The effect of dopaminergic medication on gambling disorder and impulse control: Epidemiological, clinical, and animal studies

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About the author

Mirjam Wolfschlag came to Lund University for her MSc in molecular biology in 2018. She has been a doctoral student since 2021, working with the groups Clinical Addiction Research, Restorative Parkinson Unit, and Basal Ganglia Pathophysiology with an interdisciplinary and translational approach. Born close to Munich, she obtained her BSc in nutrition science from the Technical University of Munich and worked in Iceland for some years. Her strongest professional interests are psychopharmacology and editing scientific articles. Mirjam lives in Lund with her family.

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Mirjam Wolfschlag

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DOCTORAL DISSERTATION

Doctoral dissertation for the degree of Doctor of Philosophy (PhD) at the Faculty of Medicine at Lund University,

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ABSTRACT

Background: Dopaminergic medication is classically used in neurological disorders like Parkinson's disease (PD) and restless legs syndrome (RLS), but also in psychotic disorders. As a common side effect of dopaminergic medication, patients can develop impulsive-compulsive disorders (ICDs) such as gambling disorder (GD) or compulsive sexuality. Many aspects of ICDs during dopaminergic therapy remain to be characterised, including least risky treatment strategies and vulnerable patient groups.

Methods: As a translational approach, this thesis was based on a broad variety of methods. Cross-sectional risk factors and longitudinal predictors for ICDs during dopaminergic therapy were analysed in two nationwide register studies. ICD recognition and management in clinical PD care were examined through patient questionnaires and medical records screening. In addition, the effect of different dopaminergic treatments on ICD-like behaviour was assessed in a large rat experiment including an immunohistochemical mapping of striatal neuroactivity.

Results: Findings throughout the different studies confirmed D2/3 agonists, especially ropinirole, as disadvantageous for developing ICDs, though even MAO-B inhibitor treatment was a predictor for GD. ICD-like behaviour under dopaminergic treatment in rats was independent of the PD phenotype, and the majority of ICD patients were being treated for RLS, not PD. In clinical PD care, only half of the patients reported their ICD, and involvement of psychiatric care was limited to a few, severe cases. Ex vivo tissue analysis showed reduced and shifted neuroactivity in the striatum under ropinirole treatment.

Conclusions: Our findings suggest that PD therapy for ICD risk patients should not include dopamine agonists or MAO-B inhibitors, but that levodopa, even added to other drugs, seems safe. The attention to ICDs in RLS and other non-PD patients with dopaminergic treatment needs to be increased substantially in clinical care and research. Actively screening for ICDs and improved collaboration with psychiatric care could improve clinical PD care.

Key words:
Impulse control disorder, impulsive-compulsive behaviour, gambling disorder, Parkinson's disease, restless legs syndrome, dopaminergic treatment, dopamine agonist, aripiprazole

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To Dr. rer. nat. Alexandra Kölbl (1980-2024)
and Karola Conrady (1929-2024),

Preface

My academic path has led me from nutrition science to molecular biology and to psychiatry and addiction medicine so far. Through the years, studying and researching has been a process of professional and personal development in parallel for me when I look at it now.

On the one hand, I deeply enjoy learning new things and adding new layers to my perspective. The more interdisciplinary, the better. I love creating knowledge for idealistic purposes and have always been impressed with people who did so before me. Especially the women who found their place in history, such as Hannah Arendt or Lou Salomé. It would be a dream to continue researching and writing in a way that lets me contribute to science and society with only a tiny fraction of what they did.

And then mental health has always been a personal topic as well. Psychiatric disorders run in my family and I'm the lucky one living in the 21st century in Sweden rather than Germany in the 1940s. Or the 1990s for that matter. Lund University chose to include my, until then rarely mentioned, second name in my email address and unknowingly gave a place to my grandfather's mum Anna Katharina in my work. She's a good reminder on the difficult research days why it's worth it.

I'm tremendously grateful for the last four years of learning, reflecting and starting to leave my first own marks in publishing and teaching. It's a privilege to have an occupation that doesn't have to produce an immediate profit and can focus on long-term goals instead. Within this time, I also met my life companion, got baptised in Lund's Cathedral, got my first own dog, and said goodbye to my horse after more than ten years together. And I found many new friends and lost some.

Both to those of you who will read most parts and those who, after reading this preface, will skim through the main text, start reading again when you reach the acknowledgments, and then go back to admiring the bookshelf…

…I hope you enjoy this thesis and find whatever you were looking for in it.

Abbreviations

CI	95% confidence interval
D2/3	Dopamine receptor 2 and 3
DBS	Deep brain stimulation
DSM-IV/5	Diagnostic and Statistical Manual of Mental Disorders, 4th/5th edn
GD	Gambling disorder
ICB	Impulsive-compulsive behaviour
ICD	Impulsive-compulsive disorder
ICD-10/11	International Classification of Diseases 10th/11th edn
OR	Odds ratio
PD	Parkinson's disease
pS6	ribosomal protein S6
rIGT	rat Iowa gambling task
RLS	restless legs syndrome

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Wolfschlag, M., Håkansson, A. *PloS one* **16**, e0252516, 2021. [1]

II. **Impulse control disorders in Parkinson's disease: a national Swedish registry study on high-risk treatments and vulnerable patient groups.**
Wolfschlag, M., Cedergren Weber, G., Weintraub, D., Odin, P. & Håkansson, A. *J Neurol Neurosurg Psychiatry.*, 2024. [2]

III. **Recognition, management and patient perspectives of impulse-compulsive disorders in Parkinson's disease.**
Wolfschlag, M. & Cedergren Weber, G., Timpka, J., Weintraub, D., Odin, P., Håkansson, A. *Manuscript, accepted by Journal of Parkinson's Disease in Feb'25.*

IV. **Impulsive-compulsive behaviours and striatal neuroactivity in an early parkinsonian rat model under ropinirole and L-DOPA treatment.**
Wolfschlag, M. & Espa, E., Skovgård, K., Halje, P., Cenci, MA. *Manuscript, submitted to npj Parkinson's disease in Dec'24.*

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I. **Drug-Induced Gambling Disorder: Epidemiology, Neurobiology, and Management.**
Wolfschlag, M. & Håkansson, A. *Pharmaceut Med* **37**, 37-52, 2023.[3]

II. **Impact of the COVID-19 Pandemic on the General Mental Health in Sweden: No Observed Changes in the Dispensed Amount of Common Psychotropic Medications in the Region of Scania.**
Wolfschlag, M., Grudet, C. & Håkansson, A. *Frontiers in psychiatry* **12**, 2021. [4]

Abstract

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Graphical abstract

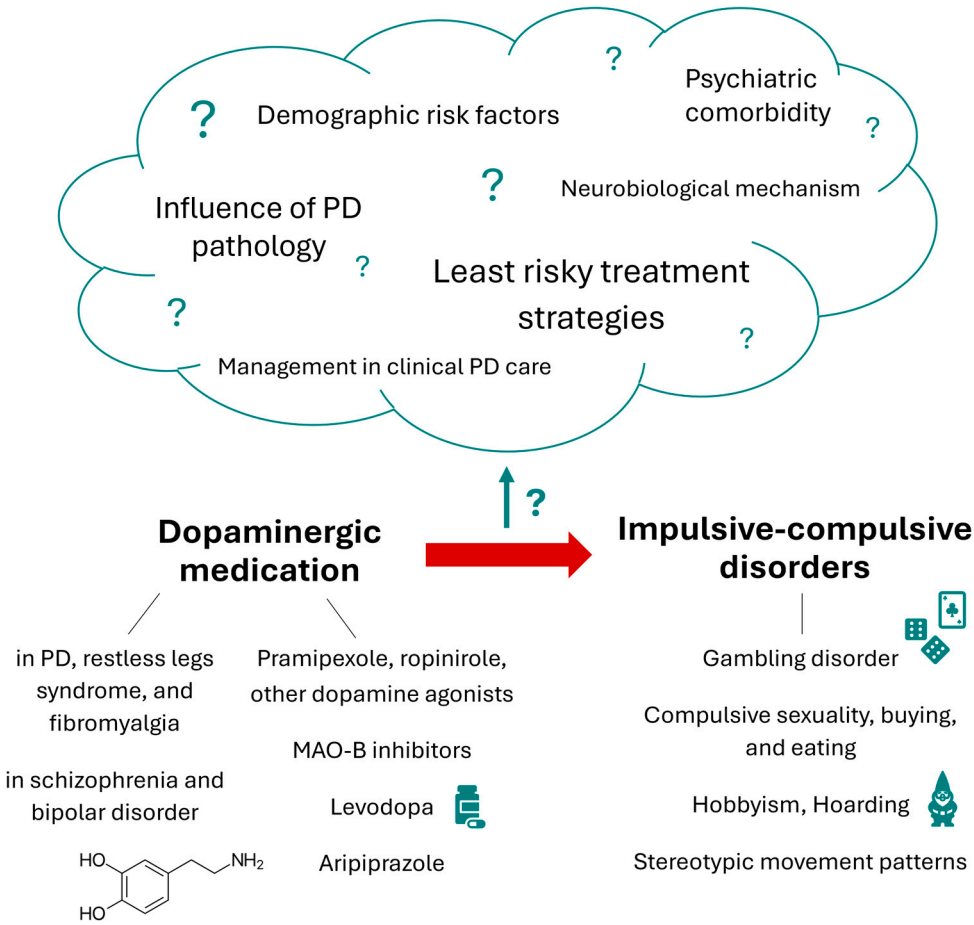

Figure 1. Graphical summary of the thesis. PD: Parkinson's disease. Symbol of dopamine molecule from Wikimedia (CC BY SA).

Popular science summaries

English

The main topic of this thesis is based on a type of medication that can decrease people's impulse control as a side effect. With reduced impulse control, it can be hard for a person to stop pursuing a certain behaviour, such as gambling or sexual activities. Usually, the affected behaviour occupies the person's thoughts excessively, demanding a lot of time, energy, and money. Therefore, impulsive behaviour can lead to severely negative consequences economically, in close relationships, and other life domains.

The types of medication that target the signalling molecule dopamine and can have impulsive behaviour as a side effect are called dopaminergic drugs. They are essential for treating Parkinson's disease, but also used in restless legs syndrome, schizophrenia, and bipolar disorder. Dopamine is involved in facilitating body movement, addiction, impulse control and mood regulation. Therefore, changing dopamine levels with medication to treat one set of symptoms can even influence its other domains. Our goal was to better understand the connection between dopaminergic drugs and a decrease in impulse control. Thus, we applied a broad variety of methods to answer our research questions, spanning from the total Swedish population and single patients, to rats and brain sections under the microscope as studied subjects.

In the first study, we examined all medication that patients with a gambling disorder in Sweden had been taking. We discovered that the treatment with a certain kind of Parkinson's medication, but also with one specific drug used to treat psychotic disorders led to a higher risk of gambling disorder.

The second study was based on all patients in Sweden that had been treated with dopaminergic medication for a neurological disorder like Parkinson's disease. Our aim was to track if they had developed a gambling disorder or another form of decreased impulse control as a consequence of their drug therapy. In addition, we wanted to understand which patients were affected the most. The main group with diagnoses suggesting reduced impulse control were restless legs syndrome patients, whereas only twenty percent were Parkinson's patients. Many were younger than the average group age, with other mental health problems such as depression or

anxiety common amongst them. We also identified specific dopaminergic drugs with an especially high risk for decreasing impulse control as a side effect.

In the third study, we focused on fewer patients in detail instead, analysing the recognition and management of impulsive behaviour in clinical care. Parkinson's patients with impulsive behaviour from the Swedish county Skåne were asked to answer a questionnaire and their health care records were screened. Most patients and health care staff members were aware of reduced impulse control as a possible side effect of Parkinson's medication. On the other hand, problems with impulsivity were rarely a topic of conversation in health care appointments. We also noticed that only a few patients with severe impulsive behaviour had been in contact with psychiatric care for help.

To improve the understanding of how dopaminergic drugs and reduced impulse control are connected biologically, we performed an animal study. Rats were treated with different Parkinson's medications and their behaviour was analysed in multiple tests. Under a specific drug treatment, rats took higher risks in a test that resembles gambling with sugar pellets instead of money. Mainly, rats with a brain state similar to Parkinson's disease were affected as much by the drugs as healthy control animals. Eventually, the rat brain tissue was used to map how brain activity in different areas changed under dopaminergic treatments.

