	Parkinson's disease
PDD	Parkinson's disease associated dementia
POMP	Percent of Maximum Possible
QUIP	Questionnaire for Impulsive-compulsive behaviors in Parkinson's disease
RDS	Reward deficiency syndrome
SNc	Substantia nigra pars compacta
SNP	Single-nucleotide polymorphism
UPDRS	Unified Parkinson's Disease Rating Scale
UKBB	United Kingdom Brain Bank
WES	Whole-exome sequencing

1 Introduction

1.1 Parkinson's disease

Parkinson's disease (PD) is a common neurodegenerative disease, first described by dr. James Parkinson (1755-1824) in 1817.[1] In his highly influential paper "An essay on the shaking palsy", Parkinson described a progressive motor syndrome characterized by "involuntary tremulous motion" (pp 227), now termed tremor; "a propensity to bend the trunk forwards, and to pass from walking to a running pace" (pp 228), now termed postural abnormalities; and bradykinesia. The French physician J.M. Charcot later termed this motor syndrome as "Parkinson's disease", and expanded the clinical description to include rigidity as a motor symptom, and noting that altered state of mind may be observed during the progression of the disease.[2] During the last 200 years, major advances have increased our understanding of the clinical features, course and pathophysiology of this devastating disease.

1.1.1 Epidemiology

PD is the second most common neurodegenerative disorder, surpassed only by Alzheimer's disease.[3] With an estimated prevalence of 1% in people over 60 years and 4% in those over 80 years, PD is far more common in the elderly population.[4] The annual incidence rate of PD ranges from 8 to 18 per 100,000 inhabitants, with the highest incidence rates being observed in patients aged between 70 and 79 years.[4-6] PD is less common in females, with a male to female ratio of 1.6:1.[5]

1.1.2 Aetiology

The aetiology of PD is unknown in most PD cases. Generally, PD is regarded as a multifactorial disease, resulting from a combination of several independent factors, including genetic susceptibility, environmental and individual factors.[7,8] Of note, for a small subset of patients with PD, familial monogenetic causes have been identified (see section 1.4 for more details on the genetics of PD). However, the overall interactions between these risk

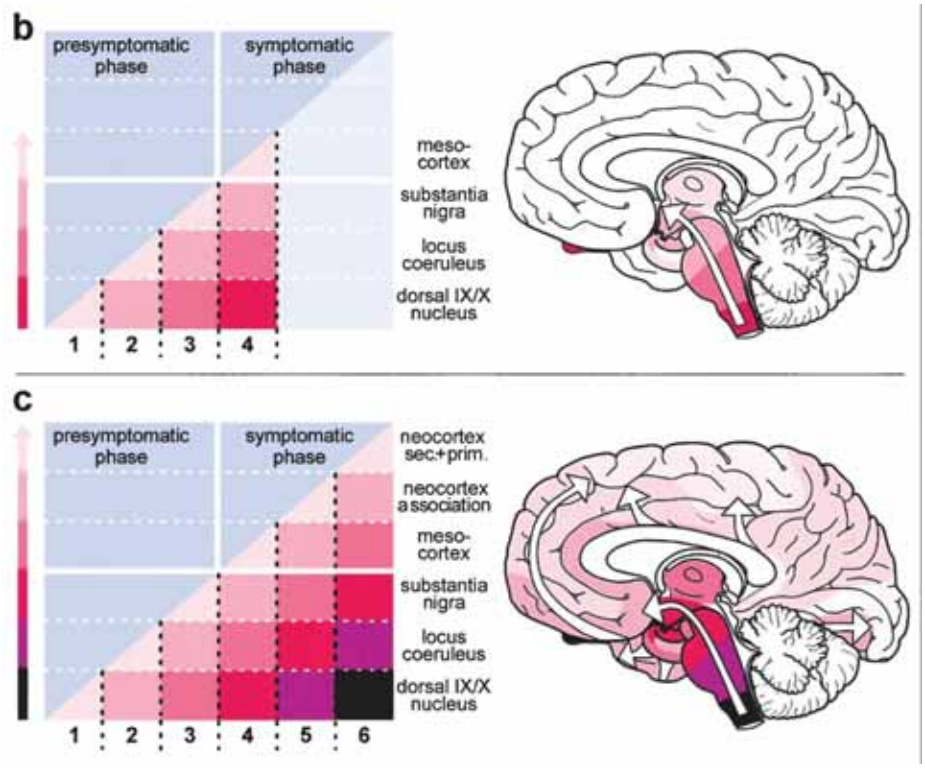
factors and how they result in the neurodegeneration and pathophysiology characterized by PD remain unknown.

1.1.3 Neuropathology

The hallmark pathological feature of PD is loss of dopaminergic neurons in the substantia nigra pars compacta (SNc). Neuronal loss in the SNc is evident at the early stages of PD and precedes the development of motor disturbances by many years.[9] The dopaminergic neurons of the SNc are essential for innervation of the basal ganglia, a subcortical structure of the brain involved in regulation of motor functioning, affective processing and prefrontal cognitive processes.[10] The SNc projects through the striatum, which is the primary afferent bundle in the basal ganglia.[11] Further projections can be divided into several functional circuits, two of which are highly relevant for the motor and non-motor symptoms of PD: the nigrostriatal pathway, which is involved in regulation of motor control; and the mesocorticolimbic pathway, which is involved in processing reward and affective processing, and executive functioning.[11-13] The activity in these pathways is mediated by two families of dopamine receptors, the D_1-like family, which includes D_1 and D_5 receptors, and the D_2-like family, which includes D_2, D_3, and D_4 receptors. The denervation of the SNc leads to reduced striatal dopamine, resulting in dysregulation of the nigrostriatal pathway and abnormal involuntary motor symptoms.[14,15]

A second hallmark pathological feature of PD is the aggregation of abnormally folded proteins, known as Lewy bodies (LBs). LBs are comprised of aggregates of misfolded α-synuclein, a protein normally involved in the regulation of presynaptic activity, and are found within neurons in the peripheral and central nervous system.[16] Although the neuropathological effect of LBs is still debated, presence of LBs is associated with cognitive, motor and behavioral disturbances. Indeed, LBs are suggested to follow a distinct neuroanatomical route that corresponds with the stages of PD development.[17] According this model of idiopathic PD, often termed the Braak hypothesis, PD is characterized by progressing brain pathology, starting in the enteric nervous system and olfactory bulb (stage 1), gradually spreading to the midbrain (stage 3) by route of the brainstem (stage 2), and ultimately

Figure 1. Six stages of brain pathology in idiopathic Parkinson's disease. Reprinted by permission from Springer Nature: J Neural Transm, 110(5), Braak et al, Idiopathic Parkinson's disease (…), pp. 519, © 2003.



Footnote: b Stage 3 pathology, characterized by continued pathological ascent, reaching the amygdalar region, the cholinergic nuclei of the basal forebrain, and the SNc. The cerebral cortex becomes involved for the first time at stage 4, commencing with the anteromedial temporal mesocortex. At this stage, clinically evident symptoms often occur. **c** The higher order association areas of the neocortex become involved in stage 5, followed by the first-order association areas and primary fields in stage 6. Growing severity of the lesions is shown by increasing degrees of shading (red, violet, black).

affecting the cortex (stage 4) and the neocortex (stage 5-6), (see figure 1).[17] This highly influential staging scheme of disease progression is not only relevant for understanding the pathophysiology of PD, but also predicts the

order of development of PD-related symptoms. For example, the development of PD-related dementia (PDD) would be expected in Braak stages 5 or 6, where the prefrontal cortex and high-order sensory association areas are affected. In addition, one would expect that disturbances highly reliant on executive functioning would develop in later stages of the disease.

The exact pathological process that result in denervation of the SNc is still debated, but current models include aggregation of misfolded proteins, disruption of autophagic catabolism and mitochondrial dysfunction, to name a few. [18,19] Neurodegeneration is also seen in other areas of the basal ganglia and the brain, and dopaminergic dysfunction is apparent in other dopaminergic pathways, such as the mesocorticolimbic pathways.[9,12,20] In addition, the clinical development of PD is characterized by the involvement of several non-dopaminergic neurons, including monoaminergic neurons in the locus coeruleus, cholinergic cells in the nucleus basalis of Meynert, and hypocretin cells in the hypothalamus.[21]

1.1.4 Genetics

Two major types of genetic risk are related to PD: 1) casual mutations, directly resulting in PD; and 2) genetic variants that modify the risk of developing PD. Familial PD is characterized by early onset and has been associated with disease-causing mutations, including the leucine rich repeat kinase 2 (*LRRK2)*, VPS35 retromer complex component (*VPS35)* and synuclein alpha (*SNCA)* genes.[8] Approximately 5-10 % of patients have monogenetic forms of PD. The majority of cases are sporadic, probably caused by a combination of environmental and genetic risk factors. A total of >92 risk loci have been identified; most of which modestly modify the risk of developing PD.[22-24] Although these genetic markers provide some insights into the pathophysiology of PD, the direct effect of genetic variants, and the interaction between environmental factors, genetic variability and the pathophysiology of PD, is still unresolved.

1.1.5 Features and symptoms

1.1.5.1 Motor features of PD

PD is characterized by a clinical syndrome known as parkinsonism. This syndrome is defined by its obligate feature **bradykinesia,** defined by slowness of movement and a progressive reduction in speed and amplitude of movement. In addition to bradykinesia, other cardinal features include resting tremor and rigidity. **Resting tremor**, often presents unilaterally in the upper extremities of undiagnosed patients and may be the first symptom the patient notices. **Rigidity** is characterized by a consistent resistance throughout the range of motion of a limb. It often starts unilaterally, typically in the same limb as resting tremor, and can lead to pain and discomfort for the patient. **Postural abnormalities** are often considered as the fourth cardinal symptom of PD, and are characterized by changes in posture and gait instability. In PD, parkinsonism is often accompanied by secondary motor symptoms, such as hypomimia, bulbar dysfunctions, respiratory disturbances and oculomotor abnormalities.

1.1.5.2 Non-motor features of PD

PD does not only affect motor functioning. During the course of PD several non-motor cortices are affected by aggregation of α-synuclein and neuronal dysregulation, resulting in several neuropsychiatric, cognitive, sleep, autonomic and sensory disturbances (see figure 2).[25-27] One or more non-motor symptoms of PD are seen in nearly all patients,[28] and may have severe impact on patients' quality of life and caregiver burden.[29,30] In the following paragraph neuropsychiatric and cognitive symptoms associated with PD are briefly presented. Remaining non-motor symptoms are not elaborated further, as they are considered beyond the scope of this thesis.

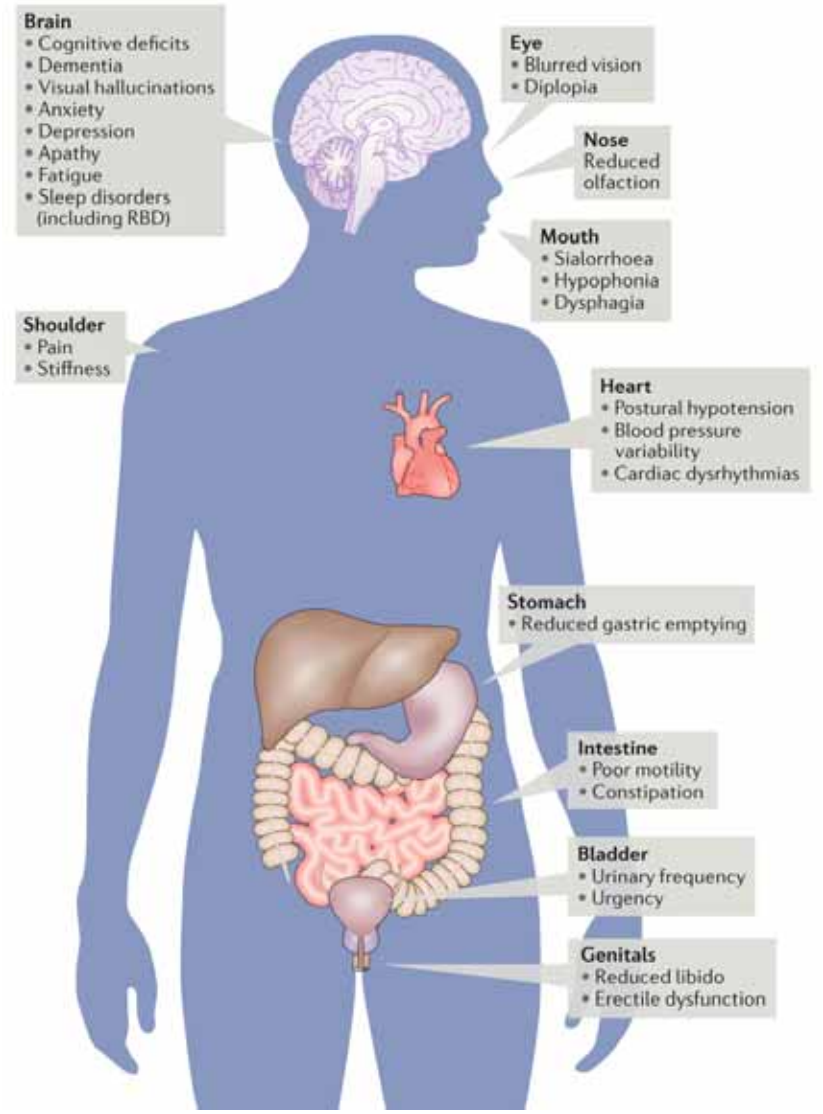
PD is associated with increased risk of neuropsychiatric symptoms, when compared to normal controls, affecting more than 50% of patients.[26,31] Depressive symptoms,[32] anxiety,[33] and apathy are most common in the early stages of PD,[34,35] with subsequent development of more severe neuropsychiatric symptoms, like psychosis, dementia or states of confusion in

later stages.[26] Multiple neuropsychiatric symptoms are also common in patients with more advanced PD.[26]

Cognitive decline is normal with increasing age, and may have negative consequences for people's quality of life and caregiver burden.[30,36] At the time of diagnosis, patients with PD have a twofold increased risk of cognitive deficits,[37] and patients exhibit accelerated decline in cognitive functioning over time,[38-41] illustrated by a mean decrease of one point per year on the Mini-Mental State Examination (MMSE) in one cohort.[42] However, the developmental trajectories of cognitive functioning differ between patients, and the timing of mild cognitive impairment (MCI) and dementia (PDD) is highly variable in PD.[43,44] MCI is a neurocognitive state characterized by cognitive decline beyond age-adjusted normative expectations. PD patients with MCI have intact daily functioning, but may have reduced performance on global cognitive tests, like MMSE or Montreal Cognitive Assessment (MoCA©), or impairment in at least two cognitive domains on domain-specific neuropsychological tests.[45] MCI is often a precursor of PDD, [41,43] especially when deficits are observed in the domains of attention, memory or executive functioning.[46-49]

According to current consensus criteria, PDD is characterized by two core features: 1) A diagnosis of PD according to current criteria; and 2) an incident dementia syndrome with slow progression, developing in the context of PD.[50] The dementia syndrome is defined as: the presence of impairment on one or more cognitive domains, which represents a clear decline from premorbid functioning, and occurs simultaneous with reduction in activities of daily life. Supportive symptoms include more specified cognitive deficits in one or more of the following domains: attention, executive functioning, visuospatial functioning, and memory. A range of neuropsychiatric symptoms may also support the PDD diagnosis. After 15 years of PD, 48 - 78 % of patients develop PDD, [50] which is often followed by nursing home placement.[51]It has been suggested that cognitive decline is caused by the neurodegenerative process of PD, which is supported by a correlation between cognitive decline and the evolution of motor symptoms and overall neuropathological staging of PD. [52,53] Indeed, MCI in PD has been associated with cortical thinning in several studies using neuroimaging.[54-57]

Figure 2. Potential non-motor features in PD. Reprinted by permission from Springer Nature: Nature Rev Neurosci, 18, Schapira et al, Non-motor features (…), pp. 438, © 2017.



Footnote: The non-motor features of Parkinson disease reflect deficits in various functions of the central nervous system and autonomic nervous system. Although some non-motor impairments precede motor abnormalities, most develop over time with progression of the underlying disease.

The pathophysiology of cognitive decline and PDD is not fully understood,[58,59] but is hypothesized to involve disturbances in dopaminergic, cholinergic and noradrenalergic pathways.[60,61] Dopaminergic dysfunctions related to prefrontal areas involved in executive functioning, cognitive flexibility and learning (termed the fronto-striatal dysexecutive syndrome[62]) have been suggested to predict cognitive development in patients with PD.[63-65] However, some authors argue that the dysexecutive syndrome might be unrelated to dementia development in PD.[62,66] In fact, data from the CamPaIGN-cohort suggest that cholinergic disturbances in posterior cortices (temporal, pariental and occipital lobes), are distinct from the dopaminergic dysfunctions, and may be predictive of dementia development.[66] Still, there might be considerable interaction between different pathophysiological processes in the development of cognition in PD. This includes genetic contributions,[67] such as the involvement of polymorphisms with marginal effects.[68,69] Thus, evidence suggests that cognitive decline and dementia in PD is casued by an interaction between the general neurodegenerative process of PD and premorbid genetic factors.[44,59]

1.1.6 Diagnosis

A definitive diagnosis of PD is ascertained by histopathological confirmation of neuronal degeneration with LBs within the SNc. Thus, no certain PD diagnosis can be established ante mortem. In the clinical evaluation of parkinsonism, differential diagnosis might be difficult, especially in the early stages of PD (see Table 1).

By applying strict diagnostic criteria, like the **United Kingdom Brain Bank (UKBB) criteria** (see Table 2), diagnostic accuracy may be improved.[70] Using the UKKB-criteria, a "definite" diagnosis is considered present if patients have a verified parkinsonian syndrome, do not fulfill any exclusion criteria and have at least three supportive prospective criteria. Although new diagnostic criteria have been developed,[71] the UKKB criteria are still widely used in clinical practice and research.

Table 1. Differential diagnoses in parkinsonian disorders. Adapted by permission from Springer Nature: Journal of Neurology, 255/suppl 5, Alves, et al, Epidemiology of Parkinson's disease, pp 19, © 2008

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

A further differentiation of the probability of a PD diagnosis can be made using the Gelb criteria from 1999.[72] These criteria reliably differentiate between possible PD, probable PD and definite PD, by evaluating the presence and number of cardinal symptoms of PD (called group A features), and the absence of alternative diagnoses (called group B features), and the treatment response to dopamine replacement therapy (DRT). According to the Gelb criteria, a definite diagnosis of idiopathic PD can only be done with histopathological confirmation.

Table 2. United Kingdom Parkinson's Disease Society Brain Bank clinical diagnosis criteria.[70]

Step 1. Diagnosis of parkinsonian syndrome

- Bradykinesia
- One of the following: Muscular rigidity, 4-6 Hz resting tremor, idiopathic postural instability

Step 2. Exclusion criteria for Parkinson's disease

- History of repeated strokes with stepwise progression of parkinsonian features
- History of repeated head injury
- History of definite encephalitis
- Oculogyric crises
- Neuroleptic treatment at onset of symptoms
- More than one affected relative
- Sustained remission
- Strictly unilateral features after 3 years
- Supranuclear gaze palsy
- Cerebellar signs
- Early severe autonomic involvement
- Early severe dementia with disturbances of memory, language og praxis
- Babinski sign
- Presence of cerebral tumor or communicating hydrocephalus on CT scan
- Negative response to large deses of levodopa (if malabsorption excluded)
- MTPT exposure

Step 3. Supportive prospective positive criteria for Parkinson's disease (≥3 symptoms)

- Unilateral onset
- Rest tremor present
- Progressive disorder
- Persistent asymmetry affecting side of onset most
- Severe levodopa-induced chorea
- Levodopa response for ≥5 years
- Clinical course for ≥10 years

1.1.7 Treatment

Currently there is no available curative treatment for PD. In the following, we will shortly address the most common pharmacological and non-pharmacological treatment options for the motor symptoms and to a certain degree the non-motor symptoms of PD.

1.1.7.1 Pharmacological treatment

First introduced in the 1960s, levodopa (LD) is the gold standard in the management of PD associated motor symptoms. As a precursor of dopamine, LD passes through the blood-brain-barrier, where it is metabolized to dopamine in the extracerebral tissue of the brain. In order to hinder peripheral metabolism in the gastrointestinal tract, LD is often given in combination with a decarboxylase inhibitor, like carbidopa or benserazidine.[73] LD is considered the most potent pharmacological treatment for motor symptoms in PD patients.[74] However, LD has diminishing effect over time and gives rise to motor complications, like dyskinesia.[73,75,76] According to the continuous dopaminergic stimulation theory, occurrence of motor complications seen in LD users is caused by molecular adaptation and pulsatile neuronal firing as a result of the short half-life of LD.[77] Treatment with LD is therefore often used conservatively in the early stages of PD, as delayed introduction of LD will also delay the development of motor complications.[76]

An alternative to LD is dopamine agonists (DAs), a class of DRT often used in hypodopaminergic conditions. DAs pass the blood-brain-barrier and stimulate postsynaptic dopaminergic receptors. DAs have high affinity to the dopamine receptors subtypes D_1, D_2 and D_3. In PD, DAs are often prescribed in the early stages of the disease due to its longer half-life (usually one daily administration) and reduced risk of developing motor complications such as dyskinesia.[76,77]

DA use is not without risk, and common side effects include nausea, vomiting, orthostatic hypotension, hallucinations, and impulse control disorders. Tapering or discontinuation of DAs have been associated with a dopamine withdrawal syndrome (DWAS), characterized by a severe cluster of physiological symptoms like orthostatic hypotension, nausea, vomiting, diaphoresis, pain, and psychological symptoms, such as depression, panic

attacks, fatigue, agitation, irritability, dysphoria, suicidal ideation and drug craving.[78]

In addition to the DRT described above, two other pharmacological interventions are common in the management of PD. First, Catechol-O-methyltransferase (COMT) inhibitors are often used adjunctive to LD, as they prevent metabolism of LD into 3-O-methyl-dopa. COMT inhibitors increase half-life and bioavailability of LD, resulting in reduced off-time. Second, monoamine oxidase type B (MAO-B) inhibitors prevent metabolism of dopamine in the striatum, and may have a slight neuroprotective effect,[79] but usually inhibitors provide a modest antiparkinsonian effect in itself.