Taken together, we explored how and why some medications can reduce impulse control from many perspectives. We could point out specific drugs that present the highest risk for impulsive behaviour and patient groups that are affected more often than others. Our results emphasise that patients with disorders other than Parkinson's disease experience reduced impulse control at least as often. Restless legs patients, in particular, will need more attention in clinical care and medical research in the future. We hope that this thesis has contributed to the development of safer therapies regarding impulse control problems, and that patients at risk can be recognised and protected in time with the help of our findings.

Svenska

Den här avhandlingen utgår ifrån att människornas impulskontroll kan försämras som en biverkning av vissa läkemedel. Med försämrad impulskontroll kan det vara svårt för en person att komma ur ett visst beteende. Typiska aktiviteter som man kan fastna i på det sättet är spel om pengar eller vissa sexuella beteenden. De som drabbas ägnar oftast överdrivet mycket tid, energi och pengar åt aktiviteten och tar lite hänsyn till konsekvenserna. Därför råkar många ut för problem som en följd, till exempel ekonomiskt eller i nära relationer.

Det finns en viss grupp av läkemedel, kallade dopaminerga läkemedel, som syftar på signalämnet dopamin och kan leda till impulsivt och tvångsmässigt beteende. De är viktiga i behandlingen av Parkinsons sjukdom men används också vid restless legs syndrom, schizofreni och bipolär sjukdom. Dopamin är inblandat i kroppsrörelser, beroende och kontroll av impulser och stämning. Således kan något av de systemen påverkas av läkemedel som används mot symptom i ett annat. Vårt mål var att få en bättre förståelse för sambandet mellan dopaminerga läkemedel och en försämrad impulskontroll. Därför bygger vår forskning på olika frågeställningar och metoder – från en skala så stor som totalbefolkningen i Sverige till en så liten som några mikrometer under mikroskopet.

I den första studien granskade vi de läkemedel som alla patienter med spelberoende i Sverige hade blivit ordinerade. Vi kom fram till att risken för att bli spelberoende var högre när man hade tagit en viss typ av Parkinson-läkemedel och med ett visst preparat vid behandling av psykotiska tillstånd.

I den andra studien undersökte vi alla människor i Sverige som hade fått behandling med dopaminerga läkemedel mot neurologiska symtom. Syftet var att ta reda på om de utvecklade spelberoende eller någon annan form av nedsatt impulskontroll som följd av medicineringen och vilken grupp som drabbades mest. De flesta personer med minskad impulskontroll som biverkning var restless legs patienter och endast tjugo procent var Parkinson-patienter. De var oftast yngre än genomsnittsåldern och led i många fall av andra psykiska besvär som depression och ångest. Vi lyckades identifiera vissa dopaminerga läkemedel med särskilt hög risk för minskad impulskontroll som biverkning.

Den tredje studien utfördes på betydligt färre personer men var avsevärt mer detaljerad än de första två. Vi bad alla Parkinson-patienter i Skåne som upplevde problem med impulskontroll att svara på en utförlig enkät och granskade dessutom deras patientjournaler. Vi fann att de flesta patienter och anställda i Parkinson-vården var medvetna om risken för minskad impulskontroll under behandlingen, men att det ganska sällan togs upp i vårdsamtal. Dessutom hanterades de allra flesta problemen med impulskontroll inom Parkinson-vården utan kontakt med psykiatrisk vård.

För att bättre kunna förstå den biologiska bakgrunden bakom försämrad impulskontroll vid dopaminerg medicinering, använde vi oss i den fjärde studien av djurmodeller. Vi behandlade råttor med samma läkemedel som används i Parkinson behandlingen och undersökte om deras beteende förändrades. Bland annat upptäckte vi att de vid en viss behandling blev mer benägna att ta större risker i ett ”spel om foder” som liknar spel om pengar för människor. I de flesta testen påverkades råttor med ett Parkinson-liknande tillstånd lika mycket av medicineringen som friska kontrolldjur. Till slut analyserades råttornas hjärnvävnad för att utreda hur aktiviteten förändras i olika hjärnområden vid dopaminerg behandling.

Sammanfattningsvis granskade vi hur och varför vissa läkemedel försämrar impulskontrollen ur olika perspektiv. Vi identifierade vilka läkemedel som har högst risk för minskad impulskontroll som biverkning och vilka patienter som påverkas oftare än andra. Våra resultat understryker att andra grupper än Parkinson-patienter drabbas i lika stor grad, främst personer med restless legs syndrom, något som behöver uppmärksammas i vården och inom forskningen. Vi hoppas att den här avhandlingen har kunnat bidra till att terapimöjligheter utan försämrad impulskontroll som biverkning kan tas fram och att man kan upptäcka och skydda riskpatienter i tid.

Deutsch

Im Mittelpunkt dieser Dissertation stehen Medikamente, die als Nebenwirkung die Impulskontrolle eines Patienten beeinträchtigen können. Wenn man wenig Kontrolle über seine Impulse hat, ist es leicht, sich übermäßig einem bestimmten Verhalten zu widmen. Typische Beispiele sind Spielsucht oder sexuelle Aktivitäten. Oft wenden die Betroffenen viel Zeit, Energie und Geld auf, um diesem Verhalten nachzugehen, meistens ohne Rücksicht auf Konsequenzen. In vielen Fällen hat das zum Beispiel finanzielle Probleme oder Schwierigkeiten in der Partnerschaft zur Folge.

Es gibt eine Gruppe Medikamente, genannt Dopaminergika, die den Botenstoff Dopamin beeinflussen und zu impulsivem Verhalten führen können. Diese Medikamente sind unverzichtbar in der Behandlung von Parkinson, werden aber auch gegen das Restless-Legs-Syndrom, bei Schizophrenie und bipolaren Störungen verwendet. Dopamin ist Teil der Regulationssysteme für Körperbewegung und positive Verstärkung und ermöglicht die Kontrolle über Impulse und Stimmungen. Dementsprechend kann eines dieser Systeme betroffen sein, wenn Symptome in einem anderen medikamentös behandelt werden. Unser Ziel war es, den Zusammenhang zwischen Dopaminergika und verringerter Impulskontrolle besser zu verstehen. Deshalb beruht unsere Forschung auf verschiedenen Fragestellungen, denen mit einer Vielfalt an Methoden nachgegangen wurde. Ausgangsmaterial unserer Studien waren Gesundheitsdaten der schwedischen Gesamtbevölkerung, einzelne Patienten, Ratten als Tiermodelle und deren Hirngewebeschnitte für die Analyse unter dem Mikroskop.

In der ersten Studie wurden Medikamente untersucht, die von Menschen mit Spielsucht in Schweden angewendet wurden. Es zeigte sich, dass das Risiko, spielsüchtig zu werden, bei Patienten mit einer bestimmten Gruppe von Parkinsonmedikamenten höher lag. Einen ähnlichen Effekt hatte ein spezielles Medikament, das gegen Psychosen zum Einsatz kommt.

Die zweite Studie basierte auf allen Patienten in Schweden, die Dopaminergika gegen neurologische Symptome verwendeten. Es wurde analysiert, ob diese Patienten im Laufe ihrer Behandlung Spielsucht oder eine andere Art von impulsivem Verhalten entwickelt hatten. Eine Kernfrage war, welche Patienten am häufigsten betroffen waren. Die größte Gruppe mit beeinträchtigter Impulskontrolle machten Restless-Legs-Patienten aus, während nur zwanzig Prozent Parkinson-patienten waren. Oft waren betroffene Patienten durchschnittlich jünger und außerdem waren andere psychische Symptome wie Depression oder Angst-störungen weit verbreitet. Des Weiteren stellten sich bestimmte Medikamente als besonders riskant in Hinblick auf eine verringerte Impulskontrolle heraus.

Für die dritte Studie wurden einige wenige Parkinsonpatienten in der schwedischen Region Skåne genauer betrachtet. Patienten, die von Problemen mit impulsivem Verhalten berichtet hatten, wurden gebeten, einen Fragebogen auszufüllen. Zusätzlich wurden aus den dazugehörigen Patientenakten Daten erhoben. Die große Mehrheit der Patienten und des Krankenhaus- oder Praxispersonals war sich einer verringerten Impulskontrolle als möglicher Nebenwirkung der Parkinson-medikamente bewusst. Allerdings waren Symptome von impulsivem Verhalten relativ selten Thema in Gesprächen zwischen Patienten und Personal. Des Weiteren wurde nur in wenigen, schweren Fällen eine psychiatrische Abteilung zu Rate gezogen.

Für ein besseres Verständnis des biologischen Hintergrundes wurden Ratten als Tiermodelle verwendet. Sie erhielten unterschiedliche Parkinsonmedikamente, um mögliche Veränderungen im Verhalten zu analysieren. Unter anderem zeigten Ratten eine Präferenz für höheres Risiko in einem „Spiel um Futter“, wenn sie mit einem bestimmten Präparat behandelt wurden. In den meisten Verhaltenstests reagierten Tiere in einem Parkinson-ähnlichen Zustand ähnlich auf die Medikamente wie gesunde Kontrolltiere. Zum Schluss wurde das Gehirngewebe dafür genutzt, Aktivitätsveränderungen in unterschiedlichen Gehirnarealen in Folge der Behandlung aufzuzeigen.

Im Großen und Ganzen wurde in dieser Dissertation aus vielen Perspektiven betrachtet, warum und in welcher Weise gewisse Medikamente die Impulskontrolle verringern. Wir konnten zeigen, dass manche Präparate mit einem besonders hohen Risiko für diese Art von Nebenwirkungen einhergehen und dass bestimmte Patientengruppen häufiger betroffen sind als andere. Unsere Ergebnisse unterstreichen, dass nicht nur Parkinsonpatienten betroffen sind, sondern vor allem Restless-Legs-Patienten mehr Aufmerksamkeit zuteilwerden muss. Wir hoffen, dass wir zur Entwicklung von sichereren Therapiemöglichkeiten mit geringeren Nebenwirkungen beitragen konnten und dass Risikopatienten in Zukunft leichter identifiziert und geschützt werden können.

Introduction

The field of psychiatry in medical research

Psychiatric disorders play a substantial role in the social and economic disease burden worldwide [5-7]. According to the World Health Organization, they ranked as the 7th (self-harm) and 10th (depressive disorders) leading causes for disability-adjusted life years in Sweden in 2021 [8]. The Public Health Agency of Sweden estimated that one in four men and one in three women was treated with antidepressants in 2022 [9]. Additionally, data from the Swedish Social Insurance Agency show that up to half of all reported cases of illness in Sweden involved a psychiatric diagnosis in 2024 (46.1-50.0%) [10].

Nevertheless, psychiatric topics are vastly underrepresented within medical research. At the medical faculty of Lund University, 20 of 427 research groups belong to psychiatric departments [11]. The Swedish Research Council awarded 241 research grants worth approximately 110 million euros within Medicine and Health in 2024 [12]. Eleven of those grants and about 4.1 million euros in total went to projects involving research questions about mental health.

Especially more research targeting the neurobiology of psychiatric disorders is needed [13-15]. Historically, the field of psychiatry, in contrast to neurology, is based on disorders involving the brain without any visible pathology at the time [16]. Today, the mechanisms of action for well-established psychotropic drugs, including dopaminergic agents, are still not fully explained [17-19]. Classically, only one group of patients responds well to the most commonly used treatment, leaving many others in need of new strategies, for instance in treatment-resistant depression [20]. In comparison, extensive resources have been dedicated to identify the full neuropathology behind brain disorders presenting mainly with neurological and cognitive symptoms during the last decades. As a result, the neurobiology of disorders like Alzheimer's or Parkinson's disease (PD) is well understood, providing additional treatment targets [21,22]. Exploring psychiatric symptoms that occur as adverse effects of pharmacotherapy is one way to increase the mechanistic understanding of mental disorders.

Psychiatry and neurology – Two disciplines working on the same organ

Geographically speaking, the distinction between neurological clinics located in the city centres versus psychiatric asylums and sanatoriums found far out in the countryside was well established in North America already in the late 19th century [23]. Even in Lund, as in many other European cities, the separation between psychiatry and somatic disciplines is still clearly visible just by comparison on a map. Both historically and in active use today, the general university hospital and the psychiatric ward in Lund are mainly located in different areas (Illustration 4).