Advanced treatment of PD

In addition to traditional pharmacological treatment, advanced interventions have been developed for PD patients with insufficient effect of standard pharmacological treatment.[80] Device-aided interventions include subcutaneous apomorphine injections, continuous subcutaneous apomorphime infusions, continuous jejunal infusion of levodopa-carbidopa intestinal gel, and deep brain stimulation. To date, comparative data between available advanced interventions is lacking. An individualized treatment approach, were comorbid neuropsychiatric disturbances, cognitive status, type and persistence of motor complications, and surgical contraindication are considered, is recommended at more advanced stages of PD.[80,81]

1.2 Impulsive and compulsive behaviors

Impulse control disorders and related behaviors (ICDs) are prevalent complications of DRT in patients with PD. In the International Classification of Diseases 11th revision (ICD-11), ICDs are characterized by a persistent failure to resist an impulse or urge to perform rewarding actions that endure despite the negative consequences.[82] Other defining criteria include an increasing sense of arousal or tension prior to the act, and an experience of pleasure, gratification or release of tension at the time of committing the act.[83] These behavioral disorders are estimated to be prevalent in 1-8 % of the general population,[83] and afflicted patients often present with significant functional impairment.[84-86] The phenomenology of ICDs includes traits of

both impulsivity and compulsivity. These terms are highly related to loss of inhibitory control, probably mediated by diminished top-down (prefrontal) control over subcortical regions. Impulsive behaviors are characterized by inhibited, premature and inappropriate actions, while compulsive behaviors are clearly repetitive and preservative.[87,88] Although disorders in the impulsive-compulsive spectrum include both impulsive and compulsive behavioral tendencies, the relative proportion of these symptoms varies in different ICDs.[87]

The nosology of ICDs has been heavily debated in recent years.[89] As these behaviors are common in the general population, and share several traits with substance use disorders, many authors have argued that ICDs, such as gambling disorder and gaming disorder, should be recognized as behavioral addictions rather than ICDs.[89-93] In addition, there are clinical, neurobiological and genetic indications suggesting that ICDs, behavioral addictions and obsessive compulsive disorders could be considered as phenotypic parallels on the same pathological spectrum.[87,93-96] Following this discussion, gambling disorder has been recognized as a behavioral addiction in the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-V) and ICD-11,[97] and gaming disorder (described as impaired control over gaming behavior, increasing priority given to gaming over other activities, and persistent or escalating gaming despite negative consequences) has also been included as a behavioral addiction in ICD-11.[82] Several clinical phenomena have been suggested to be included in the spectrum of behavioral addictions, including kleptomania, pyromania, compulsive buying, compulsive sexual behavior, buying-shopping disorder, internet addiction and binge eating disorder.[98-100] However, due to lacking empirical data, these clinical phenomena are currenly not recognized as behavioral addictions.[88,91,97,101]

In PD, a range of impulsive and compulsive behaviors have been identified: gambling disorder, compulsive sexual behavior, compulsive eating, compulsive shopping, hobbyism, punding and an addiction-like use of DRT. Although this list is not exhaustive,[102-105] these behaviors are the most prevalent ICDs in patients with PD,[106,107] and will be briefly presented in turn.

1.2.1 Gambling disorder

According to DSM-V, gambling disorder (GD) is defined as persistent and recurring maladaptive gambling behavior, resulting in clinically significant impairment or distress (see table 3).[97] GD is characterized by several impulsive behavioral patterns, like "chasing one's losses", which are further enhanced by several cognitive deficits, such as attentional bias, altered decision making and cognitive distortions.[87,92,108,109]

While gambling behavior is common in most cultures, GD is a relatively uncommon phenomenon. Prevalence estimates range from 0.2 to 5.3 % in adults worldwide, with significant variation between cultures and countries.[108,110] Risk factors include male gender, low socioeconomic status and divorce or separated marital status.[108,111] Young age has also been associated with PG, with most an age of onset of gambling problems in the mid-20s.[111] Patients

Table 3. DSM-V diagnostic criteria for Gambling Disorder.[97]

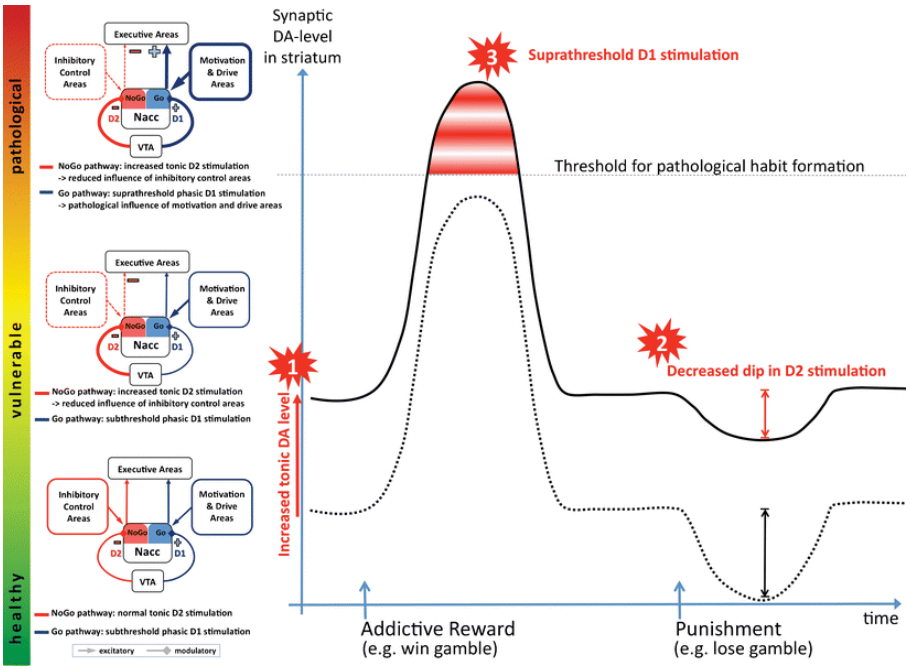
A. Persistent and recurrent problematic gambling behavior leading to clinically significant impairment or distress, as indicated by the individual exhibiting four (or more) of the following in a 12-month period: 1. Needs to gamble with increasing amounts of money in order to achieve the desired excitement. 2. Is restless or irritable when attempting to cut down or stop gambling. 3. Has made repeated unsuccessful efforts to control, cut back, or stop gambling. 4. Is often preoccupied with gambling (e.g., having persistent thoughts of reliving past gambling experiences, handicapping or planning the next venture, thinking of ways to get money with which to gamble). 5. Often gambles when feeling distressed (e.g., helpless, guilty, anxious, depressed). 6. After losing money gambling, often returns another day to get even ("chasing"one's losses). 7. Lies to conceal the extent of involvement with gambling. 8. Has jeopardized or lost a significant relationship, job, or educational or career opportunity because of gambling. 9. Relies on others to provide money to relieve desperate financial situations caused by gambling.
B. B. The gambling behavior is not better explained by a manic episode.

with GD have increased risk of developing a psychiatric comorbidity, reduced physical health, socioeconomic difficulties and higher rates of suicide. [108,110] The prognosis of GD is highly variable, ranging from episodic gambling to chronic gambling behavior.

Premorbid risk factors may also be present, including trait impulsivity, sensation seeking personality traits and genetic factors.[110,112] Findings from twin studies and gene association studies indicate that there is a considerable genetic component to the risk of GD in the general population.[110,113] GD has been associated with polymorphisms in genes related to the dopaminergic and serotonergic pathways,[110,113] which parallel findings from research on substance related addictions.[114] It has been suggested that GD and other behavioral addictions are related to a "Reward Deficiency Syndrome" (RDS), a neuropsychological state that aims to explain the relationship between genetic factors, environmental factors and addiction phenotypes.[113,115] However, genetic exploration of patients with GD is still in its infancy, and further studies are needed to fully understand the role of genetics in the development of GD.[110]

GD is the behavioral addiction with the most extensive research so far, and is therefore considered the most prototypical behavioral addiction.[87,110] Although the pathophysiology of GD is still debated,[116] the current model of GD poses it as a multifaceted disorder, with several similarities with substance use disorders.[87,110] In this model, individual vulnerability of genetic, environmental or psychological nature increases the risk of excessive dopaminergic stimulation of the mesocorticolimbic pathways, resulting in a blunted dopaminergic response to new stimuli, pathological habit formation, altered reward evaluation and loss of inhibitory control (see figure 4).[117,118] However, evidence suggest there are multiple pathways to dopaminergic dysregulation, which also involve other neurotransmitter systems, such as the serotonergic, noradrenergic and opioid system.[108,114]

Figure 4. A model of dopaminergic activity in the striatum, and subsequent influence of appetitive and inhibitory areas on executive control. Reprinted under the Creative Commons Attribution License from Springer US: Curr Neurol Neurosci Rep, 13, Probst, van Eimeren [119] (2013).



Footnote: *Right panel*, *dotted line* normal tonic and phasic DA release from the ventral tegmental area to the NAc. *Left panel, bottom* the influences of inhibitory and appetitive areas are well balanced and adequately regulated. *Solid line 1* vulnerable individuals have an increased tonic DA level, leading to reduced influence of inhibitory control areas via increased D2 receptor activation *(left panel, middle)*; *2* increased D2 receptor activation interferes with the dip following punishments; *3* adequate reinforcing stimuli now lead to suprathreshold D1 receptor stimulation, which drives the formation of pathological habits (*left panel, top)*.

1.2.2 Compulsive sexual behavior

The nature and nosology of compulsive sexual behavior (CSB) is disputed,[120] and a multitude of terms have been used to describe excessive sexual

behavior, including hypersexuality, sex addiction, nymphomania and satyriasis.[96,121] In ICD-11, CSB is categorized as an impulse control disorder and defined as a persistent failure to control sexual impulses or urges, resulting in repetitive sexual behavior.[82] This preoccupation and repetition of behavior may lead to personal neglect and loss of interest in other areas, and is persistent despite numerous efforts to reduce the behavior. Loss of satisfaction from repetitive sexual activity is also common.

Due to the lack of both data from the general population and formal diagnostic criteria, the epidemiologic and clinical profile of CSB is not well formulated. Data from a small sample of students suggest that CSB is prevalent in 2% of young adults, and associated with increased levels of psychological distress, poor self-esteem, and increased rates of social anxiety disorder, attention-deficit/hyperactivity disorder and a range of behavioral addictions.[96,122] Comorbid substance abuse is also common.[123] The neuropathology of CSB has been suggested to share several traits with gambling disorder and other behavioral addictions; i.e. dysfunctions in the mesocorticolimbic pathways may lead to aberrant regulation of reward processing and decision-making, resulting in altered cognitive processing and loss of control.[96,123] However, the neuropathology of CSB remains understudied,[121] and further studies are required to fully understand its nature.

1.2.3 Compulsive eating

Compulsive eating (CE) is characterized by uncontrolled overeating of "comfort foods", commonly containing high levels of fat and/or sugar.[124] CE is currently not recognized as a diagnostic category in itself,[125] and people with such behaviors are often diagnosed with "binge eating disorder". Although the definition and phenomenology of CE varies in studies, prevalence rates range from 1.0 to 4.6 %, with slightly higher rates in women.[98] CE has potential negative consequences with regards to both physical and mental health, such as increased risk for obesity (body mass index > 30), lower health-related quality of life and higher frequency of comorbid psychiatric disorders.[125]

CE is characterized by three behavioral tendencies: habitual overeating, overeating to relieve a negative emotional state and overeating despite adverse

consequences.[126] The pathophysiology driving these behavioral manifestations is not well understood, but emerging models suggest that it shares several traits with the pathophysiology of substance related addiction and GD.[117,125,127] CE is therefore believed to share genetic risk profiles with other addictions.[125]

1.2.4 Compulsive shopping

Compulsive shopping (CS) is characterized by excessive and uncontrolled preoccupation, urges or behaviors related to shopping or spending, resulting in adverse consequences for the individual or others.[84] As is the case with most ICDs and behavioral addictions, there has been a great deal of controversy surrounding the nomenclature and nosology surrounding CS, and currently it is not recognized as a disorder in neither the ICD-11 or the DSM-V.[95] In clinical practice patients presenting with CS-like symptoms are therefore classified using a residual category, such as the "other specified disruptive, impulse control, and conduct disorders"-category in DSM-V, or the "other specified ICDs" in the ICD-11.[95] In order to evaluate the severity of these symptoms, the use of provisional diagnostic criteria, such as those proposed by Black [84] or Lejoyeux, Tassain, Solomon, Ades [128], is reccomended.

CS occurs in 3.4 to 6.9 % of the general population, is more prevalent in women, and is typically first seen in the late teens and early adulthood.[84,129-131] Psychiatric comorbidity is common, especially in the affective and addiction / obsessive-compulsive spectrum, and CS is often seen in patients with personality disorders.[132] Due to a lack of longitudinal data, the prognosis of CS is uncertain, but cross-sectional data suggest that CS may persist for many years, and have both an episodic and continuous presentation.[95] The pathophysiology of CS is not well understood and relatively understudied.

1.2.5 Related compulsive behaviors

Related compulsive behaviors include a range of compulsive behavior manifestations, such as hobbyism, punding and walkabout. These behaviors are uncommon in the general population and mostly often seen in patients with amphetamine or methamphetamine addiction, PD or dementia.[133-136] Stereotypical behaviors are also observed in patients with developmental

disabilities, but the etiology of such behaviors are most likely different for this group.[137]

Punding includes stereotypical repetition of monotonous activities, like sorting of objects, hoarding, tinkering, grooming, or pointless walking or driving (often termed walkabout).[135] For some patients the focus of the repetitive behavior is related to previous interests and hobbies (often termed hobbyism). Patients displaying these behaviors are often deeply absorbed in their actions, and obstructing patients from performing these may result in irritability and anxiety.[135,138]

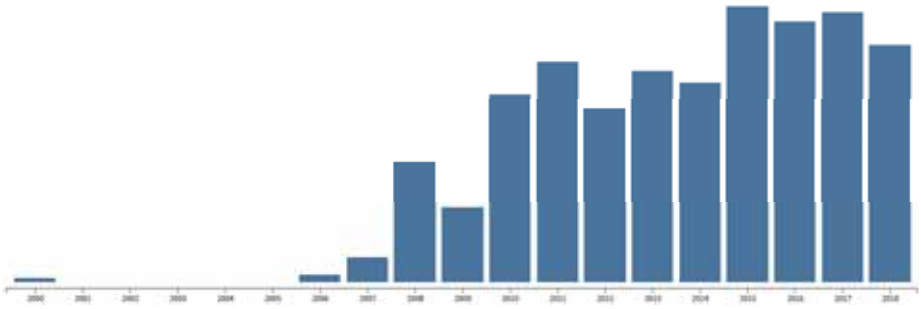
1.3 Impulse control disorders in Parkinson's disease

Despite the nosological discussion in the field, in PD research the term "ICDs" is commonly used to encompass the large array of impulsive and compulsive behaviors displayed by patients with PD. Other terms, such as "impulsive control behaviors",[139] "impulsive-compulsive behaviors",[140,141] "impulse control symptoms",[107] "impulse control and related behaviors",[142] and "impulse control and repetitive behavior disorders",[143] have also been used. In this thesis the term "ICDs" will be used to entail the range of impulsive and compulsive behaviors seen in patients with PD.

1.3.1 History of impulse control disorders

The earliest mentions of an ICD in relation to PD span back to the late 1960s, where increased libido was observed in patients using LD. [144-147] In the early 2000s, the punding and hobbyism was first described in patients with dopamine dysregulation syndrome (DDS),[135,148-150] and addiction-like overuse of dopaminergic medication sometimes seen in PD patients.[138] GD,[151,152] CE,[153] were also first recognized in at this time, and although these behaviors were first believed to be a part of DDS,[138] it was later also observed in patients without DDS.[154-156] These observations resulted in widespread scientific inquiry into the full range of ICDs, and a major increase in the rate of publications in the following years (see figure 5).

Figure 5. Number of publications per year between 1987 and 2018



Footnote: Number of publications using the terms "impulse control disorders" AND "Parkinson's disease" catalogued in the Web of Science Core Collection in the period between 1987 and 2018 (timeline starts with first publication in database) [retrieved 07.01.19].

1.3.2 Diagnosis

In patients with PD, GD, CE (diagnosed with binge eating disorder) and CSB are diagnosed according to the established diagnostic criteria of the ICD-11 or DSM-V.[82,97] In lieu of established diagnostic criteria, punding and related behaviors,[135,157] CS,[84] and DDS,[150] are diagnosed based on proposed provisional criteria. As the ICDs in PD are mainly attributable to PD-specific factors, such as the use of DRT, clinicians could use "Secondary impulse control syndrome" from the ICD-11 to specify the relation between ICDs and PD.

When assessing ICDs, the main differential diagnoses are hypomania or manic episodes, which are characterized by abnormal and persistently elevated, expansive or irritable mood, grandiosity, sleep disturbances, increased talking and distractibility and increased novelty and pleasure seeking behavior. [97]

1.3.3 Epidemiology and risk factors

The prevalence of ICDs has been estimated to range between 13.6 and 60 % among patients with PD,[140,158] far exceeding the estimated prevalence of ICDs in the general population.[83] In the largest study of ICDs to date, based on 3090 PD patients from the DOMINION-study, the overall frequency of GD, CSB, CE and CS was 13.6 %, when using the Minnesota Impulsive Disorders Interview (MIDI).[158] With the development of the self-report Questionnaire for Impulsive-Compulsive Disorders in PD (QUIP),[106] exploration of the full range of ICDs seen in PD was possible, leading to more precise frequency estimates.[139-143,159-161] Several studies have compared the frequency of ICDs and related behaviors in PD patients and controls, and a recent meta-analysis of 14 case-control studies estimated that PD patients have an odds ratio of 2.07 (1.26 – 3.48) when compared to normal controls.[162] Still, prevalence estimates vary substantially between studies, possibly due to differences in recruitment strategies and assessment procedures. Of note, most studies recruited PD patients from tertiary movement disorders centers, thereby resulting in selection bias.

Several demographic risk factors are identified, for example younger age has been associated with ICDs in several studies.[141-143,158,159,163-166] In some cohorts,[143,164,165,167] male gender has been associated with increased frequency of ICDs, although other studies did not find this.[164,168] Patients with ICDs also demonstrate increased trait impulsivity,[169,170] but emerging evidence suggest that this is related to increased severity of ICD symptoms, rather than genesis.[171] However, premorbid personality traits may still be associated with ICD symptoms.[172] In a Danish study of 490 patients with PD, presence of ICDs was significantly associated with higher scores on neuroticism and lower scores on agreeableness and conscientiousness, as measured by the NEO-Personality Inventory.[141]

ICDs may have detrimental familial, economic and legal consequences, leading to reduced levels of quality of life in affected patients.[173-175] This is also illustrated by the presence of negative coping strategies among PD patients with ICDs.[176]

1.3.4 Relation to dopamine replacement therapy

Although several demographic risk factors exist, ICDs are likely to develop in PD as a result of DRT, and in particular the use of DAs.[135,139,141-143,158,159,166,177-180] This observation has also been made in other disease groups using DAs, such as restless legs syndrome,[181] prolactinoma,[182] and fibromyalgia.[183] Although most studies have identified DAs as the main pharmacological risk factors, there are several reports of patients developing these symptoms after initiation of LD treatment.[145,148,158,184] However, the involvement of LD has been contested,[185] and appear to be most prominent in punding-related behaviors and DDS.[135,186,187] Still, the association between ICDs and DRT is clear,[162] which is illustrated by comparable ICD frequencies between *de novo* PD patients and normal controls.[107,188]

The pathophysiological effect of DAs has been subject to several studies, including experimental studies using behavioral paradigms. In one study, patients with and without ICDs completed the Balloon Analogue Risk Task in two DA-conditions ("on" and "off" DAs).[189] In this study patients with ICDs demonstrated increased risk taking when "on", while patients without ICDs did not. Similar findings are reported in other experimental studies.[190-192]

Although DA-exposure is considered the main risk factor for ICDs in PD, many patients do not demonstrate such susceptibility to this type of DRT. Therefore, it has been hypothesized that individual differences in dopamine receptor subtypes, DA signaling or cortical integrity could explain the ICD development in susceptible individuals.[193-198] In addition, prolonged exposure to exogenous dopamine has been suggested to alter the phasic and tonic activity in dopaminergic neurons, resulting in altered receptor density and physiology.[199] However, there is currently no evidence that allow clinical differentiation between patients at risk and patients without risk of ICDs when exposed to DAs.

1.3.5 Associated symptoms and cognition

In a comprehensive review and meta-analysis of patients with PD, Martini and colleagues identified significant associations between ICDs and depression, anxiety and anhedonia, a group of neuropsychiatric symptoms with a high

degree of symptom overlap.[200] These associations may have been caused by overlapping pathophysiology.[201] However, some authors have argue that more depressive symptoms in PD patients with ICDs are associated with psychological factors, such as the degree of self-awareness.[202]

As a result of disease progression, motor complications, psychotic symptoms and dementia are common in the later stages of PD.[39,75,203] Some authors have argued that motor fluctuations, psychosis and depression may comprise a risk profile for ICD development in patients with PD. Especially the association between ICDs and dyskinesias has been subject to much debate.[204] In a recent study based on data from 654 participants from the National Institute of Neurological Disorders & Stroke Parkinson's Disease Biomarkers Program, Hinkle and colleagues identified a significant association between presence of psychotic symptoms, dyskinesias and ICDs.[205] However, this association needs to be replicated in other PD cohorts.