Illustration 3. Photographs of four hospitals in Lund. Upper left: Östra sjukhuset Sankt Lars, old psychiatric hospital (1879-2013). Upper right: Gamla kirurgen, old university hospital (1868-1970s). Lower left: Psychiatric hospital at Baravägen (since 2013). Lower right: Blocket, university hospital (since 1968). Time intervals according to Sydsvenska Medicinhistoriska Sällskapet [24].

Comprehensively reviewed by Price et al. [16] and Martin et al. [23], the two medical disciplines psychiatry and neurology stem historically from the same origin. After the brain had been identified as the organ driving behaviour during the 19th century,

research was conducted mainly by neuropsychiatrists educated in both fields. When the anatomical pathology of disorders like PD and Alzheimer's disease was discovered in the early 20th century, they were classified as organic, neurological disorders and studied mainly with biological methods. In contrast, the biggest influence on psychiatry at the time was Freud's psychoanalysis, paving the way for the perception of psychiatric disorders as functional, experience-based disorders for many years to come. Even if more recent fields of research like psychopharmacology and neuroimaging have created a new bridge between the two disciplines, the general separation remains present in clinical care and research.

Both review articles, written in the early 2000s, conclude that the distance between psychiatry and neurology and their respective methods can have negative consequences for patients and research advances [16,23]. Indeed, it is well established by now that most, per definition, neurological disorders have a large psychiatric component [25,26], and that many psychiatric disorders have as much of a neuropathology as "classical" neurological disorders [13-15]. An especially important aspect is the overlap in pharmacotherapy, given that both fields are based on the same neurotransmitters and thus rely on similar drug classes. Psychiatric drug treatment can have neurological side effects, and vice versa, making a good collaboration essential to avoid severe, and perhaps unexpected, adverse effects.

Impulsive-compulsive disorders

Impulsive-compulsive disorders (ICDs), also called impulse control disorders and related behaviours, are a spectrum of behaviours with impulsive and compulsive traits [27]. Impulsivity is characterised by taking rapid, premature actions based on sudden urges that seem rewarding in the moment, while disregarding long-term consequences [28]. Many psychiatric disorders involve a lack of impulse control, manifested for instance in addiction, mania, or symptoms typical for attention deficit hyperactivity disorder (ADHD). Compulsive behaviour, on the other hand, is not reward-motivated and generally described as purposeless, repetitive, and often involuntary [28,29]. A common form of excessive compulsivity are obsessive-compulsive disorders. Since executive control and the understanding for beneficial outcomes are compromised both in impulsivity and compulsivity, both types of behaviours can be disruptive and lead to severely negative consequences for patients and their surrounding [30].

ICDs can be a consequence of the dopaminergic treatment used in PD, restless legs syndrome (RLS), and psychotic disorders [31-33]. In this context, the main four iatrogenic ICDs with a major component of impulsivity have been shown to be gambling disorder (GD), compulsive sexuality, buying, and eating. In all four cases, an excessive fixation on external rewards seems to drive maladaptive behaviour [31,34].

Additionally, compulsive habits like punding, a simple, repetitive movement pattern, can arise under dopaminergic therapy [35,36]. Other compulsive behaviours triggered by dopaminergic drugs include hoarding and hobbyism, the dedication of an excessive amount of time and energy to a specific leisure activity, possibly reaching obsessive levels [37]. Most of the ICDs mentioned have been represented poorly in diagnostic manuals for psychiatric disorders in the past, with only pathological gambling and binge-eating defined as specific diagnoses [38,39]. This has been somewhat improved in the latest version of the International Classification of Diseases (ICD-11), adding compulsive sexual behavioural disorder and hoarding as single diagnoses [40]. Nevertheless, specific ICD diagnoses are rarely applied in clinical practice, especially when the behaviour has developed as a side effect of dopaminergic medication [41].

Gambling disorder – An impulse control disorder or a behavioural addiction?

The diagnostically most well-defined ICD today is GD with an own diagnosis code already in the ICD-10 and the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [38,42]. Given that the Swedish National Patient Registries are based on the ICD-10, epidemiological research in Sweden can be performed specifically for GD patients in contrast to other ICDs. Interestingly, GD has been redefined from an ICD to the first behavioural addiction in the latest versions of the diagnostic manuals, ICD-11 and DSM-5 [40,43]. The decision was based on clinical, psychological, but also neurobiological similarities between GD and substance use disorders [44,45]. Seen from the perspective of iatrogenic ICDs, however, there is abundant evidence for GD to be one of the four major ICDs affected by dopaminergic treatment, while substance use disorders seem generally not affected by this type of pharmacotherapy [31].

The main criteria for GD include a persistent, maladaptive form of gambling for money or similar values, leading to distress and negative consequences for the patient [46]. In many cases, patients almost completely lose control over their gambling behaviour and need to increase the placed value progressively. Often, large debt is accumulated fast, and both patients and their families are impacted severely by a GD [47-51].

As in other ICDs and addictions, dopamine is involved in a pathological form of reward-related learning in GD [3,52,53]. Patients become excessively preoccupied with wins as rewards, while failing to consider the consequences of their behaviour. An interesting aspect is the uncertainty in the gambling process as an additional factor making this type of behaviour addictive [54,55]. Constant, dopamine-coded reward prediction errors possibly accelerate the manifestation of GD.

Behavioural shift towards impulsivity under dopaminergic treatment

Interestingly, behavioural traits of impulsivity and compulsivity, for example manifested as GD, can be increased pharmacologically by dopaminergic medication. If one pictures a spectrum between a hypodopaminergic and a hyperdopaminergic state, associated behaviours can be apathy and impulsivity at the extremes (Figure 2) [56,57]. Apathy has been described as low motivation to seek pleasure, also called insensitivity to reward, or as hypersensitivity to cost or effort [58,59]. In contrast, impulsivity can be characterised as the opposite state, hypersensitivity to reward or insensitivity to cost or effort.

Keeping this spectrum in mind, dopaminergic medication can externally induce a behavioural shift to the right, away from apathy towards higher impulsivity, possibly by increasing reward sensitivity [58,60]. On the one hand, this can lead to negative consequences like ICDs as an unwanted side effect of dopaminergic treatment in PD, RLS, or psychosis [31,33,61]. On the other hand, dopamine receptor 2 or 3 (D2/3) agonists like pramipexole or ropinirole have shown promising results as antidepressants, especially in patients with anhedonia and treatment-resistant depression [62-66]. Notably, even an increase in creativity under dopaminergic medication can be observed in some patients [67,68].

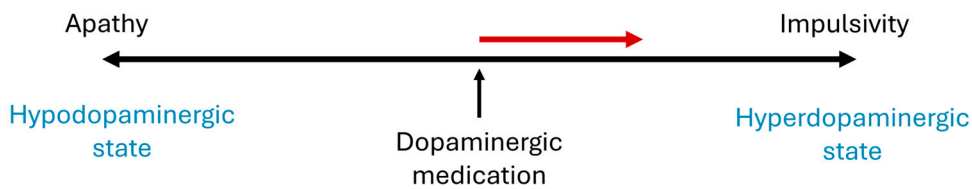

Figure 2. Schematic spectrum of apathy versus impulsivity described by the dopaminergic state [56,57].

Dopaminergic transmission and brain areas involved in iatrogenic impulse-compulsive behaviour

Explaining an increase in impulsivity by dopaminergic medication on a neurobiological level has only partly been achieved. In a brief summary, the main alterations seem to occur in the mesocorticolimbic dopamine pathway [69]. The nucleus accumbens in the ventral striatum plays a key role in reward seeking and sensitivity [70], while the dorsal striatum is involved in action selection and habit forming [31,71]. The prefrontal cortex, on the other hand, is known to be responsible for inhibiting behaviour, thus contributing to the control of impulses [72,73]. A

schematic overview over brain regions involved in dopaminergic signalling is shown in Figure 3.

Several neuroimaging studies have explored the brain regions mediating the effect of dopaminergic drugs on ICDs in PD patients [74-76]. Alterations were found mainly in different striatal and cortical areas, but the results were controversial and the lack of replicability has been criticised [77]. Many studies have described the ventral striatum to play a key role in ICDs in PD, not agreeing if the dopaminergic activity is reduced or elevated [78-82]. Additionally, changes in dopamine signalling have been detected in other striatal regions [83-86]. Experiments in rodent models under dopaminergic treatment have confirmed the involvement of both the ventral [87-89] and the dorsal striatum [90-92] in developing impulsive-compulsive behaviour (ICB). Taken together, no consensus has been reached about the areas and connectivity changes involved in ICDs under dopaminergic medication, and the role of striatal dopamine signalling could not be sufficiently described to date.

Clinical evidence has pointed out drugs acting on the inhibitory dopamine receptors D2/3 as the drug type most strongly associated to ICDs, including the two dopamine agonists pramipexole and ropinirole, and the partial dopamine agonist aripiprazole [33,93]. Seeman argues that D3 receptors are a key mediator between ICDs and dopaminergic medication, supported by a positive linear correlation between D3 selectivity and the proportion of patients developing an ICD on the respective drug [94]. In addition, a lower availability of postsynaptic D2/3 receptors [84,95,96] and presynaptic dopamine transporters in the striatum [83,85,97] has been associated with an increased ICD risk under dopaminergic medication. Taken together, a large gap in research remains to a full explanation of functional connectivity, synaptic changes, and intracellular pathways in iatrogenic ICDs.

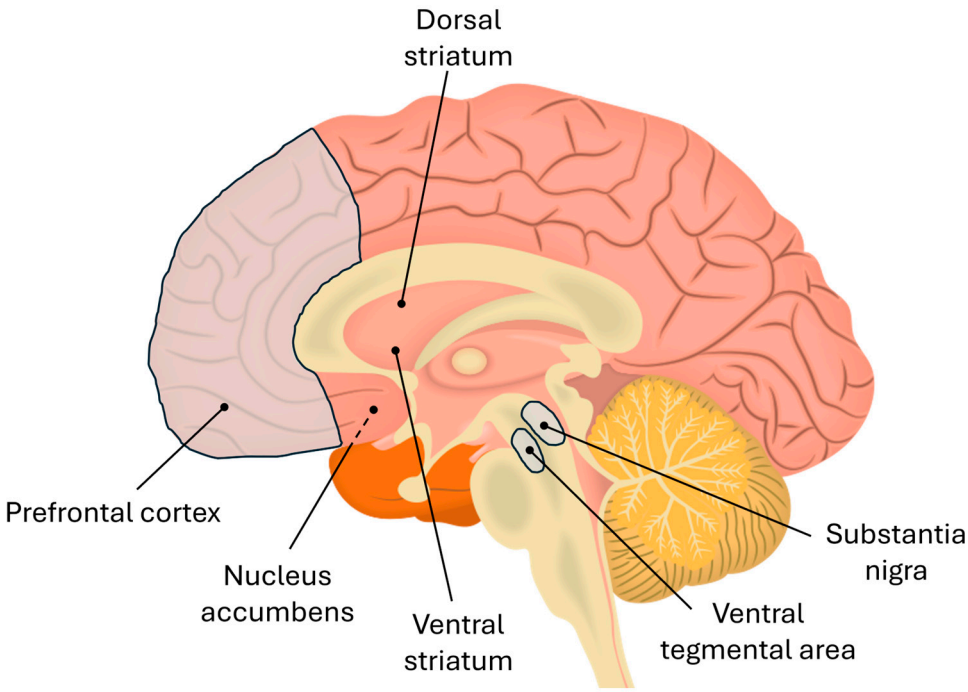

Figure 3. Schematic brain anatomy in the sagittal plane. Adapted after erico on Wikimedia Commons (CC BY, https://doi.org/10.7875/togopic.2021.023). Labelled according to the Allen Brain Reference Atlas – Adult human [98].

Impulsive-compulsive disorders in Parkinson's patients

ICDs as side effects of the dopaminergic therapy in PD have been researched quite extensively over the last years [31,93,99]. PD is a neurodegenerative movement disorder where the progressive loss of dopaminergic neurons in substantia nigra and striatum leads to decreased motor function and non-motor symptoms [100]. To compensate for the dopamine deficiency, most PD patients undergo dopamine replacement therapy [101]. Classically, this therapy consists of the dopamine precursor levodopa and dopamine receptor agonists, but also other drug classes like inhibitors of the dopamine-degrading enzyme MAO-B. Due to the progressive nature of PD, doses are typically increased during the course of treatment. As an alternative, advanced therapy options include deep brain stimulation (DBS) and subcutaneous or intestinal infusion pumps delivering dopaminergic treatment at a consistent dose.

Approximately 10-25% of all PD patients are affected by ICDs during their dopaminergic therapy and many large-scale studies have explored ICDs as a side

effect of PD therapy worldwide [102-109]. There is a general consensus that dopamine agonists, especially pramipexole and ropinirole acting on D2/3, are associated with the highest risk of developing ICDs [93,104,110-112]. Interestingly, only a few of these studies have focused on other dopaminergic drug classes or the ICD risk during a combinational therapy of levodopa and a dopamine agonist, a common clinical practice [101]. Moreover, multiple studies have targeted patient-related risk factors for ICDs during PD treatment. Male sex, younger age, and other pre-existing psychiatric disorders have been shown to be disadvantageous for developing ICDs in PD [113-116]. Nevertheless, little is known about how specific psychiatric comorbidity profiles are linked to ICDs under dopaminergic medication.

To our knowledge, no comprehensive analysis of high-risk treatments and other risk factors had been performed in a Swedish population before this thesis. Additionally, there is only limited knowledge in general about how ICDs are recognised and managed in clinical PD care in relation to evidence-based recommendations [117].

Impulsive-compulsive disorders in other populations than Parkinson's patients

In contrast to the abundant literature on ICDs in PD patients, only few studies have been conducted on ICDs under dopaminergic treatment in other patient populations. One common neurological disorder treated with PD medication is RLS, characterised by a sensation of discomfort and the urge to move the lower extremities when resting [118,119]. The neuropathology of RLS has only been partly understood and involves a dysregulation of dopamine and iron levels in the central nervous system. RLS patients are often treated symptomatically with a dopamine agonist in monotherapy or with levodopa. Typically, prescribed doses are much lower than in PD and only in some cases increased over time. Notably, some studies suggest a dose-response relationship between dopaminergic treatment and ICDs in PD patients [103,108,110,120,121]. Nevertheless, there are contradictory reports and even low-dose dopamine agonist treatment seems sufficient for ICDs as side effects [104,110,122,123]. The few existing studies on ICDs in RLS patients have mainly focused on pointing out the relationship to dopaminergic medication in general and indicate prevalences similar to PD patients [32,36,61,124,125].

Another dopaminergic drug that has received attention for potentially inducing ICDs as a side effect is the atypical antipsychotic aripiprazole [126]. Its mechanism of action as a dopamine modulator is partial agonism with high selectivity for D2/3 receptors [127]. Aripiprazole is mainly used for psychotic symptoms in schizophrenia and bipolar disorder, two diseases with distinct dopaminergic neuropathologies [128,129]. Some case studies have been published, but only few systematic studies have explored the relation between aripiprazole and ICDs [33,130]. In addition to PD, RLS

and psychiatric populations, dopaminergic medication has been linked to ICDs in patients with fibromyalgia [131] and pituitary adenomas/hyperprolactinemia [132-134].

Taken together, patients seem to develop ICDs under dopaminergic medication regardless of the underlying indication for the treatment. The level of evidence for findings in non-PD populations is low due to the lack of clinical studies, and the main large-scale findings in this field have been investigating pharmacovigilance reports [135-138]. One additional question remaining to be answered in this context is the possible impact of the neuropathology in PD on developing ICDs compared with the pathology of the other disease mentioned.

Animal models of impulse-compulsive disorders

To gain better pharmacological and neurobiological insight into the relation between ICDs and dopaminergic treatment, animal experiments are a crucial approach [28,139,140]. Many different types of tests have been developed to explore ICB in rodents, resembling ICDs in patients. For example, the Iowa Gambling Task for patients has been transferred successfully to rodent models [141]. The human test assesses decision making in a gambling context using four different card decks [142]. Each of them contains either cards for an advantageous, long-term winning strategy with smaller but many wins, or a more disadvantageous selection of cards with large but rare wins. Healthy patients are expected to identify and choose the two advantageous decks after a learning period. When applied to rodents, money rewards are replaced by sugar pellets, but the general test strategy mimics the human test [141]. Two main versions of the Iowa Gambling Task for rats have been established: The manual, maze-based rat Iowa Gambling Task (rIGT) [143], and the rat gambling task performed in operant boxes [144-146].

Other aspects of ICB in rodents under dopaminergic treatment can be explored with a variety of tests like the five-choice serial-reaction time task [147], a variable delay-to-signal task [148,149], a food hoarding task [150], or the post-training signal attenuation task [150,151]. In the compulsive checking test, the property of the D2/3 agonist quinpirole to induce compulsivity has been utilised to create an animal model for obsessive-compulsive disorders [152,153].

With the goal of mimicking ICDs in PD patients, tests for ICB under dopaminergic medication have been performed in rats with a PD phenotype [139]. The loss of dopaminergic neurons in PD can be imitated by inducing denervation in affected brain regions, often the striatum or the substantia nigra [154]. The extent and location of the denervation can vary and be limited to one hemisphere or be applied bilaterally. Typical methods used to induce dopaminergic neuron loss include lesioning with the neurotoxin 6-hydroxydopamine and creating aggregates with α-Synuclein preformed fibrils.

Rationale

As outlined in the Introduction, this thesis was motivated by multiple issues and gaps in knowledge. From a broad perspective, a larger fraction of all medical research should focus on psychiatric rather than purely somatic topics. The distribution of resources and attention reflects the public health impact of mental disorders only poorly. The knowledge about biological mechanisms behind psychiatric disorders lags especially far behind what we know about somatic diseases today.

In addition, the collaboration between the two medical fields covering brain disorders, psychiatry and neurology, can be improved substantially. Many disorders like PD or Huntington's disease present with both somatic and psychiatric symptoms, and pharmacotherapies for neurological and psychiatric purposes often target the same transmitter systems. Thus, many diseases can never be optimally addressed by one specialty only and an interdisciplinary approach is in the patients' best interest.

More specifically, the situation of patients developing ICDs under dopaminergic medication is suboptimal to date. Preventive measures like screening for risk factors and previous ICDs are not implemented systematically enough. Moreover, different treatment options have not been characterised sufficiently regarding their ICD risk. Most research has been performed in PD patients and there is little knowledge about ICDs under dopaminergic medication in other populations.

Lastly, no clear understanding of the dopamine transmission in impulse control has been reached. The role of different striatal subregions and D2/3 receptor activation remains to be fully described. No conclusive explanation has been presented for why dopaminergic treatment affects ICDs and behavioural addictions, but not addictions to psychoactive substances like alcohol.

Aims and objectives

Specific objectives

1. Describe GD and other ICDs under dopaminergic medication in the total population of Sweden (Study I & II)

2. Identify vulnerable patient groups, typical demographic features and comorbidities of GD and other ICDs under dopaminergic medication (Study I-IV)

3. Characterise favourable in contrast to high-risk treatment strategies regarding the development of ICDs (Study I-IV)

4. Investigate the impact of the PD pathology on the development of ICDs under dopaminergic treatment (Study II and IV)

5. Compare different ICDs developed under dopaminergic treatment and characterise the patient-staff communication and ICD management in clinical PD care (Study III)

6. Establish an animal model with feasible behavioural tests to explore ICDs in PD and other patient populations preclinically (Study IV)

7. Investigate the effect of chronic D2/3 agonist treatment and a PD phenotype on striatal neuroactivity in an animal model (Study IV)

Long-term goals

- Raise awareness for psychiatric disorders in a clinical context and in medical research, with special emphasis on the perception of psychiatric disorders as biological conditions
- Increase the cooperation between the fields of neurology and psychiatry to improve the treatment of diseases with both somatic and psychiatric symptoms and enable optimal pharmacotherapy
- Improve the situation for patients who develop ICDs under dopaminergic treatment, including better prophylaxis, monitoring, and ICD management
- Contribute to the general understanding of dopaminergic transmission in ICB, possibly enabling the development of drugs treating motor symptoms with fewer behavioural side effects, but also treating impaired impulse control itself in the future

Materials and methods

National register studies

The epidemiological research in this thesis was based on the Swedish National Patient Registries of inpatient and specialised outpatient care (Patientregistren för slutenvård och specialiserad öppenvård) and the Swedish Prescribed Drug Register (Läkemedelsregistret), both provided by the Swedish National Board of Health and Welfare (Socialstyrelsen). The age- and sex-matched controls from the total population in Study I were supplied by Statistics Sweden (Statistikmyndigheten SCB).

In the Nordic countries, research based on national registers is a well-established practice with many advantages [155,156]. The registers provide detailed, highly reliable healthcare data for the total population and make it possible to study rare outcomes in a relatively large number of patients. Information on diagnoses and dispensed drugs is collected longitudinally, allowing for a broad variety of study designs on pre-collected data. Nevertheless, there are certain caveats when working with register material. Patient registries list formal diagnoses given in specialised care only. Often, this leads to researching the "tip of the iceberg", while many cases go undetected because they do not contact specialised healthcare for their symptoms or do not receive a diagnosis code. This might introduce a bias towards including the most severe cases in a population and primarily patients with good access to healthcare. Additionally, diagnoses have to be treated as binary variables and there is limited information on individual symptoms or the course of a disease.

Diagnosis and procedure codes in Study I and II derived from the Swedish version of the ICD-10 diagnostic manual [38] and drug prescriptions were classified according to ATC codes [157]. An overview over the specific codes extracted from the register material is presented in Table 1.

Table 1. ICD-10, ATC, and procedure codes extracted from the register material.

Psychiatric diagnoses	**Register code**
Gambling disorder	F63.0
Other impulse control disorder	F63.1-9
Mental and behavioural disorders due to psychoactive substance use	F10-19
Schizophrenia, schizotypal and delusional disorders	F20-29
Mood disorders	F30-39
Neurotic, stress-related and somatoform disorders	F40-48
Neurological diagnoses	
Parkinson's disease	G20
Restless legs syndrome	G25.8
Other extrapyramidal and movement disorders	G20-26
Advanced therapy procedures	
Deep brain stimulation	AAG20
Gastrostomy	GA014
Antiparkinsonian dopaminergic drug prescriptions	
Pramipexole	N04BC05
Ropinirole	N04BC04
Other dopamine agonists	N04BC
Levodopa	N04BA
Monoamine oxidase B inhibitors	N04BD
Others	N04BB, N04BX
Psychotropic drug prescriptions	
Aripiprazole	N05AX12
Antipsychotics	N05A
Anxiolytics	N05B, R06AD01/2
Antidepressants	N06A
Psychostimulants	N06B
Drugs used in addictive disorders	N07B

Despite analysing the same type of data material, Study I and II comprised two different study populations and designs. Study I included all GD patients in Sweden matched with two controls each and assessed cross-sectional frequencies and risks. Thus, patients were selected for the outcome (GD) regardless of any underlying primary diagnosis or treatment. In contrast, patients in Study II were included if they had any antiparkinsonian dopaminergic drug prescription, and their course of treatment and diagnoses were followed longitudinally. Consequently, the selection was based on the exposure (antiparkinsonian dopaminergic drug prescription) and different outcomes (GD and other ICDs) could be studied in relation to predicting factors. A detailed comparison between Study I and II can be found in Table 2.

Table 2. Comparative overview over Study I and II.

	Study I	**Study II**
Study design	Cross-sectional case-control study	Retrospective cohort study
Inclusion criteria	Patients diagnosed with GD in Sweden between 2005 and 2019 plus two age- and sex-matched controls each from the total Swedish population	Patients with any antiparkinsonian dopaminergic prescription between 2005 and 2022 in Sweden
Total n	11 067	251 965
Subgroup selection	(A) Patients with any antiparkinsonian dopaminergic prescription (B) Patients diagnosed with schizophrenia, schizotypal and delusional disorders	(A) Patients with a PD diagnosis (B) Patients with an RLS diagnosis
n in subgroups	(A) 180 (B) 389	(A) 55 235 (B) 16 709
Outcome	GD diagnosis at any time during the study period	GD or another ICD diagnosis after the first antiparkinsonian dopaminergic prescription
Exposure	(A) Pramipexole or ropinirole treatment (B) Aripiprazole treatment	Treatment with different antiparkinsonian dopaminergic drugs and specific dopamine agonists
Covariates	Age, sex, psychotropic drug prescription	Age, sex, psychiatric comorbidity
Statistical tests	Logistic regression, chi square and Fisher's exact test, one-factor ANOVA	Logistic regression, chi square and Fisher's exact test, one-factor ANOVA, two-tailed binomial test

Patient questionnaire and medical records screening

In Study III, our goal was to gain detailed insight into how ICDs are handled in clinical PD care practice and how PD patients experience ICDs. We therefore developed a new patient questionnaire for ICDs in PD. The first part was based on the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease–Rating Scale (QUIP-RS) [158] and patients were asked to retrospectively report their ICB before their PD therapy was initiated, within the six months after therapy start, and at their current state when the data was collected. An example page of the first questionnaire section translated from Swedish is shown in Figure 4.