The cognitive status of PD patients with ICDs has been the subject of several papers, including two meta-analyses.[200,206] Although ICDs do not seem to be related to increased risk of "global" cognitive deficits in PD,[206,207] cognitive dysfunctions have been demonstrated in two domains related to executive functioning, specifically: reward-related decision making and set-shifting tasks.[200]

1.3.6 Assessment of impulse control disorders

Due to the potential devastating consequences of ICDs, these symptoms should be screened for throughout the course of PD. There are several screening tools and neuropsychological tests that can be used to assess the presence of ICDs in patients with PD. Two screening tools are commonly used to assess ICDs in normal clinical practice are QUIP and Movement Disorders Society's Unified Parkinson's Disease Rating Scale (MDS-UPDRS) item 1.6.[106,208]

QUIP consists of two items evaluating four ICDs and excessive dopaminergic medication use, with the addition of one item evaluating three types of compulsive behaviors. Included ICDs are: compulsive gambling, hypersexuality, compulsive eating and compulsive shopping. The three

stereotypical behavioral disorders include: hobbyism, punding and walkabout. A score of ≥1 on any question is considered a positive indication of ICD presence.[106] QUIP is validated in a US convenience sample of 157 PD patients, against published criteria for compulsive gambling,[209] buying,[128] hypersexuality,[210] eating,[209] punding,[150] hobbyism[175] and walkabout.[150] Although included in this study, the DDS-items was not validated due to low frequency of DDS in the validation cohort.[106] However, the DDS items in QUIP are still used to indicate of the presence of DDS in patients with PD.[141,142] The QUIP short form has similar psychometric properties as the full 30-item QUIP screening tool, with a sensitivity of 94%, indicating less chance of type II errors (negative predictive value 0.96). However, there is risk of type I errors when using either the 30-item QUIP or the QUIP short form (specificity = 0.79 and 0.72, respectively).[106] Consequently, in clinical practice QUIP is best suited as a screening tool, followed by a more thorough clinical interview if the screening is positive. In clinical research, QUIP has been widely used as a screening tool in large cohort studies, such as the Parkinson's Progression Markers Initiative (PPMI)-study.[107]

MDS-UPDRS item 1.6 assesses the interference of ICDs or DDS with the patients' functionality and quality of life. It is scored on a 0 – 4 Likert scale, with higher scores indicating increasing severity of ICD symptoms.

Presence and severity of ICDs can also be evaluated using the Parkinson's Impulse-Control Scale, a semistructured interview for ICDs specifically developed for the PD population.[211] MIDI is an interview schedule of nine ICDs, which has been commonly used in epidemiologic studies of ICDs.[212] Originally developed in 2008, MIDI has recently been revised in accordance with the new diagnostic criteria in DSM-V.[213] MIDI consists of two modules for each ICD: first a general screening question about the specific disorder is asked if the screening question is positive, thereafter a clinical interview based on diagnostic criteria is completed. A MIDI module is considered positive if all the items of one disorder are positive.

1.3.7 Pathophysiology

The pathophysiology of ICDs in PD is still unresolved, but current evidence suggest that ICDs may be caused by excessive dopaminergic drive in the

mesolimbic reward processing areas of the brain.[200,204] In PD, neurodegeneration of the dorsal striatum is common, while the ventral striatum, which is mainly involved in regulation of mesocorticolimbic pathways, is often intact.[214] Stimulation by exogenous dopamine could therefore lead to dysregulation of the ventral striatal pathways, which include the nucleus accumbens, and thereby produce a "hyperdopaminergic state" in the regions involved in reward related decision making, reward processing, motivation and impulse control.[204,214,215]

This state of "hyperdopaminergic drive" is suggested to be the result of several factors, including premorbid factors like genetic vulnerability.[204] Genetic risk profiles suggest that patients with PD have similar genetic variations as previously found in patients with ICDs in the general population.[216,217] Still, PD-specific factors such as reduced dopamine transporter-levels in the dorsal striatum, degeneration of dopaminergic receptors and postsynaptic dopaminergic sensitization, may also contribute to the increased risk of ICDs in PD.[196,204,218] Finally, other neurotransmitter systems such as the serotonergic system, is also likely involved in the pathophysiology of ICDs, but more studies are needed to explore these associations further.

1.3.8 Genetics

The association between ICDs and DRT, and DAs in particular, is well established. However, not all patients exposed to DAs develop ICDs, arguing for the presence of premorbid or disease-specific risk factors. Therefore, efforts have been made to explore the genetic origin of ICDs in patients with PD.

A summary of identified single nucleotide polymorphisms (SNPs) in relation to ICDs in PD is shown in table 4. The involvement of genetic variations associated with ICDs in patients with PD was first documented in a Korean cohort of 404 PD patients, where 14.4 % had ICDs, when assessed with a modified version of the MIDI. [219] In this study, the association between ICDs and SNPs in the dopamine receptor D2 (*DRD2*), *DRD3* and glutamate ionotropic receptor NMDA type subunit 2B (*GRIN2B*) genes was investigated, and increased frequency of ICDs among carriers of the AA

genotype of the *DRD3* SNP rs6280 and CC genotype of the *GRIN2B* SNP rs7301328 was identified. The involvement of SNPs in the genes encoding the D_2-like receptors (D_2, D_3 and D_4) have been of paramount interest this field due to the high affinity of DA for this class of receptors and the previous association between SNPs in these receptors and ICDs in the general population.[220,221] Several studies have investigated the genetic variance of the D_2-like receptors, but results are conflicting (see table 4). In addition, there are conflicting results of the association between SNPs in the *DRD_1*-gene, which encodes for the D_1-receptor.

While polymorphisms of *DRD* genes may result in altered expression of dopamine-receptors, dysfunction of other processes of the dopaminergic transmission may also be implicated in the pathophysiology of ICDs. Conversely, SNPs in the dopa decarboxylase (*DDC*), *COMT* and *DAT* genes, which are involved in the synthesis and transport of dopamine, have also been implicated in the pathology of ICDs. [217,222-224] Overall, genetic variations in the dopaminergic pathways may be involved in the genesis of ICDs in PD, but results are currently conflicting. However, these studies give indirect evidence in support of a dopaminergic model of ICDs in patients with PD.

Footnote for table 4: All genes are shown in *italics*. Abbreviations: SNP=Single nucleotide polymorphism; ICDs=Impulse control disorders; DA=Dopamine agonists; LED=Levodopa equivalent dosage; *DRD1-3*=Dopamine Receptor D1-3; *ANKK1*=Ankyrin repeat and kinase domain containing 1; *COMT*=Catechol-O-methyltransferase; *DDC*=Dopa decarboxylase; *DAT*=Dopamine transporter; *HTR2A*=5-hydroxytryptamine receptor 2A; *SCL6A4*=Solute carrier family 6 member 4; *TPH2*=Tryptophan hydroxylase 2; *GRIN2B*=Glutamate ionotropic receptor NMDA type subunit 2B; *OPRK1*=Opioid receptor, kappa 1; *OPRM1*=opioid receptor mu 1.

Table 4. Previous published genetic variants investigated in association with ICDs and related disorders in patients with PD.

Gene	**SNP**	**Identified variant and associated risk**
Dopamine pathway		
DRD1	rs4867798	C allele: Increased risk[225]
	rs4532	T allele: Increased risk[225]
	rs265981	No impact[225]
DRD2/ANKK1	rs1800497	T-allele: Increased risk[225,226] No impact[219,224]
DRD3	rs6280	No impact[225] CT genotype: increased risk[227,228] AA genotype: increased risk[219] No impact[225]
	rs3732783	
DDC	rs383709	-/AGAG genotype: Increased risk in DA users[217]
	rs3837091	-/- genotype: increased risk in DA users[217]
COMT	rs4680	No impact[224]
DAT	VNTR	No impact[224] Decreased risk[222,223]
Serotonergic pathway		
HTR2A	rs6313	T allele: Increased with low LED[229] GA genotype: Increased risk in DA users[217] No impact[227]
SLC6A4	5HTTLPR-region	No impact[219]
TPH2	rs6582078	GG genotype: Increased risk[223]
Glutamatergic pathway		
GRIN2B	rs7301328	C allele: Increase risk[225] CC-gentotype: Increased risk[219]
	rs1019385	No impact[219]
	rs1806201	No impact[219,227]
Opioid pathway		
OPRK1	rs702764	TC genotype: Increased risk in DA users[217]
OPRM1	rs179991	AA genotype: suggested protective for ICDs.[222]

Polymorphisms in the opioid pathways, in particular genes encoding for mu-opioid (*OPRM1)* and kappa-opioid (*OPRK1)* receptors, have been suggested to play a role in the neurocircuitry of ICDs in both in the general population and in patients with PD.[217,230,231] Although the mechanisms are not fully understood, these receptors have been suggested to regulate the dopaminergic tone in the striatum, and thus modify the risk of ICDs. This hypothesis has also received support from pharmacological studies, where the mu- and kappa-receptor antagonist naltrexone reduced the severity of ICDs in the general population.[232] However, more studies are needed to understand the involvement of the opioid-pathways in patients with ICDs and PD.

In the field of genetic association studies, there are several methodological issues that may increase the likelihood of conflicting findings and difficulties with replication of findings. Sufficient power to study the numerous candidate genes and SNPs that may be involved in ICDs in PD demands large cohorts that far exceed the site of most current PD studies. This gives rise to a common issue with generalizability between studies, and increases the chance of conflicting results and false negatives or positives. This limitation must be addressed by increasing the number of participants in a study, most commonly achieved by combining data from different cohorts. Novel computational strategies have also emerged, specifically with the introduction of penalized regression modelling. [233-236]

1.3.9 Course, prognosis and treatment strategies

The course and prognosis of ICDs in patients with PD is largely unknown, especially in the late stages of PD.[177,237-242] A major methodological problem is the lack of control groups without PD in previous studies, making estimation of the longitudinal course difficult. To date, the course of ICDs is contingent upon optimal regulation of DRT, and symptoms may alleviate adjustment or discontinuation of DAs. However, modification of DRT is not viable in all cases.[243] Complications such as DWAS, worsening of motor symptoms following discontinuation, or development of affective symptoms like depression, apathy and anxiety are common. Therefore, several efforts have been made to identify alternative pharmacological strategies, such as amantadine, naltrexone and atypical antipsychotics.[214] However, similarly to ICDs in the general population, results have been conflicting.[243-246] In the

general population, psychological interventions such as cognitive behavioral therapy (CBT) are a common treatment strategy for ICDs.[95,247] CBT has also been examined in PD patients with ICDs, with promising results.[248,249] However, to date only one trial has been completed, and the efficacy of CBT needs therefore to be evaluated in independent cohorts before clear recommendations for use in clinical practice can be made. In summary, the current clinical recommendation is to monitor ICDs carefully in PD patients, and to adjust or discontinue DAs if ICDs is present.

2 Aims of the thesis

The primary aims of this thesis were to describe the epidemiology, genetic risk and long-term trajectory of ICDs in patients with PD. To obtain this information we posed the following research questions: 1) How common are ICDs in patients with PD when compared controls; 2) what are the risk factors and clinical correlates of ICDs in patients with PD; and 3) which genetics risks are associated with ICDs in patients with PD? In order to address these questions we have

- examined the frequency of impulsive and compulsive behaviors in a population-based cohort of patients with PD and normal controls, and investigated clinical, cognitive and neuropsychiatric correlates of these behaviors in PD (paper I);
- investigated if of common genetic variants (polymorphisms) across several neurotransmitter pathways are related to ICD presence in patients with PD (paper II);
- investigated the association between dyskinesias, psychosis and ICDs in patients with PD (paper III);
- described the longitudinal evolution of ICDs in patients and normal controls, and examined the long-term cognitive changes associated with ICDs in patients with PD (paper IV).

3 Methodology

1.4 Study design

All participants in this thesis were recruited from the Norwegian ParkWest study, a prospective, population-based, multicenter cohort study of the incidence, neurobiology and prognosis of PD.[5] The Norwegian ParkWest study was approved by the Western Norway Regional Committee for Medical and Health Research Ethics, REK reference 131.04 and 2010/1700 (see appendix), and signed written informed consent was obtained from all participants at the time of inclusion to the study (see appendix).

1.5 Recruitment of patients with Parkinson's disease

The Norwegian ParkWest study is comprised of participants recruited from four counties in the Western and Southern areas of Norway: Sogn and Fjordane, Hordaland, Rogaland and Aust-Agder (total population exceeding 1 million inhabitants). All newly diagnosed patients within this region were recruited between November 1st, 2004 and August 31st, 2006. To achieve this several strategies for recruitment were implemented: 1) manual screening of all referral letters to the participating hospital neurological departments, 2) notification of general practitioners within the region of interest, 3) electronic searches for newly diagnosed patients within 3 months of the study start, 4) an electronic population screening for diagnostic codes for parkinsonism within the largest participating region, and 5) search for antiparkinsonian drug prescriptions.

Of 604 subjects screened, 265 fulfilled the diagnostic criteria for PD.[5] A total of 212 patients consented to long-term follow up, 207 of which were drug naïve at baseline. During follow up a total of 20 subjects have been re-diagnosed, and excluded from the analyses.

Evaluation of ICDs was first introduced 5 years after the baseline visit, wherein 158 patients with PD remained in study. Of these, 28 were diagnosed with PDD, and 5 patients did not respond to QUIP, yielding 125 non-demented patients eligible for study of ICDs. During the course of this thesis one patient included in paper I and II was re-diagnosed following autopsy. For

papers III and IV this participant was excluded from analyses, leaving a cohort of 124 patients included in these papers.

1.6 Control subjects

A group of 205 normal controls (NCs) were recruited from friends and spouses of patients with PD, or from social clubs for elderly in the same geographical area as the patients. In order to ensure a control population with normal aging, no exclusion criteria besides the absence of parkinsonism were imposed during recruitment. At the first evaluation of ICDs, 164 NCs were still in the study. Of these, one NC had dementia, and was excluded from further analyses. Four NCs did not respond to QUIP, leaving 159 NCs relevant for this study. An additional three NCs developed incident PD during the course of this thesis, and were excluded from analyses in paper IV.

1.7 Assessment

1.7.1 Diagnostic procedure for Parkinson's disease

A clinical diagnosis of PD was determined according to the UKBB criteria for idiopathic PD (see table 2) and the Gelb criteria.[72]

1.7.2 Assessment of impulse control disorders

ICDs were assessed using a Norwegian translation of the short form version of the QUIP (see appendix).[106] This self-report measure was first introduced at the 5 year follow-up visit in the Norwegian ParkWest study. In accordance with the original publication, a cut off score of ≥1 was defined as a positive screen for presence of ICDs.[106]

1.7.3 Assessment of motor symptoms

Progression of motor symptoms was assessed using the Unified PD Rating Scale (UPDRS), a clinician administered rating tool developed in 1987.[250] The UPDRS is widely used in clinical practice and in research settings, and has proved to be both reliable and valid in gauging the development of PD over time. The UPDRS is comprised of four subscales evaluating mental,

behavioral and mood (part I), activities of daily living (part II), motor examination (part III), and complications of therapy (part IV). In part I-III, items are scored on a five-point Likert scale (0-4), with increasing scores indicating increasing severity of symptoms. The Hoehn and Yahr (H&Y) staging scale ranges from 1 to 5, and measures impairment and disability of movement, gait and balance. [251] Increasing scores on the H&Y-scale indicate more advanced PD and more pronounced loss of independence.

In this thesis, UPDRS part II (paper I-IV), UPDRS part III (papers 1-IV) and the dyskinesias item (32) from UPDRS IV (paper III) were used.

1.7.4 Assessment of non-motor symptoms

Severity of depressive symptoms was assessed using the Montgomery and Aasberg Depression Rating Scale (MADRS),[252] a 10-item physician-administered scale completed during a clinical interview. All items are scored by defined scale steps, ranging from 0 to 6. In PD, a cut-off score above 17 indicates major depressive disorder with high specificity.[253,254] In paper I, we applied a three-factor model of MADRS (dysphoria, retardation and vegetative symptoms), as proposed by Suzuki et al.[255]

In paper I, neuropsychiatric symptomology was assessed using the 12-item version of the Neuropsychiatric Inventory (NPI).[256] The NPI is an informant-based scale that assesses presence, severity and impact of 12 neuropsychiatric domains. In order to gauge the clinical severity of each domain, a composite score based on the product of frequency and severity of every domain was calculated.

In paper I, presence of sleep disorders was evaluated using the Epworth Sleepiness Scale (ESS) and the PD Sleep Scale (PDSS). [257,258] The ESS is an 8-item scale assessing the frequency of daytime sleep or sleepiness on a 0-3 likert scale, where higher scores indicate increased frequency of sleepiness. The PDSS assesses 15 common sleep disturbances on a visual analogue scale, with higher scores indicating better functioning.

In paper III, presence of psychotic symptoms was evaluated using a semi-structured interview (see appendix).

1.7.5 Assessment of cognitive functioning

Global cognitive functioning was examined using the Mini-Mental State Examination (MMSE),[259] a 20-item clinical scale assessing several cognitive domains: orientation, registration, attention and calculation, recall, language and visual construction (range 0-30).

In order to encapsulate specific cognitive dysfunctions across four cognitive domains, a battery of neuropsychological tests minimally affected by motor performance was administered. Data from these tests were included in papers I and IV. Cognitive domains assessed include: (1) executive functioning (Semantic verbal fluency test[260] and Stroop interference condition[261]); (2) verbal memory (immediate recall, short-delay recall and long-delay recall from the California Verbal Learning Test II[262]); (3) visuospatial skills (Silhouettes and Cube subtests of the Visual Object and Space Perception Battery[263]); and (4) attention (Stroop word reading and color naming test[261]).

In paper IV, composite scores for each domain were calculated as the average of the test scores after conversion into Percent of Maximum Possible (POMP) scores, of which the maximum values were defined according to the maximum test scores of the NC group and the minimum values were set to zero.[264,265]

PDD was diagnosed according to published consensus criteria for dementia associated with PD.[50]

1.8 Genetics

In paper II, the association between ICDs and polymorphisms across several neurotransmitter pathways was investigated. These analyses were based on available whole exome sequencing (WES) data from the Norwegian ParkWest study, the procedures of which has been published by others.[19] In brief, DNA was extracted from blood by routine procedures. Exome sequencing was performed at HudsonAlpha Institute for Biotechnology (Huntsville, Alabama) using Roche-NimbleGen Sequence Capture EZ Exome v3 kit (Roche, Brussels, Switzerland) and the Illumina HiSeq platform (Illumina, San Diego, USA). In paper II, WES data from 16 genes that include four neurotransmitter

pathways (dopaminergic, serotonergic, glutamatergic and opioid) were extracted and used in further analyses.

1.9 Statistical analyses

In paper I, differences between patients and NCs were evaluated using *t* tests, Mann-Whitney tests, chi square tests and Fisher's exact tests as appropriate. Logistic regression analyses (enter method) were used to compare the risk of ICDs in patients with PD vs. NCs, expressed as odds ratios (ORs) with 95 % confidence intervals (CIs). Multiple logistic regression analysis (enter method) was used to identify independent clinical correlates of ICDs in patients. All statistical analyses in paper I were performed using IBM SPSS Statistics version 22 (Armonk, NY, USA).

In paper II, we used a threefold statistical approach. First, demographic and clinical differences between patients with and without ICDs were calculated using *t* tests, Mann-Whitney tests and chi square tests as appropriate. These analyses were performed using IBM SPSS Statistics version 24.0.0.1 (Armonk, NY, USA). Second, we used regularized generalized linear regression analysis with elastic net penalization to investigate the association between ICDs and 56 SNPs in genes linked to dopaminergic, serotonergic, glutamatergic and opioid pathways. This analysis was performed in R version 3.4.0, using the *glmmnet* package. Third, the discriminatory ability of identified genetic markers was evaluated using receiver operating characteristic curve analysis. For this analysis, the difference between the level of prediction of ICD status between a clinical model and a clinic-genetic model was estimated by evaluating differences in area under the curve (AUC) using the DeLong test. These analyses were performed using STATA IC version 14.2.

In paper III, group differences were calculated using Kruskal-Wallis tests for continuous variables and Fisher's exact tests with Monte Carlo simulation for categorical variables. The association between psychosis, ICDs and dyskinesias was investigated using logistic regression analysis. ORs with 95% CIs were also calculated. These analyses were performed using IBM SPSS Statistics version 24.0.0.1 (Armonk, NY, USA).

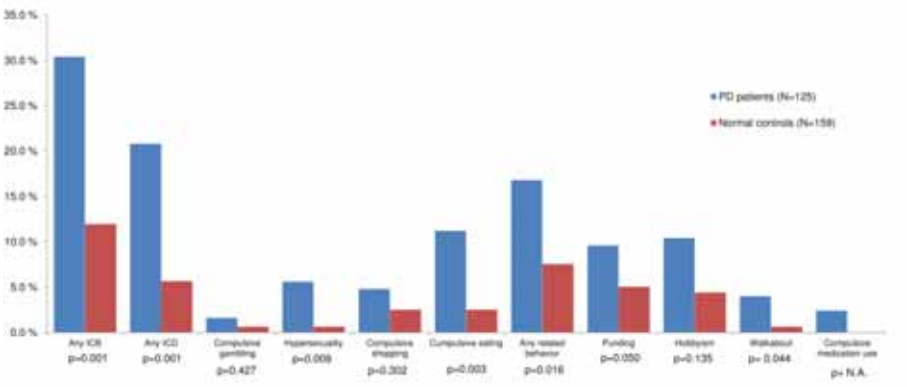
In paper IV, differences between patients and controls were evaluated using *t* tests, Mann-Whitney tests, chi square tests and Fisher's exact tests as appropriate. Age-adjusted ORs with 95 CIs for ICDs was calculated at each follow-up visit using logistic regression. In the longitudinal analysis, clinical factors associated with ICDs in patients over time were evaluated using generalized linear mixed modelling. In addition, the longitudinal association between ICD status and cognitive performance was calculated in PD patients using mixed linear regression analysis. These analyses were performed using IBM SPSS Statistics version 24.0.0.1 (Armonk, NY, USA).

4 Results

4.1 Paper I

We found a 3-fold increased odds of any ICD and more than 7-fold increased odds of multiple ICDs in patients with PD compared with NCs (see figure 6 for details regarding individual ICDs and related behaviors). Increased odds of ICDs were observed in patients using DAs, but not LD monotherapy. In multivariate models, presence of ICDs in patients was independently associated with DA treatment and depressive symptoms, but not motor symptoms or cognitive performance.

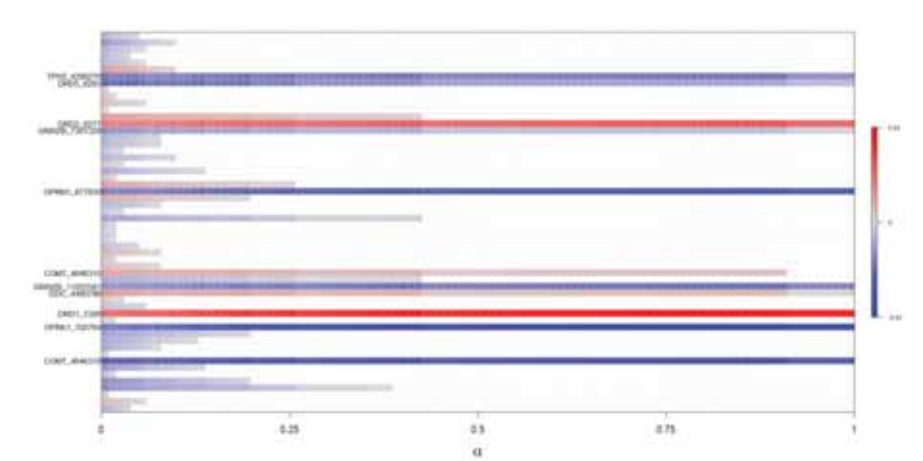
Figure 6. Frequencies of ICDs among patients with PD and normal controls.



4.2 Paper II

We identified associations between 11 SNPs across nine genes and presence of ICDs in patients with PD (see figure 7), including one novel polymorphism in the *DRD1*-gene. Four SNPs with the strongest performance in penalized regression analysis were included in a clinical-genetic model of ICDs. The SNPs most strongly associated with ICDs were rs5326 in *DRD1* (increased odds of ICDs) and rs702764 in *OPRK1* (decreased odds of ICDs).

Figure 7. Results of regularized regression with elastic net penalization for α-values between 0 and 1.



Footnote: Polymorphisms positively associated with ICDs (i.e., increases risk) are highlighted in red, while polymorphisms negatively associated with ICDs (i.e., decreases risk) are highlighted in blue, with the intensity of color reflecting the strength of association. Polymorphisms not associated with ICDs are white. Identified polymorphisms demonstrate significant association across all levels of α.

4.3 Paper III

We found a significant association between presence of psychotic symptoms and dyskinesia, but not between psychotic symptoms and ICDs.

4.4 Paper IV

We found that patients with PD had more than 4-fold increased odds of having ICDs compared with NCs during 4 years of follow-up. In patients with PD, the 4-year cumulative prevalence of ICDs was 47% and 23% developed incident ICDs during follow-up, whereas ICDs resolved in nearly 30%. ICDs were independently associated with use of DAs and younger age, but not with greater cognitive decline over time.

5 Discussion

5.1 General aspects of methodology

All papers included in this thesis are based on data from the Norwegian ParkWest study, a population-based, prospective cohort study of the incidence, neurobiology and prognosis of PD. The population-based design is one of the main strengths of this thesis, but it is not without methodological aspects worth discussing.

First, this study is contingent upon the validity of the PD diagnosis. Although a definite diagnosis of PD can only be ascertained by histopathological confirmation, the clinical diagnosis of PD is based on disease history and clinical examination. However, PD is however a complex and heterogeneous disorder and misdiagnoses are not uncommon. In order to ensure the validity of the PD diagnosis, neurologists with experience in classification and treatment of movement disorders completed all assessments of the patients in this study. A major strength of the longitudinal design of the Norwegian ParkWest study is the careful monitoring and assessment of patients to detect atypical signs or progression over time. Strict diagnostic criteria were used to increase the validity and reliability of the PD diagnoses, and supplementary investigations like magnetic resonance imaging (MRI) and [^{123}I]FP-CIT dopamine transporter imaging (DaTSCAN) were conducted to aid in the differential diagnosis. As a result, the number of re-diagnosed patients (N=20) in the Norwegian ParkWest study (currently at 12 years of follow-up) is comparable to other specialist movement disorder services.[266]

A second potential methodological limitation of this thesis is the representativeness of the Norwegian ParkWest cohort. In order to limit the risk of selection bias, the Norwegian ParkWest study sought to establish a population-based cohort of incident PD cases at baseline. The four studies in this thesis are all based on data obtained after 5 years of follow-up, i.e. time of inclusion of the QUIP, and we cannot therefore exclude the possibility that the remaining PD cohort is somehow biased compared with the original cohort at baseline. Attrition caused by death, withdrawal or missing data is common in all longitudinal studies, and this often limits the generalizability of cohorts

over time. During the first 5 years of the Norwegian ParkWest study, a total of 16% dropped out of the study due to death (4/5 patients) or withdrawal of consent (1/5 patients). Although this attrition rate is lower compared to other longitudinal PD cohorts,[267,268] any dropout from the study imposes a bias. For instance, the more fragile patients and those with faster disease progression are less likely to participate at follow-up, thereby skewing the frequency estimates of ICDs. Still, when compared to other studies of ICDs in patients with PD, the Norwegian ParkWest cohort provides data from a well-characterized and homogenous group of patients recruited using a wide-reaching, community-based recruitment strategy.

In all studies of this thesis, presence of ICDs was assessed using the self-report screening tool QUIP. Although there is low chance of false negatives, the risk of false positives using this screening tool is considered greater. This is a general trend observed in the research literature, where most studies using QUIP have slightly higher frequency estimates of ICDs when compared to other screening tools. On the other hand, studies using other tools to detect ICDs, such as MIDI, only assess the presence of the most common disorders (GD, CSB, CE and CS),[158,163,166] which reduces the scope of ICDs overall. Still, when comparing prevalence estimates of GD, CSB, CE and CS in the Norwegian ParkWest study (20.8%), with US data gathered by more comprehensive evaluation procedures (prevalence 13.8%, N = 3090),[158] the risk of overestimating the prevalence using QUIP seems clear. However, QUIP could gauge ICDs that are below the diagnostic threshold, but still pose negative effects on the patients' quality of life.

Although the use of QUIP may cause higher frequency rates of ICDs compared with semistructured interviews using diagnostic criteria, the relative proportion of ICD status between patients with PD and control subjects is considered to be reasonably accurate because the rate of false positives is expected to be similar for both patients and controls.

Papers I-III are based on cross-sectional data from the 5-year follow-up visit of the Norwegian ParkWest study. One problem associated with the use of cross-sectional data in clinical studies is the risk of identifying factors that are irrelevant for the actual clinical progression of a disease. This effect is highlighted by the unstable nature of ICDs in patients with PD, as illustrated

by the results from paper IV. This limitation has special importance in genetic association studies, where the risk of type I errors due to missing cases is not negligible. This methodological limitation could be addressed by including more patients at various stages of PD, including screening for life-time prevalence of ICDs or following patients prospectively before data analysis. In genetic studies, the aggregation of data samples from multiple, well-designed population-based cohorts would be a valid strategy to reduce the risk of type I errors.

An important methodological aspect of this thesis is the statistical models used in the four papers. In papers I and III, we used multiple logistic regression analysis to identify clinical factors (independent variables) associated with ICD status (dependent variable). Due to the magnitude of possible independent variables, variable selection was completed using the results from univariate testing. This is a common strategy in epidemiological research, but there are possible pitfalls in choosing this approach, the foremost being the risk of including empirically implausible or clinically irrelevant factors in the analysis. However, in paper I all independent variables identified using univariate analyses were expected based on previous publications and clinical practice.

In paper II, we utilized an advanced statistical approach to identify SNPs associated with ICDs. Contrasting standard regression models based on the ordinary least squares estimation, the regularized regression models are better at distinguishing between independent variables with little or no influence, and have lower risk of overfitting. These models are therefore well suited when estimating the effect of several SNPs with hypothesized limited individual effect for the dependent variable. These models also handle situations where the number of independent variables greatly exceed the number of observations, which otherwise result in overfitted models. However, the results of regularized models should be interpreted with cation, especially since calculated coefficients of a regularized model will not carry as much meaning as the coefficients of regular regression models. In addition, although the risk of traditional overfitting (i.e. <10 observations per explanatory variable) is not as relevant when using this model, there is still a risk of overfitting due to the flexibility of the estimator. This risk is however limited when the level of regularization is selected with cross-validation, as

the case in our study. Furthermore, this model could be argued to be unsuited for strict hypothesis-testing, especially since the algorithm only compute estimates of the regression coefficients. However, this method has its merits in exploratory investigations, especially when the expected effects of the independent variables are small.

In paper IV, we used a longitudinal mixed-effects regression model to estimate associations between ICD status over time and relevant independent variables. Although mixed-effects modelling is considered superior to more traditional longitudinal analysis, especially when there are more than two observations per participant, there are technical aspects of this method that could increase the bias of the model, such as the handling of age and time.[269] Mixed-effects models also handle missing data better than traditional statistical methods, where list-wide deletion is the only way to handle missing data. Although mixed-effects models are considered superior to traditional models, mixed models treat missing data as either "missing completely at random" or "missing at random". In this study, there were no indications that missing data during the 4-year follow-up were "missing not at random", but this assumption should still be considered when evaluating the results from a mixed-effects model.

5.2 Research question 1: How prevalent are impulse control disorders in subjects with and without PD?

In paper I, we completed the first population-based study to date to examine the prevalence of ICDs in patients with PD, and found that 30% of our PD cohort screened positive for at least one ICD and almost 10% for multiple ICDs. Although the estimated prevalence of ICDs in this study is comparable to some other studies using QUIP,[141,142,159,270] most prevalence estimates show great variability, ranging from 15.5% in a Korean sample to 58.3% in Spanish patients with early onset PD. [34,139,141-143,159,178,270,271] These discrepancies may be due to several methodological differences between studies, including patient characteristics, recruitment strategies and research designs. In paper I, we also found that PD patients have a 3-fold increased odds of ICDs compared with age- and gender-matched controls. This finding resonates well with other published case-control studies, as summarized in a recent meta-analysis.[162] In this meta-analysis, 14 case-control studies were included

(including paper I), herein five case-control studies using QUIP. All papers, except two investigating *de novo* patients,[107,188] demonstrated increased odds for ICDs among patients with PD. In paper IV, we completed the first longitudinal study of ICDs including both PD patients and NCs, and found a more than 4-fold increased risk of ICDs in PD compared to the control group during 4 years of follow-up.

Although cross-sectional studies provide some insight into the prevalence of ICDs in patients with PD, one major limitation of this design is the difficulty in identifying prognostic markers. In studies using cross-sectional designs, data are often gathered retrospectively, thereby increasing the likelihood of biased reporting. This limitation is especially important when investigating developmental or neurodegenerative diseases. To date, only a few longitudinal studies have examined the evolution of ICDs in patients with PD.[167,177,237-242] In the ICARUS study, more than 1000 Italian outpatients with PD demonstrated a relatively stable prevalence of overall ICD behaviors and subtypes across the 2-year prospective follow-up (range 26.5-29.3%).[177] These findings have been challenged by a recent longitudinal study of patients with early PD followed up annually up to 5 years, which demonstrated an increase in ICD prevalence from 19.7% at baseline to 32.8 % after 5 years.[241] In the same study, the 5-year cumulative incidence of ICDs was 46.1%. In comparison, we found that the 4-year cumulative frequency of ICDs in patients was 46.8% and 23.3% developed incident ICDs during the study period (paper IV). Both studies also found a high proportion of non-persistent ICDs, mainly due to changes in the DA treatment. These findings also support previous studies suggesting a high variation in time-to-onset of ICD symptoms in PD.[237]

Altogether, results from papers I and IV have provided important data to support the notion that ICDs are far more common in patients with PD than in NCs. In addition, ICDs may develop several years after PD diagnosis and initiation of DRT. Although most published data provide insight into the early years (i.e. ≤5 years) of PD, our study shows that incident ICDs may also develop in later stages of the disease.

5.3 Research question 2: What are the clinical correlates of impulse control disorders in patients with PD?

5.3.1 Demographic correlates

In previous studies, presence of ICDs in PD has been associated with several demographic, clinical, neuropsychiatric and cognitive variables.[200] In contrast to other studies, we did not identify any clear cross-sectional association between age or gender and ICDs (paper I). While current research has yielded conflicting findings on the influence of gender on ICD status in patients with PD, lower age has been associated with ICDs in most previous studies. In our study (paper I), there was a clear trend towards lower age among patients with ICDs, and the failure to replicate previous findings was most likely due to lack of statistical power in the cross-sectional analysis. However, we did find a significant association between younger age and ICDs in paper IV. Although the association between age and ICDs in patients with PD seems well-established, this association could be spurious and caused by age-related drug prescribing practices (see section 5.3.5).

5.3.2 Motor correlates

Since ICDs are common in patients with PD, early theories argued that these symptoms may be the result of a specific PD phenotype,[154] possibly with distinct prognoses with regards to clinical endpoints, such as motor progression, psychosis or dementia. If this was the case, one could expect ICDs to be associated with altered progression of motor symptoms, emergence of neuropsychiatric symptoms and cognitive decline. Consistent with findings from other PD cohorts, we did not find any association between ICDs and adverse motor functioning or disease stage, as measured by UPDRS motor score (papers I and IV) and the Hoehn and Yahr staging scale (paper I), respectively.

Dyskinesias, a common complication of long-term antiparkinsonian drug treatment in PD, especially levodopa use, are suggested to be caused by dorsal striatal changes in cellular signaling pathways due to chronic D1-receptor stimulation.[178,204] Dyskinesias may co-occur with ICDs, and according to one theory, these symptoms may share pathophysiological mechanisms. [178,204] In a

recent study exploring this hypothesis, covariance between psychosis, depression, dyskinesias and ICDs in patients with PD was identified.[205] These findings may indicate common pathophysiological substrates between dyskinesias, neuropsychiatric symptoms (psychosis in particular) and ICDs in PD. In paper III, we therefore made an effort to replicate these findings in the Norwegian ParkWest cohort, but failed to identify any significant association between ICDs and psychosis. Although our findings question this association, differences in diagnostic procedures and overall statistical power may have contributed to the various findings.[272] Still, the association between ICDs and psychosis in PD is currently uncertain, and more studies are warranted.

Altogether, there are no clear evidence suggesting that motor progression is different in PD patients with or without ICDs. The association between ICDs and dyskinesias may be evident in some PD cohorts, but more studies are needed to explore this relationship in terms of both epidemiology and pathophysiology.

5.3.3 Cognitive correlates

The association between ICDs and cognitive functioning in PD has been subject to much debate in previous studies.[200,206] A crux of this debate is the hypothesis that ICDs are associated with the progression of PD. According to the Braak staging model, one could expect the presence of ICDs to be associated with pronounced cognitive decline in dopamine-innervated prefrontal areas involved in executive functioning, cognitive flexibility and learning (also known as the fronto-striatal dysexecutive syndrome).[62] Following this hypothesis, ICDs could be associated with poorer results on performance-based cognitive tests cross-sectionally, or more pronounced cognitive decline over time. In papers I and IV, we investigated the association between ICDs and cognitive functioning across four domains using performance-based measures. Consistent with other studies,[200,240] we did not find any support for the above-mentioned hypothesis. It should also be noted that ICDs are generally associated with lower age, thereby limiting the possibility to observe "global" cognitive deficits in affected patients.

Nevertheless, more specific cognitive deficits have been observed in PD patients with ICDs. As demonstrated by a recent meta-analysis,[200] patients

with PD and ICDs have worse performance on tests of set-shifting and reward-related decision-making, i.e. two executive functions related to cognitive flexibility and decision making under uncertain conditions. These findings are somewhat expected due to the overlapping nature of these cognitive tasks and the phenomenology of ICDs. In addition, similar findings have been demonstrated using several behavioral paradigms (including the Balloon Analogue Risk Task,[189] the Iowa gambling task,[273] the Salience Attribution test,[190] and other paradigm evaluating risk taking[191,274,275]) and self-report measures[190]. However, our studies (papers I and IV) were not designed to provide data or address specific cognitive deficits in these domains, and therefore do not contribute to this discussion.

Altogether, PD patients with ICDs do not seem to experience worse global cognitive functioning than those without ICDs over time, but may display cognitive deficits specific to the realms of reward-related decision making and cognitive flexibility.

5.3.4 Neuropsychiatric correlates

A range of neuropsychiatric symptoms have been associated with ICDs in patients with PD. As demonstrated in paper I, presence of ICDs was associated with more severe depressive symptoms. This finding is supported by data from several other PD cohorts, demonstrating more depressive symptoms among PD patients with ICDs than without. In paper I, we expand previous findings by utilizing a three-factor model of MADRS, which identified higher subscores related to dysphoria and retardation in patients with ICDs, but not on vegetative symptoms. We also identified increased tendencies of apathy, irritability and agitation among patients with ICDs, but these symptoms were not significant in multivariate analyses. However, a recent meta-analysis showed that increased levels of depression, anxiety, anhedonia, apathy, irritability and agitation is observed across several studies.[200] Still, current studies have not been able to dissect if the co-occurrence of neuropsychiatric symptoms and ICDs are related to patients' coping strategies (i.e. psychologically determined) or the result of shared pathophysiological traits between affective and motivational symptoms in PD.[201,276]

Neuropsychiatric symptoms that have been associated with ICDs in patients with PD have mainly been explored using cross-sectional designs. In paper IV, we identified an association between more depressive symptoms and ICD status only at the time of initial assessment. As time progressed, patients without ICDs experienced higher MADRS scores, leading to no significant difference in MADRS scores between ICD positive and ICD negative patients for the whole study period. Although this association could be the result of remitting ICDs over time, nearly 25% also developed incident ICDs during follow-up. This finding challenges the notion of shared pathophysiology between affective symptoms and ICDs, and indicates that affective symptoms in PD patients with ICDs should be investigated more closely. Of note, DAs are reported to have some antidepressant effect in patients with PD,[25] and we cannot rule out that this may explain the lower MADRS scores over time in patients with ICDs.

5.3.5 Association between ICDs and DRT

In accordance with several other publications, we demonstrated a significant association between ICDs and DA use in both cross-sectional and longitudinal data. In the cross-sectional data, monotherapy with DAs was associated with a seven-fold increase in odds for ICDs, when comparing to NCs. Combination (DA and LD) users had a four-fold increase in odds. In paper I, we found evidence that suggest that the association between ICDs and DA is a class-effect, rather than an effect of dosage. Indeed, we did not identify an increase in levodopa equivalent dosage (LED) of DAs, when comparing patients using DAs. Although similar results have been demonstrated in other cohorts,[158,179] some studies have argued that ICDs are associated with increased DA-dosage.[141,142,270] Alleviation of ICD symptoms has also been demonstrated in patients reducing DA dosage,[239,241] suggesting that DA dose might at least be an important factor in the maintenance of ICDs. Contrasting some other studies,[158] we did not find an association between LD use or LD-dosage and the presence of ICD symptoms. Our findings do not give a definite answer to this issue, but do provide support for the notion that ICDs may be associated with a class-effect of DAs. Still, these findings are of clear clinical importance, since the use of DA is common in early management of PD.[76] As such, one of the most prominent clinical implications of this thesis is a

recommendation of caution when prescribing DA to patients with PD, and close follow up of these symptoms throughout the course of the disease. Currently, there are no biomarkers that are able to differentiate between patients at risk of ICDs if exposed to DAs, but emerging evidence from the genetic research give reason might prove useful in the future.

5.4 Research question 3: What genetic risk factors are associated with impulse control disorders in patients with PD?

The exploration of genetic variations related to ICDs in patients with PD is still in its infancy, with only a handful of papers published so far. In paper II, we identified 11 SNPs from the dopaminergic, glutamatergic, serotonergic and opioid pathways that were associated with ICD status in patients at study start. These findings both support and expand previous knowledge about the genetic architecture of ICDs in PD. More specifically, they highlight the association between ICDs and multiple vulnerabilities in the physiology of dopaminergic signaling and regulation of dopaminergic activity in the reward system. As such, the genesis of ICDs is not only dependent upon the use of DAs, but may also be contingent upon premorbid risk variants in the genome. However, more studies are needed to explore this subject in more detail.

Interestingly, several of the identified SNPs have previously been suggested to be involved in the genesis of ICDs in the general population. In the RDS model, polygenic variability has been suggested as an important premorbid factor that increases the vulnerability for ICDs on an individual level.[220] Although the precise architecture of involved genes are still being investigated, development of risk profiles based on existing knowledge have been suggested to predict the risk and prognosis of addictions and ICDs.[277] Similar efforts have been made for PD patients, yielding promising results in the prediction of ICD status in a French PD cohort,[217] and by us in paper II. However, these genetic models need replication by other research groups and preferably in much larger cohorts. In addition, genetic risk prediction using a panel of top candidate genes for ICDs might be promising, but the clinical implication of such potential markers is limited as of yet. Currently, the best way to clinically mitigate the risk of ICDs would be to consider demographic

and familial history before initiation of DA-treatment, close monitoring of impulsive and compulsive behaviors during follow up, and inclusion of care-giver information during assessments of these behaviors.

5.5 Future directions

Given the findings of this thesis and the current status of ICD research in general, there are two main avenues of research that is important for future directions.