The second part of the questionnaire focused on how ICDs were communicated between patients and clinical care staff and how ICDs were handled once recognised. Additional questions covered aspects like comorbidities, family history of addiction or ICDs, and the impact of ICDs on different domains in patients' lives. An extract of the second questionnaire section translated from Swedish can be found in Figure 5.

To conduct the study, we selected all PD patients in the Swedish region Skåne, that had self-reported ICD symptoms in the Non-Motor Symptoms Questionnaire (NMSQ) [159,160] in the Swedish quality register for PD (ParkReg) [161]. The ICD questionnaire was sent to patients' home addresses and out of 172 patients originally included, 43 answered questionnaires could be analysed. To complement patients' self-reports in the questionnaires, we also performed a screening of their medical records regarding the same topics of interest. In 46 of 172 cases, ICDs were mentioned in the medical records, of which 11 were included in the questionnaire analysis.

In general, most findings from the ICD questionnaire and the medical records screening were reported as absolute and relative frequencies. Based on the ICB ratings in the first questionnaire section, individual values of ICD severity were calculated. The increase in overall ICD severity was compared between groups using a Mann-Whitney U test. The course of different ICDs was compared between timepoints with a mixed-effect model.

B. Your behaviour AFTER your treatment for Parkinson's had started

In this section, please describe how you experienced your behaviour WITHIN THE FIRST SIX MONTHS after you had gotten your Parkinson's diagnosis.

1. I spent an excessive amount of time thinking about…

	Never	Rarely	Sometimes	Often	Very often
Gambling					
Sex					
Buying					
Eating					
A specific task or hobby					
Repeating a simple movement pattern					

2. I had a hard time controlling how much time I spent…

	Never	Rarely	Sometimes	Often	Very often
Gambling					
Sex					
Buying					
Eating					
A specific task or hobby					
Repeating a simple movement pattern					

3. Something that I felt stressed or guilty about was…

	Never	Rarely	Sometimes	Often	Very often
Gambling					
Sex					
Buying					
Eating					
A specific task or hobby					
Repeating a simple movement pattern					

4. Something that caused problems for me or others, e.g. economically or in close relationships, was…

	Never	Rarely	Sometimes	Often	Very often
Gambling					
Sex					
Buying					
Eating					
A specific task or hobby					
Repeating a simple movement pattern					

Figure 4. Example page B from the ICD patient questionnaire (translated from Swedish original).

F. Consequences of your impulsive or compulsive behaviour

1. I sought psychiatric care to get help with my impulsive or compulsive behaviour.
   - ☐ Yes
   - ☐ No

[...]

3. My impulsive or compulsive behaviour has affected the following aspects in my life negatively:

	Not at all	A bit	Quite much	Very much	Not applicable
My financial situation					
My job					
My close relationships					
My family life					
My mental health in general					
My physical health					

G. Information about impulsive or compulsive behaviour

1. a) Before you got our letter, did you know that impulsive or compulsive behaviour can be related to Parkinson's medication?
   - ☐ Yes
   - ☐ No

   If Yes:

   b) Where did you get this information?
   - ☐ I was informed by my Parkinson's care staff when I started my therapy
   - ☐ I was informed by my Parkinson's care staff later during the therapy
   - ☐ Through a patient information leaflet of my prescribed drugs
   - ☐ Other: _____

[...]

2. b) Have you told your Parkinson's care staff about your impulsive or compulsive behaviour?
   - ☐ Yes
   - ☐ No

   If Yes:

   c) Why? (Multiple answers possible)
   - ☐ My Parkinson's care staff asked about it
   - ☐ I had noticed myself that my behaviour had changed
   - ☐ A relative or friend had encouraged me to do so
   - ☐ Other: _____

   d) Was your Parkinson's care staff familiar with these types of side effects?
   - ☐ Yes
   - ☐ No
   - ☐ I don't know

Figure 5. Example pages F and G from the ICD patient questionnaire (translated from Swedish original).

Rat behaviour analysis

Study IV was based on an extensive rodent experiment including 70 adult, female Sprague-Dawley rats. They were treated chronically with one of three different types of Parkinson's therapy (levodopa monotherapy, ropinirole monotherapy, or combined therapy of levodopa and ropinirole), or saline as a control. Levodopa was administered at a dose of 24 mg/kg/day and ropinirole at 2.5 mg/kg/day. About half of the rats in all four treatment groups had undergone bilateral lesioning with the toxin 6-hydroxydopamine in the dorsolateral striatum, mimicking the dopaminergic denervation of early PD. The other half had not been subjected to toxin lesions and served as sham controls, resulting in eight experimental groups in total.

Rats were measured in a selection of behavioural tests over six weeks with the aim of describing different aspects of ICB possibly induced by the different dopaminergic drug treatments. An additional goal was to determine whether the PD-like phenotype would influence the treatment effect. Motor behaviour was assessed using well-established designs, namely the stepping test for forelimb akinesia [162] and an open field arena [163]. Furthermore, anxiety-like behaviour was examined in an open field arena [163,164] and the elevated plus maze [165]. The three main behavioural tests evaluating ICB were the rIGT [143], the compulsive checking test [152], and the tracking of active behaviours [166].

As described in the Introduction, the rIGT is a test resembling the Iowa gambling task used to assess decision making in a reward context in patients [143]. An explanatory illustration and a photograph of the arena can be found in Figure 6a. Briefly, the rats were placed in the start box and released into the choice area. Of the four possible arms to choose from, two were empty, one offered a high reward quantity at high risk (baited with three pellets which contained rewarding sugar in 30% of all trials, but bitter quinine as a punishment in 70% of all trials), and one offered a lower reward quantity at lower risk (baited with one pellet containing sugar in 80% and quinine in 20% of all trials). Animals repeated the task twelve times per day for ten days and were expected to establish the advantageous strategy to choose the option with a low-risk reward, the one-pellet arm.

The compulsive checking test was originally developed as a model for obsessive compulsive disorders [152,167]. It measures parameters that indicate abnormal, compulsive checking fixated on one or two favourite locales in the arena, called home bases, in contrast to the natural, uncompromised exploring behaviour of rats in a new environment [168]. A schematic drawing and a photograph of the arena are presented in Figure 6b. Rats were allowed to explore the arena freely for 45 minutes and compulsive behaviour was characterised by the rat returning to its home base(s) excessively often, briefly and rapidly with fewer stops in any of the other 25 locales.

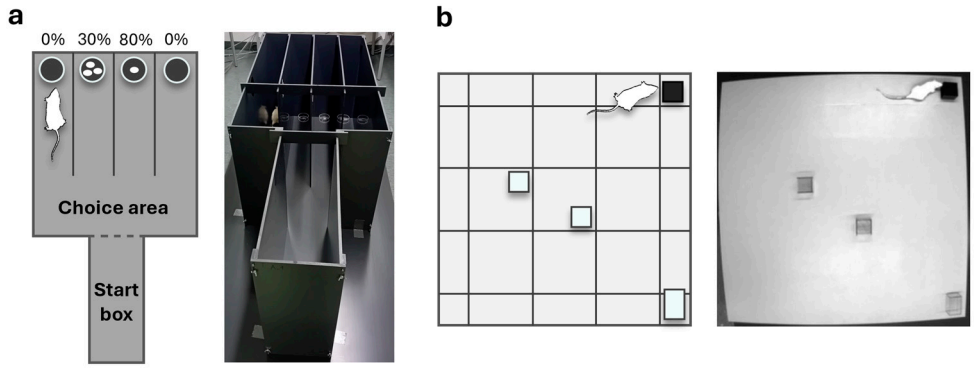

Figure 6. Schematic drawings and photographs of (**a**) the rat Iowa gambling task arena and (**b**) the compulsive checking arena (divided into 25 locales, squares are plexiglass boxes to elicit checking behaviour).

An additional method applied to identify ICB was the analysis of active behaviour patterns, possibly comparable to punding in patients [167,169]. Animals were filmed in a home cage-like environment and different active behaviours like locomoting, rearing, sniffing up, and sniffing down were classified with the event tracking software JWatcher [166,170]. Shorter bouts within each behaviour and more frequent switches between fewer behaviours were used as indicators of compulsivity.

In general, behavioural parameters were compared between experimental groups using two-factor ANOVAs and mixed-effect models considering treatment, phenotype, and their interaction. Please refer to Study IV (Appendix) for a full description of the experimental and statistical methods.

Brain tissue analysis

After the behavioural rat experiments in Study IV were concluded, the brain tissue was used to map changes in striatal neuroactivity under the different treatments in animals with and without PD phenotype. Coronal sections of the striatum were stained for phosphorylated ribosomal protein S6 (pS6) applying immuno-histochemistry. pS6 has been widely established as a cellular marker for neuroactivity and is especially sensitive to neuromodulation by external transmitters like dopamine [171,172]. In contrast to other neuroactivity markers like c-Fos, pS6 phosphorylation does not decrease due to desensitisation under chronic treatment.

After the immunohistochemical staining, three striatal sections per animal were scanned at high resolution (20X) and were processed with the image analysis software ImageJ Fiji. Inspired by Matamales et al. [173], we developed our own method based on MATLAB code to groupwise accumulate location-specific cell

counts into 2D histograms. They visualise areas of highest and lowest activity in the striatum for comparison between experimental groups. An illustration of the visualisation process is presented in Figure 7.

In a first step, all sections within one group were accumulated (see example staining Figure 7a, e.g. n=27). Their striatal outlines were traced manually and cells that were immunopositive for phosphorylated pS6 were localised and counted automatically according to predefined inclusion criteria regarding cell size and optical density. In addition to cell counts per unit area, x- and y-coordinates for striatal outlines and counted cells were obtained. Outlines were aligned to each other by applying transformation matrices for rotation, isometric scaling, and shifting on x- and y-axis to their coordinates (7b). Once aligned, coordinates of corresponding counted cells were added to each outline (7c). In the last step, the cell locations were converted into a 2D histogram showing pixels with high and low cell counts according to a colour scale (7d).

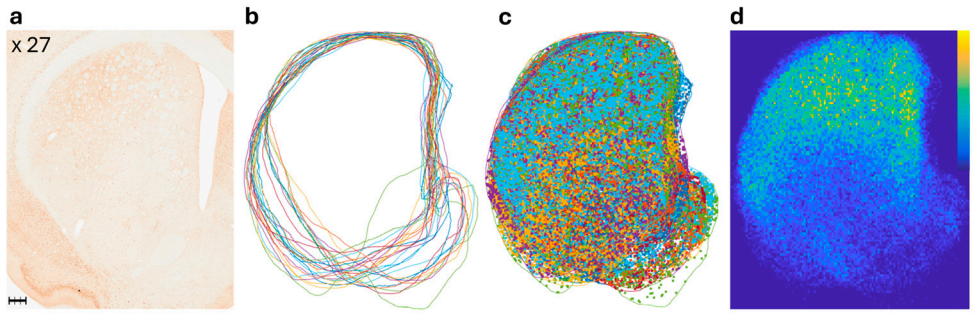

Figure 7. Visualisation process from immunohistochemical stainings of striatal sections to groupwise 2D histograms. (**a**) Example staining of a coronal striatal section, scalebar: 300 µm. (**b**) Aligned striatal outline coordinates of all sections in one experimental group. (**c**) Coordinates of aligned outlines and corresponding counted cells. (**d**) 2D histogram of cell counts per pixel, colour scale: yellow = highest activity, blue = lowest activity.

The groupwise 2D histograms were then analysed further by subtracting them from each other for pairwise comparisons of activity distributions, and by running a principal component analysis on the complete material to identify major patterns of covariance in striatal activity. To compare these major patterns between experimental groups, the coefficients of the first three principal components were used as a measure of expression. The coefficients were analysed in a two-factor ANOVA considering treatment, phenotype, and their interaction in line with the statistical analysis of the behavioural measures. Please refer to Study IV (Appendix) for a full description of the experimental and statistical methods.