Further studies designed to explore the pathophysiology and genetics of ICDs in PD are needed to better predict those patients who are at greater risk of developing ICDs if exposed to DAs. However, currently there is a lack of predictors with clinical utility. In the field of neuroimaging for example, results are largely inconsistent, possibly due to heterogeneity in methods used and differences in study populations. In addition, current hyperdopaminergic models of ICDs in PD have not been demonstrated to be causative in relation to ICDs, and further studies are needed.[278] For example, both excessive dopaminergic activity and reduced levels of dopaminergic activity have been associated with cognitive dysfunctions in decision-making and regulation of impulses. Thus, functional neuroimaging studies using task-based paradigms and event related analyses have been argued to be the methods best suited for further disentanglement of the pathophysiology of ICDs in PD.[278] Identification of biomarkers or imaging techniques that can differentiate between patients at risk of ICDs if exposed to DAs could greatly benefit clinical practice of patients with PD.

There are also important clinical aspects that need further exploration. As discussed in a recent paper, an individualized treatment approach to ICD symptoms in PD should take into account patient's neuropsychiatric profile, tolerability and motor symptoms, among other things.[246] Therefore, longitudinal studies investigating the prognosis of neuropsychiatric symptoms, motor function and dyskinesias as well as life satisfaction and caregiver stress in PD patients with ICDs are highly requested. Also, the long-term progression of PD and transition into clinical milestones, such as visual hallucinations, recurrent falls, dementia and nursing home placement, in patients with ICDs has yet to be explored.[241] Another important area of

exploration pertains to the management strategy for ICDs when once developed.[243] Currently the main strategy is discontinuing the use of DAs, but this is not feasible in all cases. Despite several efforts to identify both pharmacological and behavioral treatment approaches, no clear treatment is currently available for PD patients with ICDs.[95,243-249] Thus further investigations into efficient management strategies for PD patients with ICDs are warranted.

6 Conclusions

The overall aim of this thesis was to describe the epidemiology, genetic risk and longitudinal trajectory of ICDs in a population-based cohort of patients with PD. Therefore, we asked three research questions: 1) How common are ICDs in patients with PD compared to normal controls; 2) what are the risk factors and clinical correlates of ICDs in patients with PD; and 3) what genetics risks factors are associated with ICDs in patients with PD. Our main findings were:

1. Using cross-sectional data, we found more than 3-fold increased odds of having any ICD and more than 7-fold increased odds of multiple ICDs in patients with PD compared with matched NCs. During 4 years of prospective follow-up, patients had more than 4-fold increased odds of ICDs than the control group.
2. ICD status in PD patients at study start was independently associated with DA treatment and depressive symptoms, but not with motor function, cognitive performance or presence of psychotic symptoms. ICD presence in patients was independently associated with DA use and younger age, but not with greater cognitive decline during the 4-year follow-up period.
3. Presence of ICDs was associated with several polymorphisms across dopaminergic, glutamatergic, serotonergic and opioid transmitter pathways in patients with PD. We also identified one novel polymorphism in the dopamine receptor D1-gene.

In conclusion, the findings in this thesis point out the importance of persistent clinical assessments of ICDs in PD patients over time. Genetic screening may help identify patients at risk of ICDs if exposed to dopamine agonists.

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Appendices

Appendix 1 – QUIP Short form - Norwegian version

QUIP kortversjon til pasient

Noen av spørsmålene under kan være følsomme å svare på. Vi spør likevel, fordi vi vet dette kan være problemer enkelte sliter med, men vi er usikre på hvor mange. Slike problemer kan være bivirkninger av anti-parkinson medisiner og derfor er dette viktig.

Vi ber deg besvare ALLE SPØRSMÅL basert på NÅVÆRENDE ATFERD dersom den har vart i minimum 4 uker

A. Pengespill

	Ja	Nei
1. Synes du eller andre at du har et problem med for mye bruk av pengespill (for eksempel internettspill, lotterier, skrapelodd, veddemål, poker eller tipping)?	☐	☐
2. Har du vansker med å kontrollere bruk av pengespill (for eksempel at du gradvis har spilt mer eller ikke klarer å slutte eller å redusere bruken)?	☐	☐

B. Seksualitet

	Ja	Nei
1. Synes du eller andre at du har et problem med overdreven seksuell atferd (for eksempel at du krever sex av andre, prostitusjon, endring av seksuell orientering, masturbering, internett eller telefonbasert sex-aktiviteter, eller pornografi)?	☐	☐
2. Tenker du for mye på sex (slik at du har vansker med å holde tankene borte eller har skyldfølelse)?	☐	☐

C. Innkjøp

	Ja	Nei
1. Synes du eller andre at du har problemer ved at du kjøper for mange ting (for eksempel for mye av samme ting eller ting du ikke trenger eller ikke bruker)?	☐	☐
2. Prøver du aktivt å fortsette innkjøp (som ved å skjule at du handler, lyve, samle ting, låne av andre, opparbeider deg gjeld, stjeler eller ulovlige aktiviteter)?	☐	☐

D. Spising

	Ja	Nei
1. Synes du eller andre at du har problemer med at du spiser for mye (som å spise for store mengder eller andre typer mat enn før, eller spiser raskere enn før, inntil du føler deg overmett eller når du ikke er sulten)?	☐	☐
2. Har du trang eller lyst til å spise på en måte som du føler er overdrevet eller som skaper ubehag for deg (inkludert at du blir rastløs eller irritabel når du ikke kan gjennomføre det)?	☐	☐

E. Andre typer atferd

Synes du eller andre at du bruker for mye tid

	Ja	Nei
1. På spesifikke gjøremål, hobbier eller andre planlagte aktiviteter (som skriving, maling, hagearbeid, reparasjoner, demontering av ting, samling av ting, datamaskinbruk, prosjektarbeid osv.)?	☐	☐
2. På å repetere enkle aktiviteter (som rengjøring, rydding, undersøke gjenstander, fikle på ting, sortere ting, ordne ting)?	☐	☐
3. Kjøre eller gå uten noe mål eller spesiell hensikt?	☐	☐

F. Medisinbruk

	Ja	Nei
1. Synes du eller andre (inkludert dine leger) at du tar for mye Parkinsonmedisiner?	☐	☐
2. Har du vansker med å kontrollere din bruk av Parkinsonmedisiner (slik at du opplever sterk lyst på mer medisin eller har dårligere humør eller føler deg umotivert på lavere dose)?	☐	☐

Appendix 2 – A semistructured interview for psychosis

Rev. 26.09.13

STUDIEKODE: _____ **DATO:**____.____.20____
FØDT: ____.____.19____

PSYKOTISKE SYMPTOMER VED PARKINSON'S SYKDOM

Informasjon fra: ☐ **pasient/kontroll** ☐ **pårørende/omsorgsperson** ☐ **begge deler**

Vennligst fyll ut om pasienten/kontrollpersonen i løpet av det siste halvår har opplevd

	Varighet			Hyppighet	Intensitet
	NEI	JA <4 uker	JA ≥4 uker		
MINOR PHENOMENA				-	-
Presence				☐ D, ☐ U, ☐ S	-
Passage				☐ D, ☐ U, ☐ S	-
ILLUSJONER				-	-
Illusjoner				☐ D, ☐ U, ☐ S	-
HALLUSINASJONER				-	
Visuelle				☐ D, ☐ U, ☐ S	☐ MI, ☐ UI
Auditive				☐ D, ☐ U, ☐ S	☐ MI, ☐ UI
Taktile				☐ D, ☐ U, ☐ S	☐ MI, ☐ UI
Lukt-				☐ D, ☐ U, ☐ S	☐ MI, ☐ UI
Smak-				☐ D, ☐ U, ☐ S	☐ MI, ☐ UI
VRANGFORESTILLINGER				-	-
Paranoide tanker				☐ D, ☐ U, ☐ S	-
Sjalusi				☐ D, ☐ U, ☐ S	-
Capgras				☐ D, ☐ U, ☐ S	-
Home misidentification				☐ D, ☐ U, ☐ S	-
Annet (.....)				☐ D, ☐ U, ☐ S	-

tilbakevendende eller kontinuerlige psykotiske symptomer (se neste side for definisjon).

D = daglig MI = med innsikt
U = ukentlig UI = uten innsikt
S = sjeldnere

Utfyllende opplysninger:

a) **Hvis "Ja" for visuelle hallusinasjoner, beskriv (f. eks. dyr, mennesker, objekter):**

.....

b) **Hvis "Ja" for auditive hallusinasjoner, beskriv (f. eks. musikk, stemmer):**

.....

c) **Hvis "Ja" for flere typer psykotiske symptomer, forekommer disse**
☐ Isolert - hvilke.....
☐ Samtidig - hvilke.....
☐ Av og til isolert, av og til samtidig

d) **Hvis "Ja", har noen av de psykotiske symptomene vært til stede i løpet av de SISTE 4 uker?**
☐ JA
☐ NEI

Rev. 30.06.11

Definisjon/beskrivelse av psykotiske symptomer

"Minor psychotic phenomena"

- ***"Presence":*** følelse av at noe/noen er tilstede i rommet uten at det/de er det
  → "Har du hatt en livaktig opplevelse av at noen er tilstede i rommet sammen med deg – uten at det faktisk er noen der?"

- ***"Passage":*** følelse av at noe/noen passerer forbi.
  → "Har du erfart en kort opplevelse av at noe beveger seg forbi deg, for eksempel et dyr eller menneske, når det faktisk ikke var noen der?"

Illusjon
"Sanse-/synsbedrag". Et reelt visuelt objekt oppfattes som noe annet enn dét det er.
→ "Har du opplevd at noe du ser på ser ut som noe annet? For eksempel at et merke på veggen ser ut som et insekt? Eller en lampe som et menneske? Annet?"

Hallusinasjon
Sanseopplevelse uten at det foreligger en ytre påvirking av sanseorganet.
→ "Har du sett mennesker, dyr eller ting som faktisk ikke var der – uten at det var en gjenstand som ble seende ut som noe annet enn hva det faktisk var?"

Vrangforestilling
Oppfatninger som ikke samsvarer med virkeligheten, er åpenbart urimelige, og som normalt ikke deles av andre. (f.eks. paranoide trekk, sjalusi, "misidentifikasjonsyndromer")

- ***Capgras***
  Vrangforestilling om at en venn, slektning, eller nært familiemedlem har blitt byttet ut med en identisk kopi.

- ***Home misidentification***
  Vrangforestilling om at en bolig har blitt byttet ut med en identisk kopi.

Appendix 3 – Ethical approval

UNIVERSITETET I BERGEN
Det medisinske fakultet
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http://www.etikkom.no/REK/

Regional komité for medisinsk forskningsetikk Vest-Norge (REK Vest)

Bergen, 01.09.04
Sak nr: 04/6168

Professor Jan Petter Larsen
Sentralsjukehuset i Rogaland
Postboks 8100
4068 STAVANGER

Ad prosjekt: Parkinsonstudien på Vestlandet - PARKVEST. Motoriske og ikke-motoriske problemer hos pasienter med Parkinson sykdom. En prospektiv kohort-studie av pasienter med tidlig Parkinson sykdom (REK Vest nr. 131.04)

Det vises til ditt brev datert 13.08.04 med svar på komiteens merknader.

REK Vest v/leder har vurdert saken. Også i skrivet til kontrollene bør en ta inn avsnittet om biobank. Når det gjelder Biobankloven og spørsmålet om tilbakekall av samtykke (§13) har det vært en del diskusjon om hva som er korrekt formulering. En formulering som nå er akseptert av direktoratet er følgende (kursiv): "Det er frivillig å delta og du kan når som helst trekke deg fra studien uten å oppgi grunn og uten at det får noen negative konsekvenser for deg. *Allerede innsamlede data vil ikke bli slettet og informasjon samlet inn om deg vil fortsatt kunne brukes i forbindelse med denne studien. Du har imidlertid rett til å få vite hva slags informasjon som fortsatt vil bli oppbevart.*"

På vilkår av at ovennevnte tas til følge er studien endelig klarert fra denne komité sin side men vi ber om å få kopi av rettede skriv.

Vi ønsker dere lykke til med gjennomføringen og minner om at komiteen setter pris på en sluttrapport, eventuelt en kopi av trykt publikasjon når studien er fullført.

Vennlig hilsen

Grethe Seppola Tell
leder

Appendix 4 – Informed consent

FORESPØRSEL OM DELTAGELSE I STUDIE OM PARKINSONS SYKDOM

Tittel:
Parkinson-prosjektet på Vestlandet og i Aust-Agder - PARKVEST

Du er blitt spurt om å delta i en undersøkelse om Parkinsons sykdom. Før du bestemmer deg er det viktig at du forstår hvorfor undersøkelsen blir gjort og hva dette vil innebære for deg. Les denne informasjonen nøye og diskuter med legen dersom det er noe som er uklart.

Hva er formålet med undersøkelsen?
Parkinsons sykdom er en såkalt nevrodegenerativ lidelse som kan gi problemer med bevegelighet i tillegg til andre typer problemer. Disse andre typer problemer vil kunne omfatte følelse av lite energi, søvnvansker om natten eller om dagen, humørendringer eller kognitive problemer. Det er relativt lite kunnskap om disse ikke-motoriske problemer hos pasienter med Parkinsons sykdom. Hensikten med undersøkelsen er å kartlegge disse hos en stor gruppe av pasienter med sykdommen helt fra diagnosen blir stillet for første gang. Videre ønsker undersøkelsen å få en god oppfølging av hvordan pasienter med sykdommen får det over tid. Det er derfor meningen at de som sier ja til å være med i studien vil få et tilbud om oppfølging over mange år fra Nevrologisk poliklinikk. Data som blir samlet inn på denne måten kan lære oss mye om hvilke problemer som oppstår, men også hvilke faktorer som synes å være bestemmende for hvordan sykdommen utvikler seg. Dette er viktig for å få en god oversikt over problemer helsevesenet må være oppmerksom på hos pasienter med Parkinsons sykdom og også legge forholdene til rette for å prøve å behandle sykdommen i sin fulle bredde på en best mulig måte for den enkelte pasient. Verken ledere eller medarbeidere har økonomiske interesser tilknyttet prosjektet.

Hvorfor er jeg blitt spurt?
Du har blitt bedt om å vurdere å delta i denne undersøkelsen fordi det er mistanke om at du har Parkinsons sykdom. Diagnosen Parkinsons sykdom kan være vanskelig å stille helt fra begynnelsen av og det kan vise seg etter en tid at dette var feil hos deg, men mistanken om dette foreligger ut fra de opplysningene som legen har om deg på det nåværende tidspunkt. Omtrent 200 pasienter med Parkinsons sykdom vil bli forespurt om å delta i denne undersøkelsen. Pasientene vil komme fra de tre vestlandsfylkene og fra Aust-Agder.

Må jeg delta?
Det er frivillig å delta og du kan når som helst trekke deg fra studien uten å oppgi grunn og uten at det får noen negative konsekvenser for deg. Allerede innsamlede data vil ikke bli slettet og informasjon samlet inn om deg vil fortsatt kunne brukes i forbindelse med denne studien. Du har imidlertid rett til å få vite hva slags informasjon som fortsatt vil bli oppbevart. Det er imidlertid svært viktig at du gir beskjed til din behandlende nevrolog om at du ikke lenger ønsker å være med i undersøkelsen. Dersom det viser seg at du ikke har Parkinsons sykdom vil du også bli tatt ut av undersøkelsen.

Hvilke konsekvenser har det for deg å være med i undersøkelsen?
Det å være med i undersøkelsen medfører at du må møte til avtalte kontroller ved Nevrologisk poliklinikk. Dette vil skje noe hyppig til å begynne med, men etter hvert 2 ganger i året. Hvor hyppig du må komme til undersøkelse i begynnelsen er avhengig av blant annet hvor godt

1

man eventuelt får medikamenter til å virke for deg. Imidlertid vil du ved neste undersøkelse måtte sette av relativt mye tid og for noen vil det være best å være innlagt i 1 døgn i sykehuset for å få gjort unna alle undersøkelsene på en mest mulig effektiv måte for deg og for din lege. Det vil bli aktuelt å hente informasjon fra sykehusets journal om dine eventuelle tidligere sykdommer, dersom du har ligget inne på sykehuset før. Samtidig som det vil medføre at du må møte frem til undersøkelse og svare på en rekke forskjellige spørsmål, vil du også være sikret en fast og velkvalifisert oppfølging i forbindelse med sykdommen over tid gjennom det å være deltager i undersøkelsen. Det å delta i undersøkelsen har ikke påvirkning på valg av medisiner du vil få. Disse vil bli gitt slik som det vurderes å være mest mulig optimalt for deg.

Biobank:
I tillegg til vanlige blodprøver vil en del av prøvene bli lagret i en såkalt biobank til senere undersøkelser for kjente eller mulige markører for Parkinsons sykdom. Dette innebærer både biokjemiske og genetiske prøver. Eksempler er parkin- eller alpha synuclein-genene, som i dag utgjør kjent risiko faktor for sykdommen. Prøvene skal kun brukes til diagnostikk, ikke til genetiske eksperimenter. Resultatene fra disse undersøkelsene og blodprøvene vil bli slettet innen utgangen av 2014.

Konfidensialitet:
Den informasjon vi samler inn om deg og din sykdom vil bli lagret i en datamaskin. Disse opplysninger vil bli behandlet konfidensielt og etter regler bestemt av myndighetene. Alt datamateriell vil bli anonymisert når prosjektet avsluttes ved utgangen av 2014. Prosjektet er meldt til Personvernombudet for forskning, Norsk samfunnsvitenskapeklig datatjeneste.

Bruk av innsamlede data:
Den informasjon som blir samlet inn om deg og alle de andre som deltar i undersøkelsen vil være utgangspunkt for vitenskapelige studier av hvordan Parkinsons sykdom utvikler seg over tid. Denne informasjon vil bli brukt til å lage vitenskapelige publikasjoner. Opplysninger som fremkommer i publiseringer vil ikke kunne tilbakeføres til enkeltpersoner. For øvrig vil din fastlege bli informert om at du deltar i undersøkelsen.

Ansvarlig for prosjektet:
Ledelsen for prosjektet er:
Professor Jan Petter Larsen fra Sentralsjukehuset i Rogaland
Professor Ole-Bjørn Tysnes fra Haukeland Universitetssykehus

Dine kontaktpersoner er:

Ansvarlig lege: ..... Tlf.....

Ansvarlig sykepleier..... Tlf.....

SAMTYKKE

Jeg har mottatt og lest en kopi av pasientinformasjonen og har fått anledning til å stille spørsmål om studien.
Jeg samtykker i å delta i undersøkelsen.

Signatur:..... Navn: .....(Blokkbokstaver)
(pasient)

Dato:..... Dateres av pasienten

2

PARKVEST
Forespørsel om å delta i forskningsprosjekt (del 2)

Du har sagt deg villig til å være med i den første delen av Parkinson undersøkelsen som gjennomføres på Vestlandet og i Aust-Agder. Vi vil i tillegg spørre deg om å delta i del 2 av prosjektet. Formålet med denne del av undersøkelsen er å oppnå mest mulig informasjon om immunsystemet til pasienter med Parkinsons sykdom. Denne informasjonen er svært viktig for bedre å kunne forstå redusert energi og for å finne markører for hvordan sykdommen utvikler seg senere.

Deltakelse i denne delen av undersøkelsen fører med seg at du sier deg villig til å gjennomføre en spinalvæskeundersøkelse. Undersøkelsen vil bli gjort poliklinisk og innebærer at det blir tatt en prøve av ryggmargsvæsken. Selve innstikket kan være noe smertefullt, men undersøkelsen vil bli utført av en erfaren lege. Noen kan få hodepine etter undersøkelsen. Den går vanligvis over etter få dager.

Alle som tar del i undersøkelsen kan når som helst trekke seg fra denne. Deltakelse i denne delen av forskningsprosjektet er uavhengig av å ta del i del 1 av forskningsprosjektet. Det å trekke seg fra undersøkelsen får ingen konsekvenser for den videre behandlingen ved Nevrologisk avdeling.

Jan Petter Larsen
Professor/Klinikkdirektør
Klinikk for spesialmedisin
Stavanger Universitetssykehus

Samtykkeerklæring:

Jeg har lest informasjonen og ønsker å delta i undersøkelsen.

Navn: .....

Sted: ..... Dato: .....

Paper I

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Research Report

Impulsive and Compulsive Behaviors in Parkinson's Disease: The Norwegian ParkWest Study

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Abstract.
Background: Impulsive and compulsive behaviors (ICBs) are frequent in Parkinson's disease (PD), but data from population-based cohorts is lacking.
Objectives: To determine the frequency and associated demographic, clinical, neuropsychiatric and cognitive features of ICBs in a population-based PD cohort.
Methods: This cross-sectional study included 125 patients with PD and 159 age- and gender-matched normal controls recruited from the Norwegian ParkWest study. Participants underwent comprehensive neurological, neuropsychiatric and neuropsychological assessments. ICBs were assessed using the Questionnaire for Impulsive-Compulsive Disorders in PD short form. Multiple logistic regression analyses were performed to compare the odds of ICBs between groups and to identify independent correlates of ICBs in PD.
Results: 30.4% of patients reported at least one ICB, with an odds ratio (OR) of 3.2 (95% confidence interval [CI] 1.8–5.9) compared with controls. Multiple ICBs were experienced by 8.8% of patients vs 1.3% of controls (OR 7.6, 95% CI 1.7–34.8). Compared to controls, the ORs of having an ICB were 7.4 (95% CI 2.6–20.9) in patients taking DA without levodopa, 4.6 (95% CI 2.3–9.3) in those treated with both DA and levodopa, and 1.2 (95% CI 0.5–3.2) in patients using levodopa but not DA. In multivariate models, ICB status in patients was independently associated with DA treatment and depressive symptoms, but not with other dopaminergic medications, motor function, or cognitive performance.
Conclusions: Patients with PD treated with DA, but not other dopaminergic medications, have increased odds of having ICBs compared with age- and gender-matched controls. This has implications for individualized patient management and follow-up.