Ethical considerations

All work in this thesis was approved by the Swedish Ethical Review Authority (Etikprövningsmyndigheten; Study I: Dnr 2019-01559, Study II: Dnr 2021-05752-01, Study III: Dnr 2022-06160-01) or the Ethical review board for animal experiments Malmö-Lund (Djuförsöksetiska nämnd Malmö-Lund; Study IV: Dnr 5.8.18-01398/2020). Risk-benefit analyses were performed prior to each study and the negative impact on humans and animals involved was minimised as much as possible.

The largest ethical concern in this thesis was the animal experiment in Study IV. Seventy rats underwent an extensive behavioural experiment over the course of ten weeks, entailing mild to moderate stress and mild to moderate physical pain. Stressful and potentially harmful factors during the experiment included being kept in an unnatural, confined environment, handling and restraining by the researchers, stereotactic brain surgery under anaesthesia inducing toxin lesions, postoperative impairments, daily subcutaneous injections with acidic drugs, and food deprivation.

Several measures were taken to keep the negative effects on the animals as low as possible according to the 3R principles (replace, reduce, refine) [174,175]. We evaluated, that no other method than a rodent experiment was suitable to answer our research questions. Given that we purposely induced behavioural changes in healthy individuals by drug treatment and relied on ex vivo material after the experiment, a design with human patients was impossible. On the other hand, we were dependent on a model that allows the study of human-like behaviour [139] and could not apply the experiment to a more primitive species or other laboratory designs based on human tissue. The number of animals was kept as low as possible while still providing sufficient statistical power for eight experimental groups. We designed a compact study where animals underwent several behavioural tests and provided tissue for an ex vivo analysis afterwards to reduce the number of animals needed for possible further experiments. Suffering due to stress and pain was kept to a minimum during the experiment, for example by applying anaesthetics and pain management drugs, and by habituation to new environments. Food deprivation was limited to the least extent feasible for the experimental design.

An additional ethical consideration in the thesis was the accumulation of nationwide patient data for Study I and II [176]. Even if research on register data holds very few risks for the study population in general, concerns about data protection apply, given the large collection of sensitive patient data like diagnoses, operations, and drug prescriptions. Moreover, data can be indirectly identifiable by a combination of common variables, especially in small patient groups with rare diagnoses like GD. Thus, several steps were taken to ensure the security and the anonymity of the patient information. We only worked with randomised study IDs to combine different registers, not with personal identity numbers or patient names. The

Swedish National Board of Health and Welfare destroyed the key that had made the IDs identifiable after delivery. Only researchers involved in the project had access to the primary data and they were handled exclusively in the research facility. Communication outside the research team and published results were based on group level and metadata only.

Study III held a comparable risk regarding data protection for a smaller number of patients but with far more detailed, sensitive health care information. Therefore, similar strategies as in Study I and II were applied for data storage and management. Furthermore, patients answering the questionnaire were exposed to a minor psychological risk, considering that the questions included sensitive and possibly stigmatised topics. We offered no direct follow-up or support regarding ICDs to the participants, but asked them to contact their clinical PD care for professional help with their behaviour if necessary.

Results

Summary of the main findings

- In the total Swedish population, treatment with pramipexole/ropinirole and aripiprazole were risk factors for GD.
- Almost 80% of all patients under antiparkinsonian dopaminergic treatment were not PD patients, but presumably RLS patients in large part.
- An RLS diagnosis given in specialised care was, in contrast to other neurological diagnoses, a clear risk factor for developing ICDs.
- Younger age at the start of dopaminergic therapy was a risk factor for developing ICDs both in PD and RLS patients.
- Male sex was a risk factor for developing ICDs in PD, but not in RLS.
- Patients with ICDs under dopaminergic medication presented with strong psychiatric comorbidity pre- and post-diagnosis, especially anxiety and substance use disorders.
- D2/3 agonists, especially ropinirole, were clearly associated with developing ICDs, as was the treatment with MAO-B inhibitors.
- Levodopa treatment alone and in addition to D2/3 agonists did not increase the risk for ICDs in humans or rats. DBS seemed to be beneficial for alleviating ICDs.
- ICDs under dopaminergic therapy occurred independently from a PD pathology in patients and a rat model.
- Dorsolateral striatal lesions mimicking denervation in PD showed increased neuroactivity, detected by pS6-immunopositive cell counts in rat brains.
- Only half of PD patients with ICD symptoms brought up their ICB in clinical PD care, and only fourteen percent were actively asked about it.
- Involvement of psychiatric care was rare for PD patients with ICDs and often limited to severe cases.
- Ropinirole treatment reduced neuroactivity in the striatum and shifted the main activity to central and medial regions in an ex vivo rat brain analysis.

Impulsive-compulsive disorders under dopaminergic medication in the total Swedish population

Novel in the context of the total Swedish population, in Study I we confirmed the association between GD and the three major drugs that have been reported with ICDs as side effects, namely the D2/3 agonists pramipexole and ropinirole, and the partial dopamine agonist aripiprazole. The GD frequency was much higher in the group treated with either of the D2/3 agonists (70%) compared with patients treated with other antiparkinsonian dopaminergic drugs (39%, Figure 8a). Consequently, pramipexole or ropinirole treatment was a cross-sectional risk factor for GD (Odds ratio (OR)=3.2, 95% confidence interval (CI)=1.4–7.6, p=0.008) in a logistic regression corrected for the covariates age, sex, and general mental health state, measured by psychotropic drug prescriptions (Figure 8b).

GD frequencies were notably elevated in patients with schizophrenia, schizotypal and delusional disorders in comparison to the whole study population (79% vs 33%). Within in this subgroup, an aripiprazole prescription was an additional factor increasing the GD frequency (89% with aripiprazole vs 71% without, Figure 8a). In a logistic regression corrected for age and sex, an aripiprazole prescription was a risk factor for GD (OR=3.4, CI=1.9–6.1, p<0.001; Figure 8b).

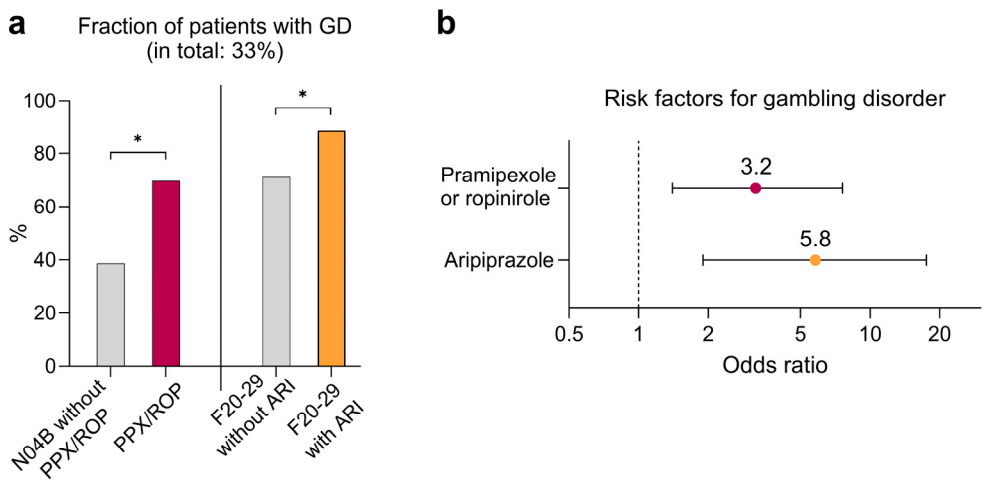

Figure 8. **Relative frequencies and odds ratios for GD under pramipexole/ropinirole (PPX/ROP) or aripiprazole treatment (ARI) in a case-control design.** n(PPX/ROP) = 149, n(ARI) = 170. **(a)** Fraction of patients with GD in treatment groups (red, orange) and their respective reference group without the treatment (grey). *: p(chi square) ≤ 0.001, N04B: antiparkinsonian dopaminergics, F20-29: schizophrenia, schizotypal and delusional disorders. **(b)** Odds ratios with 95% confidence intervals from logistic regressions for GD under PPX/ROP and ARI treatment.

In Study II, we characterised all patients in Sweden with antiparkinsonian dopaminergic prescriptions regarding ICDs. About 22% (55 235 of 251 965) were PD patients, 7% had a formal RLS diagnosis (16 709), 4% had another neurological diagnosis (9443), and 68% (170 578) had no neurological diagnosis from a specialist. Referring to common prevalences of RLS [118] and by skimming the prescription texts for dispensed medication, we assumed that most patients in the last group were being treated for RLS symptoms, either diagnosed in primary care or without a formal diagnosis. We also expected a fraction of this group to be patients with fibromyalgia, hyperprolactinemia, and pituitary adenomas, additional indications for antiparkinsonian dopaminergic treatment [131,132,134].

Of the in total 246 patients diagnosed with an ICD after the dopaminergic treatment had been initiated, 22% (55) were PD patients, and 16% (39) formally diagnosed RLS patients. Additionally, 11% (27) had another neurological diagnosis, and the remaining 51% (125) had not received any neurological diagnosis in specialised care. Logistic regression with the underlying neurological disorders as covariates revealed an RLS diagnosis given in specialised care to be a clear risk factor both for developing GD (OR=5.6, CI=2.3-14, p<0.001) and other ICDs (OR=5.0, CI=1.9-13.5, p=0.001) under antiparkinsonian dopaminergic treatment (Figure 9).

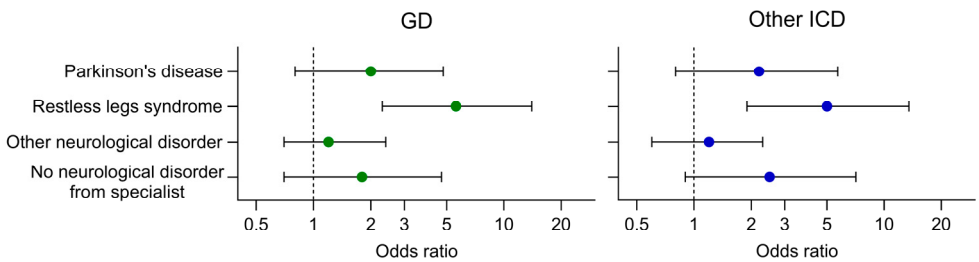

Figure 9. **ICD odds ratios for underlying neurological disorders.** Odds ratios with 95% confidence intervals for GD and other ICDs. Derived from one logistic regression each including all four categories of neurological disorders. n=251 965.

Demographic factors

Three different human study populations allowed for a broad analysis of demographic factors for developing ICDs under dopaminergic treatment in this thesis (Table 3). GD patients in general, regardless the underlying cause, were a young group at diagnosis (36 ±12 years) and mostly men (78%). Men were slightly overrepresented among GD patients with schizophrenia, schizotypal and delusional disorders without an aripiprazole prescription (85%, p=0.027). Otherwise, this patient group did not deviate from the general demographic characteristics in GD. GD patients under antiparkinsonian dopaminergic treatment, on the other hand, were older and less often male than other GD patients, especially when prescribed pramipexole or ropinirole (51 ±13 yrs, p<0.001 ; 57% men, p<0.001).

PD patients were an old population (72 ±10 yrs at first dopaminergic prescription) and 59 % of them were men. Compared with other PD patients, those who developed ICDs were substantially younger at their first dopaminergic prescription (GD: 50 ±8 yrs, p<0.001; other ICD: 55 ±15, p<0.001). In addition, they were more likely to be men than other PD patients (GD: 83%, p=0.010; other ICD: 81%, p=0.019). Both younger age and male sex were confirmed as predictors for GD and other ICDs in logistic regressions (GD younger age: OR(-10 yrs)=3.8, CI=3.0-4.8, p<0.001; GD male sex: OR=3.1, CI=1.2-8.2, p=0.024; other ICD younger age: OR(-10 yrs)=3.1, CI=2.4-3.9, p<0.001; other ICD male sex: OR=2.7, CI=1.0-7.2, p=0.045).

PD patients with ICD symptoms in Skåne county were of slightly younger age (68 ±11 yrs at data collection) and more often male (74%) than expected from the total Swedish population. GD patients were men disproportionally often compared with patients with other ICDs (92% vs 68%, p=0.036). A linear regression showed no age or sex effect on the increase in self-reported ICD severity during PD therapy.