Keywords: Parkinson's disease, impulse control disorders, QUIP, dopamine agonists, neuropsychiatry

INTRODUCTION

Impulsive-compulsive behaviors (ICBs) are recognized as serious neuropsychiatric complications in Parkinson disease (PD), with potentially devastating

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personal, social and financial consequences [1, 2]. These abnormal behaviors include the four major impulse control disorders (ICD) pathological gambling, compulsive shopping, binge eating and hypersexuality [1]. These behaviors are ego-syntonic and impulsive in nature, characterized by an effort to obtain arousal and gratification and cognitive biases [3–5]. In addition, a range of related behaviors have been described in PD, including punding, hobbyism, walkabout and compulsive dopaminergic medication overuse [6]. The related ICBs are ego-dystonic and compulsive in nature, associated with a calming or anxiolytic effect on the patient [5, 6].

Reported prevalence estimates of ICBs in PD vary considerably, ranging from 6% to almost 35% [1, 7]. Potential explanations include differences in the definition and assessment of ICBs, dopaminergic treatment, and patient selection, with most studies performed at highly-specialized movement disorders centers. In addition, since only few studies included normal control subjects, little is known about the risk of ICBs in PD relative to the general population [8–10]. Such information would, however, be important given that social, cultural and economic factors are likely to influence the prevalence of ICBs.

ICBs in PD have been associated most consistently with dopaminergic medication, and dopamine agonist (DA) treatment in particular [9, 11]. Other proposed determinants include premorbid personality traits, younger age, male gender, and depression and anxiety [12]. However, evidence in this respect is not unequivocal and even less clear for a range of other features within the spectrum of motor and non-motor symptoms associated with PD.

Against this background, we investigated the risk and determinants of ICDs and related impulsive-compulsive behaviors in a population-based PD cohort and normal controls (NCs) using comprehensive and standardized assessments of ICBs, as well as neurological, neuropsychiatric and cognitive functioning.

MATERIALS AND METHODS

Study design and participants

All participants were derived from the Norwegian ParkWest project, a population-based longitudinal study of the incidence, neurobiology and prognosis of PD. Details of the case ascertainment and diagnostic procedures to recruit a population-representative PD cohort have been published elsewhere [13]. Briefly, patients with newly diagnosed PD and NC subjects were recruited from four counties in Western and Southern Norway between 2004 and 2006, and followed prospectively by movement disorders neurologists with standardized clinical examinations. Assessment of ICBs was introduced at the 5 year re-examination, in which 155 patients with PD and 159 NCs participated. Of these, we excluded 28 patients and 1 control subject due to dementia [14, 15]. Thus, 125 non-demented PD patients and 159 NC subjects were eligible for this cross-sectional study of ICBs in PD. All PD patients met the National Institute of Neurological Disorders and Stroke and the United Kingdom PD Society Brain Bank criteria for PD [16, 17]. All participants were Caucasian.

Standard protocol approvals, registrations, and patient consents

The study was approved by the Regional Committee for Medical and Health Research Ethics, Western Norway. Signed written informed consent was obtained from all participants.

Assessments

A standardized examination program was administered by trained members of the ParkWest study group. Information regarding demographic variables, lifestyle factors, clinical history, and medication was obtained during semistructured interviews. Motor severity and disease stage were assessed by the Unified PD Rating Scale (UPDRS) and Hoehn and Yahr scale. Levodopa equivalent doses (LEDs) were calculated according to published recommendations [18].

For assessment of ICBs, the self-report short form version of the Questionnaire for Impulsive-Compulsive Disorders in PD (QUIP) was completed by all participants [19]. The QUIP is designed to detect clinically significant impulse control disorders (compulsive gambling, sexual behavior, shopping and eating) and related impulsive-compulsive behaviors (punding, hobbyism, walkabout, and compulsive use of dopaminergic medication), and has been demonstrated to be a valid self-assessment screening instrument for ICBs in patients with PD [20]. Participants with positive response to one or more screening questions of the QUIP were classified to have ICB [20].

Cognitive function was assessed using the Mini-Mental State Examination (MMSE) as a measure of global cognition [21]. In addition, a comprehensive

neuropsychological test battery [Stroop test [22], Semantic verbal fluency test [23], California Verbal Learning Test II (CLVT-II) [24], and Silhouettes and Cube subtests of the Visual Object and Space Perception Battery (VOSP) [25]] was administered by trained study nurses to assess a wide range of cognitive domains: attention (Stroop word reading and color naming), executive functioning (Semantic verbal fluency, Stroop interference condition), verbal memory (CVLT-II), and visuospatial skills (VOSP). A diagnosis of PD dementia (PDD) was determined according to published criteria [14], as described previously [26].

Neuropsychiatric symptoms were assessed using the 12-item version of the Neuropsychiatric Inventory (NPI) [27]. A composite score (product of frequency and severity; range 0–12) was calculated for each neuropsychiatric symptom. The validity of the NPI has been established [27], and high reliability in PD has been reported [28]. In addition, more comprehensive assessments of depressive symptoms, daytime sleepiness, and night-time sleep problems were performed using the Montgomery and Aasberg Depression Rating Scale (MADRS) [29], the Epworth Sleepiness Scale [30], and the PD Sleep Scale [31]. To identify possible subcomponents of depressive symptoms, we applied a three-factor model of MADRS as suggested by Suzuki et al. [32].

Statistical methods

All statistical procedures were performed using IBM SPSS Statistics version 22. Group differences were analysed using *t* tests, Mann–Whitney tests, χ^2 tests and Fisher exact tests as appropriate. Logistic regression analyses (enter method) without and with adjustment for potential confounders (age, gender, MADRS and MMSE-scores) were used to compare the risk of ICBs in patients with PD vs controls, expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Since the unadjusted and adjusted analyses yielded similar results, unadjusted OR and CI are reported in the manuscript. Multivariate logistic regression analysis (enter method) was also applied to assess independent correlates of ICBs in patients with PD. For this purpose, variables attaining a significance level of $p < 0.10$ in univariate analyses were considered for inclusion as independent variables in multivariate models, with the presence or absence of ICBs as the dependent variable. Two-tailed p values < 0.05 were considered statistically significant.

RESULTS

Participant characteristics

Patients with PD had slightly lower MMSE and higher MADRS scores than age- and gender-matched NCs, but there were no between-group differences regarding lifestyle factors, daytime sleepiness, or night-time sleep problems (Table 1).

Frequency of ICBs

The frequencies of ICDs and related behaviors in patients and controls are illustrated in Fig. 1. Overall, 30.4% (38/125) of patients and 11.9% (19/159) of controls reported at least one ICB, yielding an OR of 3.2 (95% CI 1.8–5.9; $p < 0.001$). Multiple ICBs were reported by 8.8% of patients (28.9% of those with ICBs) compared with 1.3% of controls (10.5% of controls with ICBs). The corresponding OR for multiple ICBs was 7.6 (95% CI 1.7–34.8; $p = 0.009$).

ICDs were reported by 20.8% (26/125) of patients and 5.7% (9/159) of controls (OR 4.4, 95% CI 2.0–9.7; $p < 0.001$). The frequencies of ICD subtypes in patients vs controls were as follows: compulsive gambling 1.6% vs. 0.6%, hypersexuality 5.6% vs. 0.6%, compulsive shopping 4.8% vs. 2.5%, and compulsive eating 11.2% vs. 2.5%.

Related impulsive-compulsive behaviors were reported by 16.8% (21/125) of patients and 7.5% (12/159) of controls (OR 2.5, 95% CI 1.3–5.3; $p = 0.018$). The frequencies of related behavior subtypes in patients vs. controls were as follows: punding 9.6% vs. 5.0%, hobbyism 10.4% vs. 4.4%, walkabout

Table 1
Characteristics of patients with PD and normal controls

Characteristics	PD patients (N = 125)	Normal controls (N = 159)	*P* value
Male, *n* (%)	75 (60.0%)	81 (50.9%)	0.128
Age, y	70.3 (9.4)	70.8 (9.0)	0.674
Smoking[a], *n* (%)	16 (12.8)	17 (10.7)	0.161
Alcohol use[a], *n* (%)	86 (68.8)	119 (74.8)	0.259
MMSE score	27.8 (2.5)	28.7 (1.5)	**0.001**
MADRS score	3.8 (4.4)	1.5 (2.9)	**0.001**
ESS score	5.8 (4.0)	6.5 (4.4)	0.244
PDSS score	124.7 (17.5)	123.6 (17.3)	0.597
Duration of PD, y	7.4 (1.8)	–	–
UPDRS motor score	22.7 (10.6)	–	–
Hoehn and Yahr stage	2.2 (0.6)	–	–

MMSE = Mini-Mental Status Examination; MADRS = Montgomery and Aasberg Depression Rating Scale; ESS = Epsworth Sleepiness Scale; PDSS = Parkinson's Disease Sleep Scale. Data are mean (SD) unless otherwise indicated. [a]Previous or current use. Bold values indicate significant *P*-value.

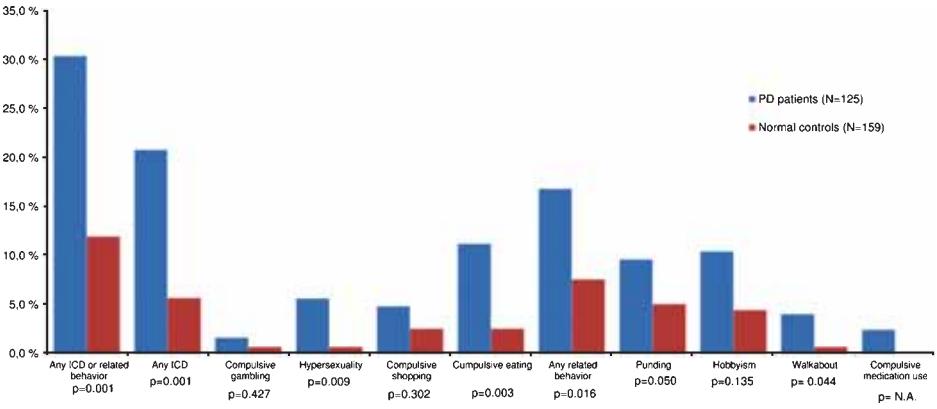

Fig. 1. Frequencies of ICBs among patients with PD and normal controls. ICB = Impulsive-compulsive behavior; PD = Parkinson disease; ICD = Impulse control disorder. Group differences are indicated by significance levels.

4.0% vs. 0.6%, and compulsive dopaminergic medication use 2.4% vs. 0%. We did not identify a gender difference between patients with the different ICB types.

Demographic and clinical correlates

Patients with ICBs were younger than patients without ICBs ($p = 0.054$), but there were no between-group differences in gender distribution, lifestyle factors, disease duration, motor severity, disease stage, daytime sleepiness or night-time sleep problems (Table 2). No patients had a history of deep brain stimulation.

Neuropsychiatric and neuropsychological correlates

Compared to patients without ICBs, those with ICBs had higher MADRS total scores and MADRS subscores related to dysphoria and retardation (Table 2). In addition, NPI items regarding depression, agitation, apathy, and irritability were more common in patients with than without ICBs (Table 3). In contrast, there were no significant between-group differences in global cognition or neuropsychological measures of attention, executive functioning, verbal memory, or visuospatial abilities (Supplemental Table). Supplemental analyses including only patients on DA treatment ($n = 78$) yielded similar results (data not shown).

Medication effects

There were no differences in monoaminooxidase-B inhibitor (MAO-B) use, levodopa use or dose, DA LED, or total LED between patients with or without ICBs (Table 2). However, patients with ICBs were more likely to use DA than those without ICBs.

The distribution of ICBs stratified by treatment is summarized in Table 4. The highest frequency was observed among patients using DA only (50%), followed by those on both DAs and levodopa (38.3%), and patients taking levodopa but not DAs (13.9%). Compared to controls, the corresponding ORs were 7.4 (95% CI 2.6–20.9; $p < 0.001$) for those on DAs only and 4.6 (95% CI 2.3–9.3; $p < 0.001$) for combination users. Patients using levodopa only had no increased odds of ICBs compared to controls (OR = 1.2; 95% CI 0.5–3.2; $p = 0.723$). Compared to patients with a single ICB, patients with multiple ICBs did not use higher dosage of dopamine agonist ($t = 1.20$, $P = 0.240$).

Combined analysis

A multivariate model with ICB status as dependent variable and age, MADRS score, and DA treatment as independent variables, showed significant effects for higher MADRS score (OR 1.2, 95% CI 1.1–1.3; $p = 0.001$) and DA treatment (OR 6.4, 95% CI 2.0–20.4; $p = 0.001$), but not age (OR 1.0, 95% CI 0.9–1.0; $p = 0.429$).

Table 2
Clinical and demographic characteristics of patients with and without ICBs

Characteristics	ICB positive ($n = 38$)	ICB negative ($n = 87$)	P value
Demographic			
Male, n (%)	26 (68.4)	49 (56.3)	0.204
Age, y	67.9 (7.7)	71.4 (9.8)	0.054
Smoking[a], n (%)	7 (18.4)	12 (13.8)	0.507
Alcohol use[a], n (%)	26 (68.4)	64 (73.5)	0.556
Clinical			
Duration of PD, y	7.4 (1.6)	7.4 (1.9)	0.367
UPDRS motor score	23.8 (10.5)	22.2 (10.7)	0.381
Hoehn and Yahr stage	2.2 (0.5)	2.2 (0.6)	0.598
MMSE score	28.4 (1.8)	27.5 (2.8)	0.108
MADRS score	5.4 (5.1)	3.1 (3.9)	**0.009**
Dysphoria subscore	1.0 (1.4)	0.4 (0.9)	**0.003**
Retardation subscore	2.6 (2.4)	1.4 (2.1)	**0.006**
Vegetative subscore	1.8 (1.3)	1.3 (2.0)	0.292
ESS score[d]	5.6 (5.1)	5.9 (3.5)	0.283
PDSS score[d]	121.8 (22.5)	126.0 (14.5)	0.775
Medication			
DA use, n (%)	32 (84.2)	46 (52.9)	**0.001**
Levodopa use, n (%)	29 (76.3)	74 (85.1)	0.238
Total LED[b]	730.6 (343.3)	658.4 (275.9)	0.522
DA LED[b]	293.7 (132.4)	289.5 (150.0)	0.896
Levodopa dose[c]	505.2 (279.1)	408.7 (266.7)	0.107
MAO-B use	13 (34.2)	31 (35.6)	0.878
Antidepressant use, n (%)	5 (13.2)	11 (12.6)	0.937

MMSE = Mini-Mental Status Examination; MADRS = Montgomery and Aasberg Depression Rating Scale; ESS = Epsworth Sleepiness Scale; PDSS = Parkinson's Disease Sleep Scale; DA = Dopamine agonist; LED = Levodopa equivalent dose; MAO-B = Monoaminooxidase-B inhibitor. Data are mean (SD) unless otherwise indicated. [a]Previous or current use. [b]Among DA users. Patients using only levodopa ($n = 43$) excluded. [c]Among levodopa users. Patients using only DA ($n = 18$) excluded. [d]N = 102. Bold values indicate significant P-value.

Table 3
Neuropsychiatric characteristics in patients with and without ICBs

NPI item	NPI score, mean (SD)		Proportion with positive NPI score, n (%)		P value[a]
	ICB positive ($n = 34$)	ICB negative ($n = 71$)	ICB positive ($n = 34$)	ICB negative ($n = 71$)	
Delusions	0.1 (0.7)	0.0 (0.4)	2 (5.9)	1 (1.4)	0.244
Hallucinations	0.1 (0.3)	0.1 (0.8)	1 (2.9)	3 (4.2)	0.999
Agitation	0.7 (1.9)	0.2 (0.8)	8 (23.5)	5 (7.0)	**0.028**
Depression	1.4 (2.3)	0.4 (1.3)	16 (47)	11 (15.5)	**0.001**
Anxiety	0.4 (1.1)	0.2 (0.9)	4 (11.8)	5 (7.0)	0.467
Euphoria	0.0 (0.2)	0.0 (0.0)	1 (2.9)	0 (0.0)	0.324
Apathy	1.3 (2.2)	0.6 (1.6)	11 (32.4)	10 (14.1)	**0.029**
Disinhibition	0.2 (0.7)	0.2 (1.1)	4 (11.8)	3 (4.2)	0.210
Irritability	0.9 (2.0)	0.1 (0.4)	9 (26.5)	7 (9.9)	**0.027**
Aberrant motor behavior	0.3 (1.4)	0.0 (0.0)	2 (5.9)	0 (0.0)	0.105
Sleep disturbance	2.8 (3.1)	1.6 (2.4)	17 (50.0)	29 (40.8)	0.337
Appetite disturbance	2.0 (3.4)	1.2 (2.7)	11 (32.4)	14 (19.7)	0.155
NPI total	10.8 (9.3)	4.8 (5.8)	28 (82.4)	43 (60.6)	**0.021**

ICBs = Impulsive-compulsive behaviors; NPI = Neuropsychiatric Inventory. NPI data missing in 4 with ICB and 16 without ICB. [a]χ^2 test. Bold values indicate significant P-value.

Table 4
Frequency and odds of ICBs in patients stratified by treatment

Characteristics	DA only users ($n = 18$)	DA and levodopa users ($n = 60$)	Levodopa only users ($n = 43$)
ICB positive, n (%)	9 (50.0)	23 (38.3)	6 (13.9)
Multiple ICBs, n (%)	3 (16.6)	7 (11.6)	1 (2.3)
OR* for any ICB, (95% CI)	**7.4 (2.6–20.9)**	**4.6 (2.3–9.3)**	1.2 (0.5–3.2)

Bold indicates significance ($p < 0.05$). ICBs = Impulsive-compulsive behaviors; OR = Odds ratio; DA = Dopamine agonist. *Compared to controls ($n = 159$).

A second model that included age, DA treatment and positive NPI scores (score ≥ 1) regarding agitation, depression, apathy and irritability as independent variables, showed significant effects for NPI depression (OR 4.0, 95% CI 1.2–13.4; $p = 0.022$) and DA treatment (OR 5.7, 95% CI 1.6–19.7; $p = 0.006$), but not age (OR 1.0, 95% CI 0.9–1.0; $p = 0.269$) or other NPI symptoms (data not shown).

DISCUSSION

The main finding of this population-based study was that patients with PD have a 3-fold increased odds of ICBs compared with age- and gender-matched controls. About 30% of our PD cohort screened positive on the QUIP for at least one ICB and almost 10% for multiple ICBs. Presence of ICBs in PD was strongly and independently associated with DA treatment and depressive symptoms, but not with other clinical or demographic variables, levodopa treatment or neuropsychological measures of attention, executive function, memory or visuospatial skills. These findings have implications for individualized patient management and follow-up.

All ICB subtypes were more common in patients than in NCs, particularly hypersexuality, compulsive eating and walkabout. These findings clearly underline the importance of screening for related behaviors beyond the major ICDs in patients with PD. Compared to our population-based estimate of 30.4% ICBs in PD, previous studies from Mexico, Finland and Denmark reported both lower and higher ICBs rates, ranging from 14.9% to 34.8% [10, 33, 34]. However, these studies comprised convenient PD samples and no control group, making comparisons difficult. Indeed, we are aware of only one other controlled study reporting comparative data on the broad range of ICBs in PD. However, that study investigated drug-naïve patients and found similar ICBs rates compared to healthy controls, affecting about 20% in each group [8]. The frequency of ICBs in our control group was substantially lower, probably reflecting differences in sample recruitment and characteristics, as well as social, cultural and economic factors. These are important to consider when comparing the occurrence of ICBs between continents and countries.

ICBs in patients with PD have consistently been associated with dopaminergic medication, and DA use in particular. Our population-based data support and extend this observation, showing a more than 7-fold increased odds of ICBs among patients using DA but not levodopa, compared with NCs. In contrast, the association of ICBs with levodopa treatment has been less clear and a matter of debate. While some authors reported that levodopa treatment is associated with ICDs in PD [12], others argue that this finding may be an artefact of including patients with comorbid dopamine dysregulation syndrome who are taking high-dose levodopa [35]. Therefore, it has been claimed that levodopa remains a first-line choice in patients at high risk of ICDs and is essential to maintain antiparkinson efficacy in patients who need to reduce or stop DA treatment. Our findings seem to support this view, as the highest odds of ICBs was observed among DA only users, whereas the frequency of ICBs among patients not taking DAs was similar to that observed in NCs.

While ICBs were strongly associated with DA treatment, they were not related to DA dose in our cohort, suggesting a drug class rather than drug dose effect. A caveat of this conclusion is that our study did not differentiate between severe and less severe ICBs, making identification of a potential drug dose effect difficult. Although similar observations have been made previously [10], others report ICBs in PD to be associated with higher DA dosages [35–37]. This is also in line with the common clinical observation that down titration of DA dosage may alleviate ICB symptoms in patients with PD.

Despite conflicting findings, some studies argue that other antiparkinson drugs, such as monoaminoxidase-B (MAO-B) inhibitors and amantadine, may be associated with increased risk of ICBs [38–41]. While amantadine was not used in our cohort, we found no association between treatment with MAO-B inhibitors and frequency of ICBs.

We found strong associations between ICBs and depressive symptoms in our cohort, specifically symptoms of dysphoria and retardation. Although depressive symptoms were mild or even subclinical (i.e. under the cut-off for clinical significant depression in PD [42]) in most patients, the association with ICBs was consistent across several measures (NPI depression item and MADRS) and independent in multivariate analysis. Despite consistent evidence in multiple studies [33, 34, 43, 44], the relationship between ICBs and depressive symptoms in PD is not fully understood. However, it has been hypothesized that denervation of afferent dopaminergic neurons may result in sensitization of the subcortical motivational reward pathways. When exposed to exogenous DAs, affected patients may experience fluctuating symptoms of both depression and ICBs [44].