RLS patients were in general of medium to older age (61 ±17 yrs at first dopaminergic prescription) and the majority was female (63%). Even in this population, developing ICDs was associated with a drastically younger age at first dopaminergic prescription (GD: 45 ±10 yrs, p<0.001; other ICD: 35 ±11, p<0.001). There was no significant shift in sex distribution in RLS patients with ICDs (65% and 69%, respectively). Logistic regressions confirmed younger age as a predictor for GD and other ICDs in RLS patients (GD: OR(-10 yrs)=1.7, CI=1.3-2.1, p<0.001; other ICD: OR(-10 yrs)=2.4, CI=1.8-3.3, p<0.001).

Table 3. Age and sex distribution in human study populations (Study I-III).

	Age (yrs, mean ±SD)	**Male** n (%)	**Female** n (%)	**Total** N (100%)
GD patients [a]	36 ± 12	2880 (78%)	809 (22%)	3689
N04B without PPX/ROP	49 ± 19*	8 (67%)	4 (33%)	12
PPX/ROP	51 ± 13*	58 (57%)*	45 (43%)*	104
F20-29 without ARI	37 ± 11	133 (85%)*	23 (15%)*	156
F20-29 and ARI	34 ± 10	116 (77%)	35 (23%)	151
PD patients [b]	72 ± 10	32 751 (59%)	22 484 (41%)	55 235
With GD	50 ± 8*	24 (83%)*	5 (17%)*	29
With another ICD	55 ± 15*	22 (81%)*	5 (19%)*	27
PD patients with ICD symptoms in Skåne county [c]	68 ± 11	58 (74%)	20 (26%)	78
With GD	68 ± 8	20 (91%)*	2 (9%)*	22
With other ICD	68 ±13	38 (68%)*	18 (32%)*	56
RLS patients [b]	61 ± 17	6182 (37%)	10 527 (63%)	16 709
With GD	45 ± 10*	8 (35%)	15 (65%)	23
With another ICD	35 ± 11*	5 (31%)	11 (69%)	16

a: in the total Swedish population 2005-2019, age at GD diagnosis; **b**: in the total Swedish population 2005-2022, age at first antiparkinsonian dopaminergic prescription; **c**: from Swedish quality register for PD in 2023, age at data collection; **N04B**: antiparkinsonian dopaminergics; **PPX/ROP**: pramipexole or ropinirole; **F20-29**: schizophrenia, schizotypal and delusional disorders; **ARI**: aripiprazole; * age: $p<0.05$ compared with the main study population in a t test or Dunnett's multiple comparison test following one-factor ANOVA; * sex: $p<0.05$ in chi square/Fisher's exact test compared with patients without this characteristic in the same subpopulation.

Psychiatric comorbidity

In this thesis, all four studies contributed to understanding psychiatric comorbidities of ICDs under dopaminergic treatment. Logistic regressions in Study I identified psychotropic drug prescriptions, indicating general mental health issues, as an independent risk factor for GD in patients with antiparkinsonian prescriptions (OR=5.8, CI=1.9-17.5, p=0.002). Additionally, GD frequencies were much higher in patients with schizophrenia, schizotypal and delusional disorders than in the total study population, regardless of aripiprazole prescriptions (79% vs 33%, $p<0.001$).

A main objective of Study II was to characterise psychiatric comorbidity before and after patients under PD therapy were diagnosed with an ICD (Figure 10). Common psychiatric diagnoses and prescriptions as events before an ICD diagnosis were used to identify predictors for developing an ICD (fully coloured bar parts). Mood and

anxiety disorders occurred with higher frequencies before any ICD (GD: 28% vs 12%, p=0.021, and 24% vs 9%, p=0.014; other ICD: 22% vs 12%, p=0.041, and 44% vs 9%, p<0.001) (Figure 10a). Additionally, alcohol use disorders were especially common before a GD diagnosis (10% vs 2%, p=0.011), and other substance use disorders before other ICD diagnoses (15% vs 2%, p<0.001). Consequently, alcohol use disorders were a predictor for GD in PD patients (OR=4.2, CI=1.1-15.6, p=0.033), while anxiety disorders and other substance use disorders were predictors for other ICDs in PD patients in logistic regression (OR=7.0, CI=3.0-16.7, p<0.001; OR=5.7, CI=1.8-18.2, p=0.004, respectively).

The only significant elevation in psychotropic prescriptions prior to ICDs in PD patients was found for drugs used in addiction, such as naltrexone, nicotine, or opioid replacement drugs, before a GD diagnosis (14% vs 2%, p=0.004) (Figure 10b). Thus, drugs used in addictive disorders were an additional predictor for GD in logistic regression (OR 5.9, CI=2.0-17.1, p=0.001). When screening for an increase in psychiatric comorbidity after ICD diagnoses under PD therapy, GD patients seemed slightly more affected than other ICD patients (Figure 10, checked bar parts). Especially mood and anxiety disorders, and antidepressant prescriptions increased after a GD diagnosis. Notably, newly introduced antipsychotic prescriptions were excessively high after all ICD diagnoses.

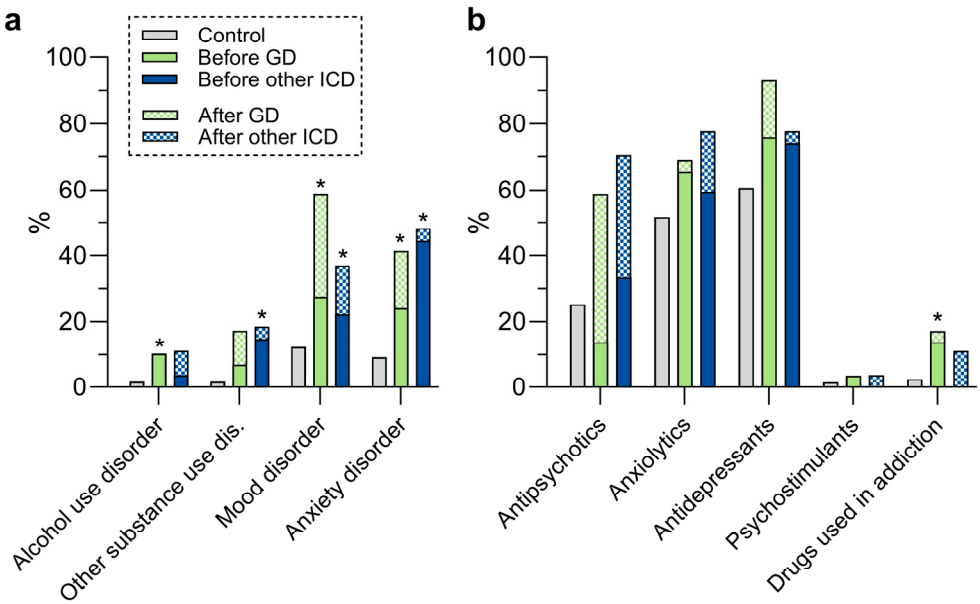

Figure 10. Relative frequencies of psychiatric comorbidity parameters in PD patients. n(controls)=55 170, n(GD)=29, n(ICD)=27**. (a)** Common psychiatric diagnoses. **(b)** Psychotropic drug prescriptions. *: p(Fisher's exact) < 0.05 for comparing prescriptions before a diagnosis to controls.

In Study III, PD patients with ICB reported psychiatric and cognitive comorbidities with sleep disturbances (63%), lack of motivation (56%), and vivid dreams (56%) being most common. Similar to the findings in Study II, 30% each reported depression and anxiety, 10% an alcohol use disorder, and 2% other substance use disorders.

Finally, in addition to causing ICB and hyperlocomotion in a rat model in Study IV, treatment with ropinirole also increased the time spent in the inner zone of an open field arena and the open arm entries in the elevated plus maze (data not shown, see Appendix – Study IV, Figure 2d and 3a,b). Both behavioural parameters indicate a reduction of anxiety and higher risk taking in rodents [163-165].

Advantageous versus high-risk dopaminergic treatment strategies

Identifying the safety or risk of different treatment strategies regarding ICDs was included as an objective in all four studies in this thesis. Study I comprised a general confirmation of the D2/3 agonists pramipexole and ropinirole, and the partial dopamine agonist aripiprazole being high-risk drugs for ICDs. Study II contained a more extensive analysis comparing different antiparkinsonian drug classes and specific dopamine agonists in PD patients (Figure 11). Prescription frequencies in the six months before an ICD diagnosis were compared with those during the full study period for control patients by calculating the ratio between them and applying a Fisher's exact test.

Dopamine agonist prescriptions were more common before ICD diagnoses than in controls (GD: 66% vs 48%, frequency ratio=1.4, p=0.058; other ICD: 78% vs 48%, frequency ratio=1.6, p=0.003) (11a). Moreover, MAO-B inhibitors were prescribed excessively often before a GD diagnosis compared with the control group (48% vs 26%, frequency ratio=1.8, p=0.006). Adding levodopa to the dopamine agonist or MAO-B inhibitor treatment did not seem associated with a higher risk for ICDs, given that the frequencies of cotreatment were similar to levodopa prescription frequencies before an ICD diagnosis in general.

Within patients receiving any dopamine agonist, no significantly elevated frequencies were detected for the prescription of any specific dopamine agonist before ICD diagnoses (11b). Nevertheless, the prescription frequency for ropinirole in the six months before an ICD relative to controls (frequency ratio=0.9-1.1) was almost double as high as the relative frequency for pramipexole (0.5-0.6).

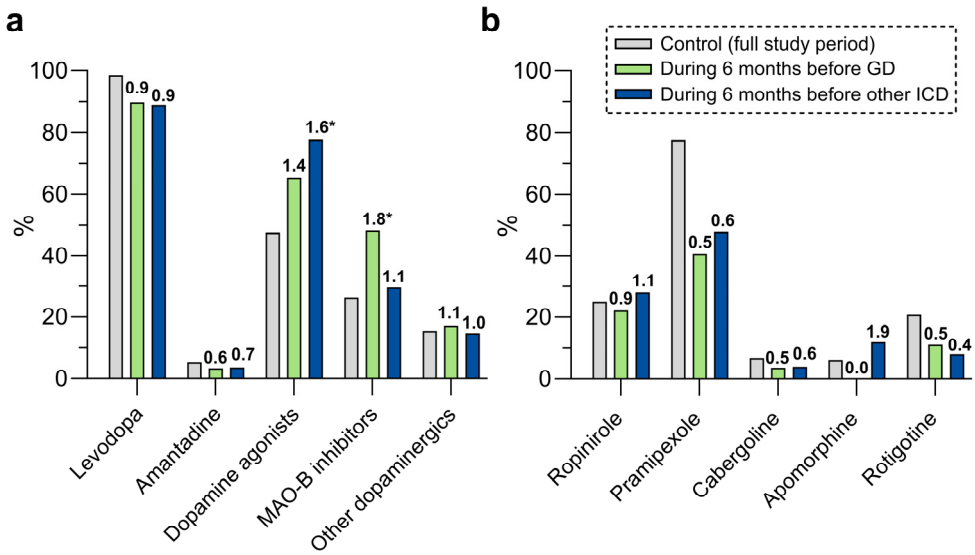

Figure 11. Relative frequencies of dopaminergic prescriptions in PD patients. Labelled with frequency ratios in comparison to control group, *: p(Fisher's exact) < 0.05. **(a)** Dopaminergic drug classes. n(controls)=55 170, n(GD)=29, n(other ICD)=27. **(b)** Specific dopamine agonists. n(controls)=26 273, n(GD)=27, n(other ICD)=25.

Looking at the results from Study III, our epidemiological findings were mostly supported by patient reports (n=43). Drugs mentioned in relation to worsening ICB were pramipexole (5x), rotigotine (2x), apomorphine (1x), and dopamine agonists in general (1x). Measures that in the patients' experience improved ICB were switching to levodopa (2x), discontinuing pramipexole (2x), and lowering the dose of rotigotine (1x). Notably, 67% of all patients under DBS treatment reported an alleviating effect on their ICB (6/9), while none reported worse ICB due to DBS.

According to the screened medical records, strategies for ICD management in clinical PD care in Skåne county were mainly focused on avoiding or reducing dopamine agonist use. Dopamine agonist treatment was discontinued in 15% of all ICD patients (7/46), and the dose was reduced in 39% (18/46). In one patient (2%), the administration was changed from immediate release to depot, and for six additional patients (13%) dopamine agonists were pointed out as disadvantageous regarding their ICD.