Presence of ICBs in our PD cohort was not related to other clinical or demographic measures. For example, we were unable to identify significant difference in gender between patients with and without ICBs. In line with previous studies [12, 34, 43], patients with ICBs in our cohort were younger than those without. However, age was not independently associated with ICBs in multivariate analysis that also took into consideration the effects of DAs, which often are the preferred dopaminergic treatment in younger patients with PD. Furthermore, we were not able to demonstrate any association between ICBs and motor disability or disease duration, nor cognitive impairment. Although altered reward and stimulus valuation have been reported in patients with PD and ICBs [3, 4, 9], global cognitive functioning has usually been demonstrated to be preserved [43, 45], in line with our findings. Indeed, a recent longitudinal study in PD even reported lower cognitive decline in patients with than without ICBs [45].

These observations argue against ICBs in PD being a consequence of more widespread brain pathology and rather suggest that the vulnerability to DAs in a substantial subset of patients reflects genetic susceptibility. In support of this, a recent study in PD found that 57% of the variance in ICB incidence was explained by common genetic variants, and that differentiation between patients at risk and patients without risk of ICB development may be possible using a broad candidate genetic panel [46]. These results are promising and highlight the involvement of premorbid genetic factors of multiple neurotransmitter systems in the pathogenesis of ICBs in PD. Continued research into potential genetic markers of ICBs might translate into clinical practice and make identification of at-risk patients possible.

Our study has both strengths and limitations. Major strengths include the population-based design, the well-characterized PD cohort, the comprehensive clinical, neuropsychiatric and cognitive assessments, and the age- and gender-matched control group from the same geographical area. We consider the use of the QUIP, a validated screening instrument covering a broad range of ICBs [20], another strength of our study, although we recognize that the short form version applied in this study does not allow to determine the severity of ICB symptoms, which is a relative limitation. We also recognize the assessment of ICBs by self-report as a potential limitation of this study, as affected individuals not always recognize ICBs as problematic [20]. Using QUIP, only moderate inter-rater reliability has been found between patients and their caregivers, arguing for a risk of false negatives in the absence of informant-based information on ICBs in PD [47, 48]. On the other hand, we are aware that the QUIP may overestimate the frequency of ICBs. However, this is most likely true for both patients and controls and should therefore not impact the odds ratios between these two groups. Another study limitation is the cross-sectional data presented here. However, these data extend previous evidence by demonstrating that ICBs are very common in the general PD population, with a more than 3-fold increased risk compared to matched control subjects. Importantly, this increased risk of ICBs in PD was driven by patients on treatment with DA, whereas levodopa per se was not associated with ICBs in our population-based cohort. Clinicians are therefore advised to demonstrate caution when administering DAs and to routinely screen for ICB symptoms in PD, as patients not always spontaneously report ICBs in daily clinical practice. Given the very limited long-term data in this field, collection of longitudinal data in our population-based study is ongoing and will hopefully provide further valuable insights into important aspects related to the causes, evolution and consequences of ICBs.

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CONFLICT OF INTERESTS

The authors have no conflict of interest to report.

SUPPLEMENTARY MATERIAL

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Paper II

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ORIGINAL RESEARCH
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Dopaminergic and Opioid Pathways Associated with Impulse Control Disorders in Parkinson's Disease

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Introduction: Impulse control disorders (ICDs) are frequent non-motor symptoms in Parkinson's disease (PD), with potential negative effects on the quality of life and social functioning. ICDs are closely associated with dopaminergic therapy, and genetic polymorphisms in several neurotransmitter pathways may increase the risk of addictive behaviors in PD. However, clinical differentiation between patients at risk and patients without risk of ICDs is still troublesome. The aim of this study was to investigate if genetic polymorphisms across several neurotransmitter pathways were associated with ICD status in patients with PD.

Methods: Whole-exome sequencing data were available for 119 eligible PD patients from the Norwegian ParkWest study. All participants underwent comprehensive neurological, neuropsychiatric, and neuropsychological assessments. ICDs were assessed using the self-report short form version of the Questionnaire for Impulsive-Compulsive Disorders in PD. Single-nucleotide polymorphisms (SNPs) from 17 genes were subjected to regression with elastic net penalization to identify candidate variants associated with ICDs. The area under the curve of receiver-operating characteristic curves was used to evaluate the level of ICD prediction.

Results: Among the 119 patients with PD included in the analysis, 29% met the criteria for ICD and 63% were using dopamine agonists (DAs). Eleven SNPs were associated with ICDs, and the four SNPs with the most robust performance significantly increased ICD predictability (AUC = 0.81, 95% CI 0.73–0.90) compared to clinical data alone (DA use and age; AUC = 0.65, 95% CI 0.59–0.78). The strongest predictive factors were rs5326 in *DRD1*, which was associated with increased odds of ICDs, and rs702764 in *OPRK1*, which was associated with decreased odds of ICDs.

Conclusion: Using an advanced statistical approach, we identified SNPs in nine genes, including a novel polymorphism in *DRD1*, with potential application for the identification of PD patients at risk for ICDs.

Keywords: Parkinson's disease, impulse control disorders, addiction, elastic net, OPRK1, DRD1

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INTRODUCTION

Patients with Parkinson's disease (PD) have a threefold increased odd for developing impulse control disorders (ICDs) and related compulsive behaviors when compared to controls (1, 2). These behaviors are characterized by lacking control of rewarding behaviors, such as gambling, sexual activity, eating, and buying. In addition, patients may also develop a preoccupation with hobbies, punding behaviors, and an addiction-like pattern of dopaminergic medication use. Although common in PD, ICDs are not merely a result of PD pathology (3), but are closely associated with the use of dopaminergic replacement therapy (DRT), such as dopamine agonists (DAs) (1, 2, 4). Still, not all patients develop ICDs when exposed to dopaminergic medications, arguing that some individuals are more susceptible to DRT than others. Previously identified demographic-risk factors, such as familial history of addiction, increased impulsivity, and novelty-seeking traits (1, 5), argue that the individual vulnerability may be of genetic origin.

To date, the evaluation of ICD susceptibility in PD has primarily focused on independent associations of single genetic variants. Several studies have reported an association between ICD development in PD patients and genetic polymorphisms in dopamine receptor (*DRD1–3*) and glutamate receptor (*GRIN2B*) genes (6–9), while individual studies also point toward a potential association with genetic polymorphisms in serotonin receptor (*HTR2A*), dopamine transporter (*DAT1*), and tryptophan hydroxylase 2 (*TPH2*) genes (10, 11). Recently, the spectrum of monoaminergic ICD candidate genes was expanded through the identification of a polymorphism in *OPRK1*, which encodes an opioid receptor, as the strongest genetic predictive factor in a clinical–genetic model designed to predict the occurrence of ICDs in early PD in the Parkinson's Progression Markers Initiative (PPMI) cohort (12). The authors further reported that the inclusion of a panel of candidate-genetic variants improved the prediction of incident ICDs (identifying up to 76% of incident ICD cases in early-stage PD patients) compared to prediction based on clinical variables alone (12), arguing for the potential clinical utility of genetic testing. The authors estimated that common genetic variants accounted for 57% of the variance of ICD incidence among PD patients in the PPMI study. This heritability estimate is comparable to estimates from the general population, but current knowledge about individual risk genes is limited. We suggest that several neurotransmitter systems may contribute to ICD pathogenesis, and multiple genes within one system may play a crucial role in the pathogenesis of these behaviors.

To date, the identification of patients at risk of ICDs remains a primary aim in clinical research. Although several genetic polymorphisms have been suggested to aid clinical identification of ICD risk, most published studies utilize a candidate-gene approach based on previously published findings. In this study, we aimed to determine the association of genetic polymorphisms across several neurotransmitter pathways using an advanced statistical approach. A secondary aim was to investigate the clinical utility of a genetic panel in the prediction of ICD status in patients with PD.

Abbreviations: PD, Parkinson's disease; ICD, impulse control disorder; QUIP, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease; SNP, single-nucleotide polymorphism; ROC, receiver-operating characteristics; AUC, area under the curve; DRT, dopaminergic replacement therapy; DA, dopamine agonist; PPMI, Parkinson's progression markers initiative; UPDRS, Unified Parkinson's Disease Rating Scale; LED, levodopa equivalent dose; MAF, minor allele frequency; EN, elastic net; LD, linkage disequilibrium.

MATERIALS AND METHODS

Study Design

This cross-sectional study is based on participants from the Norwegian ParkWest study, a population-based longitudinal study of incident PD. The ParkWest cohort is composed of patients with newly diagnosed PD and normal control subjects recruited from four counties in Norway between 2004 and 2006, who were prospectively followed up by movement disorder neurologists. A detailed presentation of the diagnostic procedures and case ascertainment has previously been published (13). Screening for ICDs was first introduced at 5-year follow-up, and this study included 155 patients with PD who still remained in the study after 5 years of follow-up. Of these, 28 patients were excluded due to dementia and two due to missing data on Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP), leaving 125 patients eligible for this study. Patients with missing information on relevant genetic variants ($n = 6$) were removed from this study.

Clinical Measures

A standardized examination program was administered by trained members of the ParkWest study group. Information regarding demographic variables, lifestyle factors, clinical history, and medication was obtained using semi-structured interviews. Severity of motor symptoms was assessed using the Unified Parkinson's Disease Rating Scale (UPDRS) part III (14). Self-evaluated functioning on activities of daily life and complications of dopaminergic therapy were assessed using UPDRS parts II and IV. Hoehn and Yahr (H&Y) was used to assess disease stage (15). Levodopa equivalent doses (LEDs) were calculated according to published recommendations (16). Mini-Mental State Examination (MMSE) was used to assess global cognitive functioning (17). The Montgomery and Aasberg Depression Rating Scale (MADRS) was used to assess depressive symptoms (18). Lastly, ICDs were assessed using the self-report short form version of the QUIP (19). Participants with a positive response to one or more screening questions of the QUIP were classified to have ICD (20).

Candidate Gene and Variant Selection

Of the 125 patients eligible for this study, 119 had previously been characterized by whole-exome sequencing (WES) (unpublished material). We selected 16 genes (*ADRA2C*, *DRD1–5*, *SLC6A3/DAT1*, *DDC*, *COMT*, *SLC6A4/5HTTLPR*, *TPH2*, HTR2A, OPRM1, OPRK1, *GRIN2B*, and *BDNF)* based on established roles in candidate neurotransmitter pathways, or a published involvement in ICD and related behaviors in either patients with PD or in non-PD

populations. This was achieved by performing a literature search, and the genes identified were involved in four neurotransmitter pathways (dopaminergic, serotonergic, glutamatergic and opioid) (6–12). All variants (n = 185) present in the candidate-gene regions were extracted using ingenuity variant analysis (Qiagen, CA, USA) and filtered to retain only those with minor allele frequency (MAF) >0.5 in the ParkWest and the 1,000 genomes project (n = 71). A further 12 single-nucleotide polymorphisms (SNPs) were removed based on a high linkage disequilibrium (LD) measured using the Broad Institute SNP Annotation and Proxy Search (SNAP) (21). In addition, two SNPs that have frequently been studied in ICDs in PD, but which were not in the original data extraction, were also included: rs1800497 in *ANKK1* was extracted from the WES data and rs6280 in *DRD3* was genotyped using a custom-made TaqMan SNP-genotyping assay (Thermo Fisher Scientific), as described (22). For further analysis, the genotypes were converted to carrier status, and five variants removed due to a carrier frequency >95% in the study population.

Statistical Analyses

Statistical procedures were performed using IBM SPSS Statistics version 24.0.0.1, R 3.4.0 and STATA IC 14.2. Group differences were analyzed using t-tests, Mann–Whitney tests, χ^2–tests, and Fisher exact tests as appropriate.

Performing an extensive investigation of genetic variants associated with ICDs is inherently difficult due to the large number of possible variants identified in a single neurotransmitter pathway. The number of variants (p) will often exceed the number of participants (n) in the study. In these cases ($p >> n$), the traditional strategies for multivariable regression modeling will fail. An option here is to assume a sparse solution, i.e., that only a small subset of variants are involved in a single neurotransmitter pathway. Recent advances in statistical modeling, such as elastic net (EN) regularized generalized linear regression, reduce the number of predictors by penalizing those that do not have enough prediction power. This allows one to reduce the risk of overfitted models and increase the generalizability to other cohorts (23, 24). In this study, regularized logistic regression with EN penalization was used to identify SNPs associated with ICDs. Regularized regression with EN is well suited for model selection of high-dimensional data, as is often the case in analyses of genetic polymorphisms in clinical cohorts (23, 25). In addition, EN handles variants with high LD and multiple SNPs from one neurotransmitter pathways well (26).

Elastic net analyses were performed in *R*, using the *glmnet*-package (27). The level of regularization parameter λ was chosen as the minimal λ that yielded prediction error estimated by cross-validation within one standard error from its minimal value. In the *glmnet*, the parameter α decides the balance between l_1 and l_2 regularizations, of which the former is the regularization used in Lasso regression (α = 1) and the latter is used in Ridge regression (α = 0). In our analyses, the EN was repeated for all α from 0 to 1, with 0.01 increments. Non-zero estimated coefficients consistent throughout the entire range of α support the evidence of associations between relevant SNPs and ICD status.

The discriminative ability of the biomarkers with regard to ICD diagnosis was assessed from receiver-operating characteristic (ROC) curve analysis. The test variable was the predicted probability from logistic regression with ICD diagnosis (yes/no) as outcome. In order to not overfit the model, the four SNPs with a most robust performance in EN analysis were selected as candidate SNPs. Robustness of candidate SNPs was defined by the consistency of the estimated B-values in EN analyses (which are visually represented by color in **Figure 1**). The ROC curve was plotted with preselected clinical variables alone (age and either DA use), for the genetic variables alone (genetic model), and with the clinical and candidate SNP data combined (clinical–genetic model). Area-under-the-curve (AUC) values were compared using DeLong test.

RESULTS

Demographic and Clinical Characteristics

Demographic and clinical characteristics are presented in **Table 1**. Of 119 patients in the study, 29.4% (35/119) reported at least one ICD. Patients with ICD did not differ from patients without ICD in terms of sex, education, duration of PD, MMSE scores, or scores on UPDRS II, III, or IV, but patients with ICDs tended to be younger (p = 0.050) and scored significantly higher on MADRS (p = 0.010). Patients with ICDs also used DA more frequently (p = 0.001) and had a higher total LED (p = 0.017). DA dosage was not different when comparing DA users with ICDs with those without ICDs (p = 0.958).

Variant Selection

The complete results from EN analyses are presented in **Figure 1**. Fifty-six SNPs were identified across the genes selected for analysis (Table S1 in Supplementary Material), and 11 SNPs from four neurotransmitter pathways were robustly associated with ICDs across all levels of α in the EN analysis (**Figure 1**; **Table 2**). Specifically, carriers of the minor alleles of the *DRD1* rs5326, *DRD2* rs6277, COMT rs4646315, and DDC rs4490786 SNPs were associated with an increased risk of ICDs. Carriers of the minor allele of the *OPRM1* rs677830, *OPRK1* rs702764, *GRIN2B* rs1105581 and rs7301328, *COMT* rs4646318, TPH2 rs4290270, DRD5 rs6283 SNPs were associated with a decreased risk of ICDs. Of these, the *DRD1* rs5326, *OPRK1* rs702764, *OPRM1* rs677830, and *COMT* rs4646318 were most robustly associated with ICD status and thus considered candidate variants.

Prediction of ICDs

The prediction of ICDs was estimated by using ROC curves with AUC (**Figure 2**). In the clinical model, ROC curves plotted with the clinical variables age and DA use yielded an estimated AUC of 0.68 (95% CI 0.59–0.78). In this analysis, DA use [odds ratio (OR) 4.5; 95% CI 1.5–13.5; p = 0.006] was associated with the presence of ICDs. The genetic model, consisting of the SNPs *DRD1* rs5326, *OPRK1* rs702764, *OPRM1* rs677830, and *COMT* rs4646318, yielded an estimated AUC of 0.70 (95% CI: 0.61–0.79). Of these, one variant, the *DRD1* SNP rs5326, was significantly associated with ICDs (OR 2.9; 95% CI 1.1–7.6; p = 0.026).

In the clinical–genetic model, we included four candidate SNPs identified in the EN analyses, resulting in an estimated

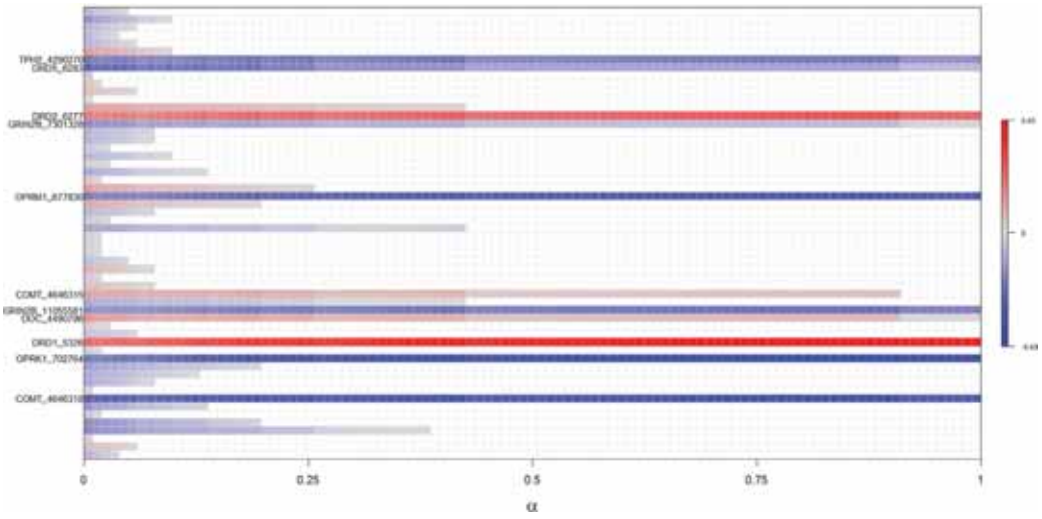

FIGURE 1 | Results of regularized regression with elastic net penalization for α-values between 0 and 1. Polymorphisms positively associated with ICDs (i.e., increases risk) are highlighted with red, while polymorphisms negatively associated with ICDs (i.e., decreases risk) are highlighted in blue, with the intensity of color reflecting the strength of association. Polymorphisms not associated with ICDs are white. Identified polymorphisms demonstrate significant association across all levels of α.

TABLE 1 | Demographic and clinical characteristics.

Characteristics	Total (n = 119)	ICD (n = 35)	No ICD (n = 84)	p-Value[a]
Age	70.5 (9.3)	67.9 (7.7)	71.6 (9.7)	**0.050**
Male, *n* (%)	74 (62.2)	25 (71.4)	49 (58.3)	0.180
Education	11.6 (3.2)	11.49 (3.0)	11.7 (3.3)	0.803
Duration of PD	7.4 (1.8)	7.3 (1.4)	7.4 (1.9)	0.658
Mini-Mental State Examination	27.8 (2.6)	28.5 (1.7)	27.5 (2.8)	0.063
Montgomery and Aasberg Depression Rating Scale	3.9 (4.4)	5.5 (5.1)	3.2 (4.0)	**0.010**
UPDRS II	10.7 (5.4)	12.0 (6.0)	10.1 (5.0)	0.126
UPDRS III	22.7 (10.8)	23.8 (10.7)	22.3 (10.9)	0.422
UPDRS IV	1.8 (1.7)	2.0 (1.8)	1.7 (1.7)	0.369
Hoehn and Yahr stage	2.2 (0.6)	2.2 (0.6)	2.2 (0.6)	0.920
DA users, *n* (%)	75 (63.0)	30 (85.7)	45 (53.6)	**0.001**
Total LED	619.0 (350.2)	740.7 (354.9)	568.2 (333.7)	**0.017**

PD, Parkinson's disease; UPDRS, Unified PD Rating Scale; DA, Dopamine agonist; LED, Levodopa equivalent dosage; ICD, Impulse control disorder.
[a]*Group differences between patients with and without ICDs.*
Significant p-values are highlighted in bold.

AUC of 0.81 (95% CI 0.73–0.90). This 13% point increase in AUC between the clinical and the clinical–genetic model was statistically significant ($p = 0.003$). Similarly, the 11% point increase in AUC between the genetic and the clinical–genetic model was also significant ($p = 0.008$). In the clinical–genetic model, DA use (OR 7.4; 95% CI 2.1–26.2; $p = 0.002$) was again associated with increased odds of ICDs, and the significant genetic predictors *DRD1* SNP rs5326 (OR 6.1; 95% CI 1.9–19.6; $p = 0.003$) and *OPRK1* SNP rs702764 (OR 0.2; 95% CI 0.1–0.8; $p = 0.040$) were associated with an increased and a decreased risk of ICDs, respectively. Full details of the clinical and the clinical–genetic models are presented in **Table 3**.

DISCUSSION

In this study, we identified an association between ICDs and SNPs in the dopaminergic, glutamatergic, serotonergic, and opioid neurotransmitter system using an advanced statistical procedure. Using four polymorphisms from this panel significantly increased the level of prediction of ICD status beyond known clinical risk factors. These results confirm and expand existing knowledge about the genetic architecture of ICDs in PD. To date, this is the most extensive investigation of polymorphisms in relation to ICDs in PD.

Guiding Clinical Practice Using Genetic Markers

Despite new insights into the pathophysiology of ICDs in PD, a consistent model for clinical differentiation between patients with high and low risk of ICDs has still not been developed. Although younger age has been associated with ICDs in several cohorts, DA is more often prescribed to younger patients than that to older. As evident in the clinical model of ICD risk, age is not significantly associated with ICDs when controlling for

TABLE 2 | Characteristics of identified SNPs in elastic net analysis.

Gene	SNP	Location[a]	Transcript[b]	Protein	MAF[c]		Association with impulse control disorders in ParkWest[d]
					ParkWest	1,000 genomes	
DRD1	rs5326	5:175443193	c.-94G > A		0.14	0.17	+
DRD2	rs6277	11:113412737	c.957C > T	p.Pro319Pro	0.50	0.24	+
OPRM1	rs677830	6:154107531	c.1231C > T	p.Gln411Ter	0.29	0.15	–
OPRK1	rs702764	8:53229597	c.843A > G	p.Ala281Ala	0.11	0.24	–
GRIN2B	rs11055581	12:13675725	c.1125 + 20A > G		0.18	0.10	–
COMT	rs4646318	22:19967324	c.466 – 1212G > A		0.07	0.07	–
TPH2	rs4290270	12:72022455	c.1125A > T	p.Ala375Ala	0.64	0.49	–
DRD5	rs6283	4:9783007	c.978C > T	p.Pro326Pro	0.60	0.39	–
GRIN2B	rs7301328	12:13865843	c.366C > G	p.Pro122Pro	0.46	0.44	–
DDC	rs4490786	7:50476616	c.1041 + 8G > A		0.18	0.20	+
COMT	rs4646315	22:19964374	c.615 + 75G > C		0.19	0.17	+

SNPs, single-nucleotide polymorphisms; MAF, minor allele frequency.

[a]Genome location in GRCh38 assembly.

[b]Transcript position of most severe consequence according to the Human Genome Variation Society guidelines (28).

[c]MAF in the patients of the ParkWest cohort or 1,000 genomes project.

[d]"+" indicated a positive association with ICDs in the ParkWest cohort and "–" indicates a negative association with ICDs in the Park cohort.

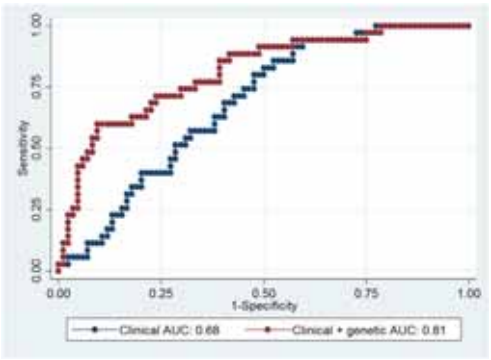

FIGURE 2 | Receiver-operating characteristic (ROC) curves for prediction of impulse control disorders (ICDs). The blue curve was plotted with clinical variables (age and dopamine agonist use), while the red curve was plotted with clinical and the four candidate single-nucleotide polymorphisms. Area under the curve (AUC) for each model is indicated in the figure.

DA use (**Table 3**). Even though DA use is the predominant risk factor for ICDs in patients with PD, DA is still a preferred drug in the early stages of PD due to the diminishing effects of levodopa over time. Therefore, the identification of risk factors that predict ICDs *before exposure* to DA is important to guide clinical practice. Genetic panels have been advocated to be a clinically useful predictor of disease and may be especially important when investigating common polymorphisms, which may have a small effect size and be contingent upon gene-by-environment interactions. Recently, a predictive genetic panel for ICDs in PD has been proposed. Kraemmer and colleagues utilized a panel of 13 candidate polymorphisms, which in concert with clinical variables resulted in an AUC of 76% (95% CI 70–83%) for prediction of ICDs. Our findings support the use of a genetic and clinical model in the prediction of ICDs in PD and also advocate for an approach in which genetic variants are selected based on not only the previously published literature but also using a statistical approach that can handle a gamut of variants. Using such an approach, we have replicated the finding that OPRK1 rs702764 is associated with ICDs when controlling for DA use and identified a novel association between an SNP in *DRD1* and ICDs. In addition, we also identified a sparse clinical–genetic model with a high degree of prediction [AUC of 81% (95% CI 73–90%)] of ICD status, using only four candidate SNPs.

Dopaminergic Pathways

When controlling for DA use and age, we identified two genes with polymorphisms that were independently associated with ICDs (**Table 3**). rs5326 is positioned in the 5′ untranslated region (UTR) of the *DRD1* gene, which encodes the dopamine receptor D1, and was associated with an increased risk of ICDs. The D1 receptor is the most abundant dopamine receptor in the central nervous system, particularly expressed in the prefrontal areas, and is considered a modulator of dopaminergic activity (29). Stimulation of D1 receptors by agonists or illicit drugs (like cocaine and amphetamine) has been suggested to trigger punding and hobbyism behaviors in both patients with PD and patients with addiction (30). Previously, polymorphisms in the noncoding regions of *DRD1* (rs4867798 in the 3′-UTR and rs4532 in the 5′-UTR) have been associated with ICDs in a Malaysian PD cohort (8). Furthermore, polymorphisms in *DRD1* have been linked to ICDs, neuropsychiatric disease, problem gambling, addiction, and cognitive functioning in non-PD populations (31, 32). Risk variants of rs5326 have been associated with a decreased *DRD1* expression, a reduced cognitive functioning in both healthy males and bipolar patients, and an increased risk of neuropsychiatric disorders, such as schizophrenia and heroin addiction (33–36).

TABLE 3 | Association between ICD status and a clinical, genetic, and clinical + genetic model.

	Clinical model		Genetic model		Clinical + genetic model	
Factor	**OR (95% CI)**	***p*-Value[a]**	**OR (95% CI)**	***p*-Value[a]**	**OR (95% CI)**	***p*-Value[a]**
(Intercept)	0.6	0.756	0.1	0.099	1.1	0.948
Age	1.0 (0.9–1.0)	0.434	–	–	1.0 (0.9–1.0)	0.234
DA use	4.5 (1.5–13.5)	**0.006**	–	–	7.4 (2.1–26.2)	**0.002**
DRD1 rs5326	–	–	2.9 (1.1–7.6)	**0.026**	6.1 (1.9–19.6)	**0.003**
OPRK1 rs702764	–	–	0.3 (0.1–1.1)	0.072	0.2 (0.1–0.9)	**0.040**
OPRM1 rs677830	–	–	0.5 (0.2–1.2)	0.105	0.5 (0.2–1.3)	0.153
COMT rs4646318	–	–	0.3 (0.1–1.5)	0.140	0.2 (0.1–1.5)	0.117

OR, odds ratio; 95% CI, 95% confidence interval; DA, dopamine agonist; ICD, impulse control disorder.
[a]Single factor association from stepwise logistic regression with ICD status as dependent variable.
Significant p-values are highlighted in bold.

Few studies have investigated the *DRD1* gene with regard to ICDs in PD, while considerable effort has been made in identifying polymorphisms in *DRD2* and *DRD3*, mostly due to the established importance of these genes in ICDs in the general population and the high affinity of DAs to these receptors (37, 38). In our data, the rs6277 SNP in *DRD2* was robustly associated with ICDs in the EN analysis, but was not a strong individual predictor of ICD in regression analysis. rs6277 has previously been associated with individual differences in cognitive functioning, reward processing, and impulsivity (39–45). Although the association between ICDs and the rs6277 is novel, it should be noted that this SNP has not been included in previous studies of ICDs in PD. Several other genetic variants in *DRD2*, including rs6277 neighboring SNP rs1800497 (Taq1A), have been studied in PD and found to be associated with ICDs, although not in all studies (6–8, 12).

The D1 and D2 receptors have been suggested to have opposing roles in reward processing, modulating reward and avoidance-based learning, respectively (46). However, the precise interplay between polymorphisms in *DRD1* and *DRD2* and the presentation of ICDs is largely unknown. One theory suggests that polymorphisms in the promoter region of *DRD1* can affect mRNA stability and result in a lower expression of the D1 receptor itself (8, 32). Given the modulating role of the *DRD1* gene in dopaminergic signaling and reward processing, patients with polymorphisms may be prone to a hyperdopaminergic state when exposed to DRT. Similarly, some authors have speculated that polymorphisms in *DRD2*, like the Taq1A polymorphism, may result in modifications in the protein structure of the receptor and ultimately lead to a reduced expression of the D2 receptor (8). This theory is supported by neuroimaging studies that have identified low D2/D3 receptor availability in ventral striatum in patients with ICDs [see (47) for a review]. However, it is still unknown if polymorphisms in these SNPs can result in a reduced expression of D1 and D2 receptors and, if so, if these polymorphisms result in functional dysfunctions, like aberrant reward processing. In order to test these theories, studies at the cellular and molecular levels are needed.

Opioid Pathways

The second polymorphism having an independent association with ICDs was rs702764, located in the kappa-opioid receptor (*OPRK1*) gene. This polymorphism was negatively associated with ICDs in the clinical–genetic model. *OPRK1* encodes the kappa-opioid receptor 1 (KOR1), which is one of four-related opioid receptors in the brain. KOR1 is involved in processes such as feeding behavior, pain management, and addiction. In rodent models, the *OPRK1* gene has been shown to modulate dopaminergic tone, suggesting that *OPRK1* is involved in reward processing (48, 49). Previously, the TC genotype of the *OPRK1* SNP rs702764 has been associated with incident ICDs (12). The neurophysiology between KOR1 and dopamine signaling is not fully understood, but some authors have suggested that the opioid receptors mu1 (MOR1) and KOR1 have opposing roles in the modulation of basal dopaminergic tone in the nucleus accumbens (50–52). Thus, the involvement of the *OPRK1* in modifying the risk of ICDs may be of special interest due to the potential for pharmacological interventions with opioid antagonists. The opioid antagonist naltrexone, which has high affinity to the MOR1 and KOR1, has been deemed efficacious in reducing the severity of other ICDs, such as hoarding and compulsive disorders in the general population. To date, only one trial with PD patients has been published (53). Although naltrexone was not associated with change on the Clinical Global Impression scale, naltrexone was associated with significant changes in QUIP score, arguing that further studies are warranted.

The possible association between polymorphisms in dopamine and opioid receptors and ICDs is interesting, as they are also considered candidate genes for what has been termed "reward deficiency syndrome," a hypothesized neuropsychological state characterized by decreased feelings of satisfaction caused by gene-by-environment interactions (37, 54, 55). This theory, composed of evidence from ICD patients without PD, suggests that polygenic variability, given the right environmental factors, could result in a hypodopaminergic state that causes insensitivity to reward and results in an atypical reward-seeking behavior, as often seen in patients with behavioral or chemical addictions. However, the current models of ICDs in PD suggest that ICDs in PD are a result of a hyperdopaminergic state, caused by exogenous dopamine and possibly exacerbated by frontal cognitive dysfunctions (56, 57). Based on these observations, one might argue that although ICDs in patients with PD and patients without PD are similar in terms of phenotype and share genetic risk profiles, the gene-by-environment profiles and pathophysiology might differ in the two populations.

Strengths and Limitations

There are several limitations that should be considered. First, we have not validated our findings in an external cohort, making generalization or clinical utility of these findings impossible before replication. Despite this, our approach positively identifies variants previously associated with ICDs in the PPMI study (12) and provides new insights into the genetic architecture of ICDs in PD. A second limitation is the use of QUIP as a definition of ICDs. This measure has high sensitivity, but lacks specificity and may inflate the frequency estimates of ICDs. Third, causative relations between the identified genetic polymorphisms and ICDs are difficult to infer based on the current research design. Due to the involvement of DA in ICD development, one might argue that the identified SNPs could increase the risk of DA use, rather than ICDs. We have attempted to meet this challenge by adopting a clinical–genetic model that controls for DA use. Strengths of this study include the use of patients with and without ICDs that are matched in terms of motor impairment and H&Y stage. As argued by Cormier and colleagues, investigations into the genetic architecture of ICDs in PD should include matched groups in terms of motor impairment, H&Y stage, and DA LED (58). Although patients differed in terms of total LED, patients with ICDs were not significantly different than patients without ICDs in terms of DA LED. Lastly, we argue that using an advanced statistical approach that yields robust findings when analyzing a large amount of variants is a major strength of this study.

CONCLUSION

Our findings demonstrate that a genetic panel (DRD1, OPRK1, OPRM1, and COMT) can provide valuable information with regard to the clinical differentiation between PD patients at risk of ICDs and PD patients without risk. Using an advanced statistical approach, we also identified one novel polymorphism associated with ICDs in PD. Although promising, our results need replication in other, larger cohorts.

ETHICS STATEMENT

All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Regional Committee for Medical and Health Research Ethics, Western Norway.

AUTHOR CONTRIBUTIONS

AE was involved in the conception, design, statistical analysis, interpretation of data, and writing of the first draft. JG and KP were involved in the conception, design, interpretation of data, and supervision of the study. ID and AU were involved in statistical analysis and interpretation of data. JG, CT, and JC were involved in the analysis of genetic data. GA and OT were involved in the conception and study supervision. All authors made critical contributions and approved this manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at http://www.frontiersin.org/articles/10.3389/fneur.2018.00109/full#supplementary-material.

TABLE S1 | Included genes in regularized regression with elastic net penalization.

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Paper III

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Is psychosis associated with impulse control disorders in Parkinson's disease?

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We read with interest the paper by Hinkle and colleagues on the association between psychosis, impulse control disorders (ICDs) and dyskinesias (DKs) in patients with Parkinson's disease (PD) [1]. This study is a welcome addition to the literature emphasizing that ICDs and DKs might be behavioral manifestations of similar pathophysiological processes in the basal ganglia [2]. Hinkle and colleagues demonstrated that psychotic symptoms were associated with both ICDs and DKs, arguing that psychosis may share common pathological pathways with loss of self-regulatory processes in motor and non-motor domains [1].

We recently reported the frequency and clinical correlates of ICDs in a population-based PD cohort from Norway, but did not include data on psychosis or DKs in our analyses [3]. We have now conducted additional analyses on this cohort, in order to replicate the findings by Hinkle and colleagues. For a detailed description of the study protocol and procedures, please refer to our previous publication [3]. In short, we included 124 non-demented patients from the Norwegian ParkWest study. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Regional Committee for Medical and Health Research Ethics, Western Norway. ICDs were assessed using the Questionnaire for Impulsive Compulsive Disorders in PD (QUIP), using a positive response to one or more question as an indication of ICD. A cutoff score of ≥ 1 on item 32 from the Unified PD Rating Scale (UPDRS) part IV was used to indicate presence of DKs. Psychotic symptoms were assessed using a semi-structured interview based on the most recent diagnostic criteria, that obtained information about the presence, duration, frequency and intensity of minor psychotic symptoms (presence and passage phenomena), illusions, hallucinations and delusions (including symptoms of capgras) [4].

Demographic and clinical findings are summarized in Table 1. Similar to Hinkle and colleagues, we performed separate logistic regression analyses with ICD status or DK status as dependent variables, using odds ratio (OR) with 95% confidence intervals (CIs) as an expression of association between variables. In the unadjusted model, we found that presence of psychotic symptoms was indeed associated with DKs (OR = 3.4, 95% CI 1.1–10.0; P = 0.028), but not ICDs (OR = 1.4, 95% CI 0.5–3.6; P = 0.530). Adjusting for age at testing and total LED or DA use did not change the results.

Table 1
Patient characteristics by presence of ICDs and DKs (n = 124).

Variable	No ICDs or DKs (N = 76)	DKs only (N = 10)	ICDs only (N = 30)	ICDs and DKs (N = 8)	P value[a]
Age at testing, years	71.2 (9.7)	71.6 (11.2)	68.0 (7.2)	67.2 (9.9)	0.148
Male, n (%)	46 (60.5)	3 (30.0)	23 (76.6)	3 (37.5)	**0.029**
Duration of PD, years	7.5 (1.9)	6.3 (1.0)	7.6 (1.7)	6.7 (0.8)	**0.039**
Levodopa use, n (%)	63 (82.9)	10 (100.0)	22 (73.3)	7 (87.5)	0.306
Levodopa dose, mg/day	344.3 (300.4)	437.5 (118.6)	318.3 (241.6)	637.5 (477.9)	0.068
DA use, n (%)	39 (51.3)	7 (70.0)	25 (83.3)	7 (87.5)	**0.009**
DA LED, mg/day	158.5 (183.8)	158.5 (180.1)	261.6 (170.9)	193.9 (121.4)	0.053
UPDRS II	10.1 (4.9)	9.0 (4.3)	11.9 (6.7)	11.9 (3.4)	0.314
UPDRS III	22.5 (10.6)	19.2 (12.0)	24.6 (10.7)	20.9 (9.6)	0.544
MMSE	27.5 (2.7)	28.1 (2.6)	28.3 (2.0)	28.8 (0.9)	0.283
MADRS	2.9 (3.9)	4.7 (4.1)	5.0 (5.2)	6.9 (4.5)	**0.008**
Psychotic symptoms, n (%)	12 (15.8)	3 (30.0)	4 (13.3)	4 (50.0)	0.090

[a] P values pertain to Kruskal-Wallis test for continuous variables and Fisher's exact test with Monte Carlo simulation (Confidence interval 99%, 1000 iterations) for categorical data. Significant P values are highlighted in **bold**. Abbreviations: ICDs = Impulse control disorders; DKs = Dyskinesias; PD = Parkinson's disease; DA = Dopamine agonist; LED = Levodopa equivalent dosage; UPDRS = Unified Parkinson's Disease Rating Scale; MMSE = Mini-Mental State Examination, MADRS = Montgomery and Aasberg Depression Rating Scale.

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In conclusion, we were able to replicate Hinkle and colleagues findings on the association between DKs and psychosis, but our results do not support any association between ICDs and psychosis. Reasons for the latter finding may include differences in patient characteristics and measures used to define DKs and ICDs between cohorts. For example, Hinkle and colleagues used one question from the MDS-UPDRS to evaluate ICD status, which may underestimate the frequency of ICDs compared with self-administered screening tools like the QUIP. Although the MDS-UPDRS include most of the ICDs associated with PD, compulsive eating and compulsive shopping are not covered in the instructions and may therefore be overlooked during the clinical interview with the patient. As a consequence, clinical evaluation using the MDS-UPDRS may have identified only the most severe cases of ICDs, rather than the full spectrum of these potentially disabling non-motor symptoms. Therefore, we recommend future investigations on psychosis and ICDs to take into account the full range of ICDs associated with PD.

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Supplemental Materials

Figure E-1. Flow chart of patients with PD and normal control in the ParkWest study. "Initial assessment"= 5-year follow up visit

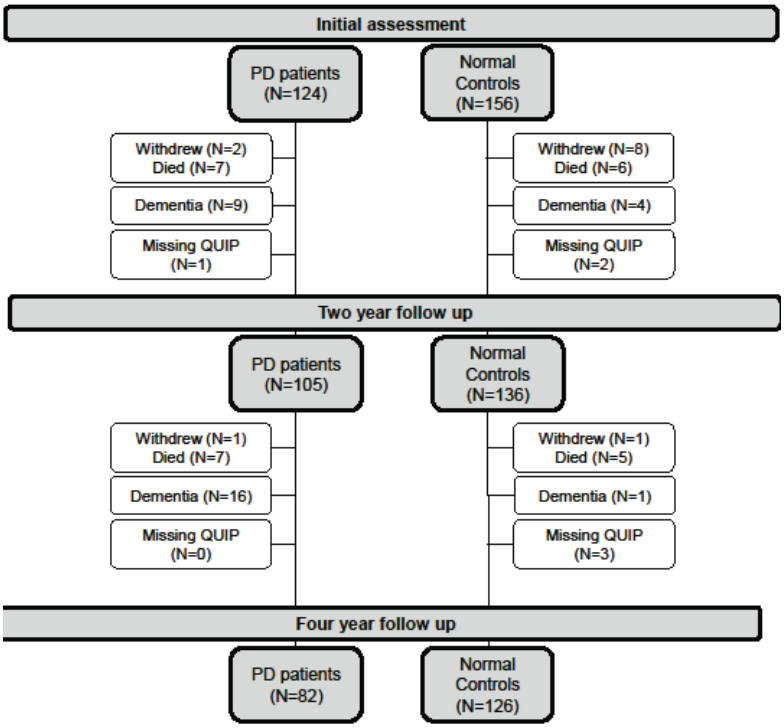

Table E-2. Evolution of ICB symptoms in PD patients over 2 and 4 years of follow-up

	4-year follow up (N=82)				2-year follow up (N=23)		
Characteristics	**No. (%)**	**Year 5 visit**	**Year 7 visit**	**Year 9 visit**	**No (%)**	**Year 5 visit**	**Year 7 visit**
Never ICBs	39 (47.6)	0	0	0	13 (56.5)	0	0
Non-persistent ICBs	7 (8.5)	x	x	0	2 (8.7)	x	0
	3 (3.7)	x	0	x			
	11 (13.4)	x	0	0			
	7 (8.5)	0	x	0			
Persistent ICBs	4 (4.9)	0	x	x	4 (17.4)	x	x
	6 (7.3)	x	x	x			
Uncategorized ICBs	5 (6.1)	0	0	x	4 (17.4)	0	x

E-3. Results from mixed linear regression models for 4 cognitive domains.

In mixed linear regression models, change in MMSE scores was associated with male gender (B=-1.13, 95 % CI -1.81 – -0.43; P=0.002), higher age (B=-0.09, 95 % CI -0.13 – -0.06; P<0.001) and DA use (1.51, 95 % CI 0.9 – 2.1, P<0.001), but not ICB status. Change in POMP scores for the executive domain was associated with male gender (B=-9.71, 95 % CI -12.72 – -6.70; P<0.001), higher age (B=-0.85, 95 % CI -1.02 – -0.66; P<0.001), follow-up time (B=-2.04, 95 % CI -3.65 – -0.43, P=0.013) and DA use (B=6.21, 95 % CI 3.2 – 9.3, P<0.001), but not ICB status. Change in POMP scores for the attention domain was associated with male gender (B=-12.5, 95 % CI -15.48 – -9.61; P<0.001), higher age (B=-0.65, 95 % CI -0.82 – -0.48; P<0.001) and DA use (5.94, 95 % CI 3.0 – 8.9, P<0.001), but not ICB status. Change in POMP scores for the visuospatial domain was associated with high age (B=-0.54, 95 % CI -0.75 – -0.34; P<0.001), but not ICB status. Lastly, change in POMP scores for the verbal memory domain was associated with male gender (B=-9.71, 95 % CI -12.72 – -6.70; P<0.001), high age (B=-1.10, 95 % CI -1.35 – -0.84; P<0.001), follow-up time (B=-2.56, 95 % CI -5.09 – -0.04, P=0.046), PD duration (B=2.18, 95 % CI 0.87 – 3.49, P=0.001) and DA use (B=8.40, 95 % CI 3.8 – 13.0, P<0.001), but not ICB status.