In Study IV, one of the main goals was to compare the behavioural effects of three different PD therapy options in rats: Levodopa in monotherapy, the D2/3 agonist ropinirole in monotherapy, and a combinatory treatment of both levodopa and ropinirole. Developing the advantageous strategy to choose the low-risk option in the rIGT was impaired in rats treated with ropinirole (Figure 12a). Both in monotherapy and combined with levodopa, the fraction of advantageous choices under ropinirole treatment was much closer to chance level compared with saline or levodopa treatment alone. Only on the last trial day, some understanding of the advantageous strategy seemed to develop even under ropinirole treatment.

When tracking active behaviours, the average length per bout for the common behaviours sniffing up, rearing, and sniffing down was strongly reduced under ropinirole treatment, regardless of levodopa cotreatment (12b). Combined with an increase in switching between behaviours (data not shown, see Appendix – Study IV, Figure 4c), the reduced bout length indicated compulsive-like behaviour.

Increased compulsivity was shown additionally in the compulsive checking test. The frequency of checking, adjusted for the expected frequency to account for hyperlocomotion, was increased under ropinirole treatment independent of additional levodopa treatment (12c). Similarly, the stops between home base checks were reduced in rats treated with ropinirole alone or combined with levodopa (12c'). Together with the reduced visit and return time to the home base(s) (data not shown, see Appendix – Study IV, Figure 5d,e), these ropinirole-induced changes confirmed compulsive checking behaviour. Findings in all three tests used to assess ICB pointed out ropinirole as the high-risk option for ICB consistently and independent of levodopa cotreatment. Levodopa itself had no or little effect on ICB in all parameters.

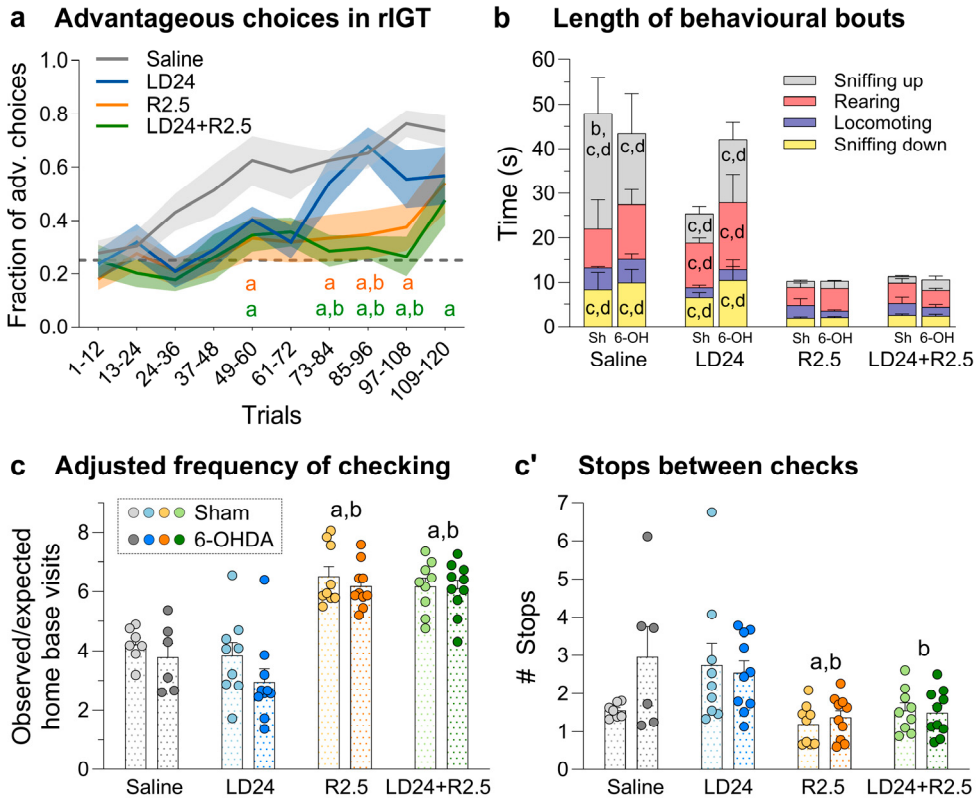

Figure 12. Effect of different dopaminergic treatments on ICB in intact and parkinsonian rats. Analysed with two-factor ANOVA or mixed-effect model followed by Tukey's multiple comparison test. **(a)** Fraction of advantageous choices in rat Iowa gambling task (rIGT) in rats with PD phenotype tested on ten days (12 trials/day). Chance level (25%) marked as dashed line. n=25. **(b)** Time per bout in active behaviours. n=69. **(c)** Ratio observed/expected home base visits in compulsive checking test. n=70. **(c')** Number of stops between checks at home base(s). n=70. **a**: p<0.05 vs Saline; **b**: p<0.05 vs LD24; **c**: p<0.05 vs R2.5; **d**: p<0.05 vs LD24+R2.5; **Sh**: Sham; **6-OH/6-OHDA**: 6-hydroxydopamine lesioned; **LD24**: Levodopa 24 mg/kg/day; **R2.5**: Ropinirole 2.5 mg/kg/day.

The impact of the Parkinson's neuropathology

As pointed out in the Introduction, the role of the dopamine-depleted state in PD for developing ICDs under dopaminergic treatment is still under discussion. In Study II, we performed a broad analysis of all Swedish patients with ICDs under dopaminergic treatment and found that only 22% were being treated for PD (see second chapter of Results). The fraction of RLS patients with ICDs was disproportionally high, and an RLS diagnosis given in specialised care was a risk factor for GD and other ICDs in logistic regression. In this population, ICDs under dopaminergic therapy occurred clearly independent of a PD pathology and the findings might even indicate, that patients without the loss of dopaminergic neurons are at higher risk for ICDs.

In addition to this epidemiological perspective, Study IV targeted the impact of PD pathology as one major objective in a rat model of PD. Compulsive checking was present in animals treated with ropinirole, both in intact and parkinsonian rats. Two-factor ANOVA detected a treatment effect on the adjusted frequency of checking, but no significant effect for the phenotype or the interaction between the two covariates (Figure 12c; $F(\text{treatment})_{3,62}$ =36.9, $p<0.001$; $F(\text{phenotype})_{1,62}$=2.9, p=0.096; $F(\text{interaction})_{3,62}$=0.5, p=0.681). Similarly, the number of stops between checks was reduced by ropinirole treatment but not affected by the phenotype or their interaction (Figure 12c'; $F(\text{treatment})_{3,62}$=7.3, $p<0.001$; $F(\text{lesion})_{1,62}$=1.8, p=0.183; $F(\text{interaction})_{3,62}$=1.9, p=0.141).

Furthermore, the time per bout of different active behaviours was reduced under ropinirole treatment, indicating stereotypical behaviour patterns. This effect was not influenced by the phenotype or the interaction between phenotype and treatment in any observed behaviour either (Figure 12b; Sniffing up: $F(\text{treatment})_{3,55}$=14.8, $p<0.001$; $F(\text{phenotype})_{1,55}$=0.01, p=0.904; $F(\text{interaction})_{3,55}$=2.3, p=0.084. Rearing: $F(\text{treatment})_{3,51}$ =5.1, $p<0.001$; $F(\text{phenotype})_{1,5}$=1.2, p=0.271; $F(\text{interaction})_{3,51}$=0.5, p=0.673. Locomoting: $F(\text{treatment})_{3,39}$=1.8, $p<0.001$; $F(\text{phenotype})_{1,39}$=0.2, p=0.633; $F(\text{interaction})_{3,39}$=0.2, p=0.902. Sniffing down: $F(\text{treatment})_{3,48}$=9.8, $p<0.001$; $F(\text{phenotype})_{1,48}$=1.2, p=0.279; $F(\text{interaction})_{3,48}$=0.7, p=0.530). The effect of ropinirole treatment was present equally in intact and parkinsonian rats in all parameters characterising compulsive checking and stereotypical active behaviour (data only partially shown, Appendix – Study IV, Figure 4 and 5). The rIGT was only performed by rats with PD lesions and did not allow for conclusions about phenotype differences.

While PD-like dopaminergic denervation did not influence ropinirole-induced ICB in rats, differences between the intact and PD phenotype were detected on a cellular activity level. Under all four treatments, the toxin-lesioned area localised in the dorsolateral striatum showed higher counts of pS6-immunopositive cells per unit area than the total striatum, indicating an increase in neuroactivity. Moreover,

principal component analysis identified a major pattern of covariance in striatal activity, that resembled this hyperactivity of the dorsolateral, denervated area (Figure 13a). Comparing the coefficient of this principal component between experimental groups as a measure of expression for this specific covariance pattern, clear differences between intact and parkinsonian animals were found (Figure 13b). Interestingly, dopaminergic treatment seemed to increase the expression differences between animals with and without PD lesions, especially the combinational therapy with ropinirole and levodopa.

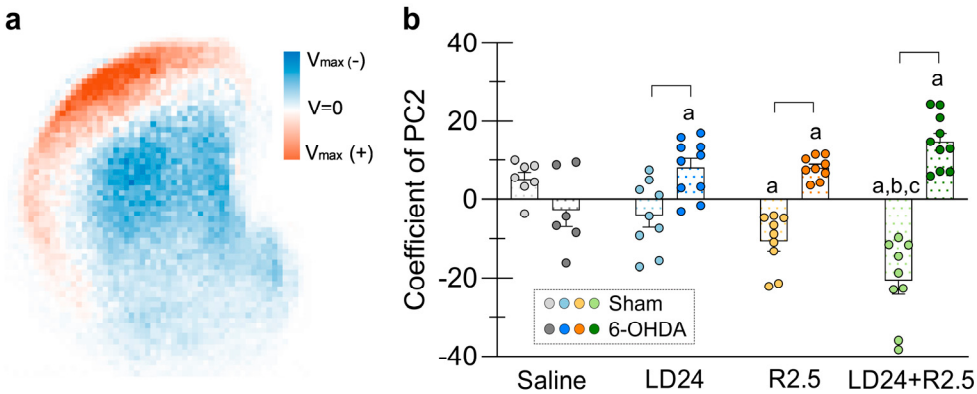

Figure 13. Effect of PD phenotype on striatal neuroactivity patterns in rats under dopaminergic treatment. (a) Principal component 2 (PC2) from a principal component analysis based on 2D histograms of striatal neuroactivity in all experimental groups. Colour scale shows local variance, V_{max} = maximal variance. Covariance is present in pixels with the same variance sign (positive: red, or negative: blue) and antivariance in pixels with opposite variance signs (red vs blue). **(b)** Coefficient of principal component 2 as index of expression of the covariance pattern in each experimental group. Two-factor ANOVA followed by Tukey's post hoc test. n(independent animals)=69, n(sections)=411. **a**: $p<0.05$ vs Saline; **b**: $p<0.05$ vs LD24; **c**: $p<0.05$ vs R2.5; **bracket**: $p<0.05$ sham vs 6-OHDA; **6-OHDA**: 6-hydroxydopamine lesioned; **LD24**: Levodopa 24 mg/kg/day; **R2.5**: Ropinirole 2.5 mg/kg/day.

Communication and management of impulsive-compulsive disorders in clinical Parkinson's care

Study III comprised a detailed analysis of how ICDs are handled and experienced in clinical PD care on the example of patients with ICD symptoms in Skåne county in Sweden. Information was collected through patient questionnaires and screening medical records. One main subject of interest was the information and patient-staff communication about ICDs. Most patients reported previous knowledge about the possibility to develop ICDs during their PD therapy (72%, 31/43), and 56% (24/43) had noticed behavioural changes in relation to their medication themselves. On the staff side, in 96% of the screened medical records PD medication was mentioned directly as the assumed reason behind the ICD (44/46).

Despite well informed patients and staff, analysing the communication about ICDs in clinical PD care revealed important issues (Figure 14). In 49% of all cases, the patient had been informed about ICDs as a possible side effect by their PD care staff (blue fractions, "was informed", 21/43). Only 49% of PD patients with ICD symptoms had told their PD care staff about them (red fractions, "told staff", 21/43), and merely 14% had been actively asked about ICD symptoms during their PD therapy (white and light blue fractions, "was asked", 6/43). For 35% of PD patients experiencing ICB, no communication about this had taken place in their clinical PD care (grey fraction, 15/43).

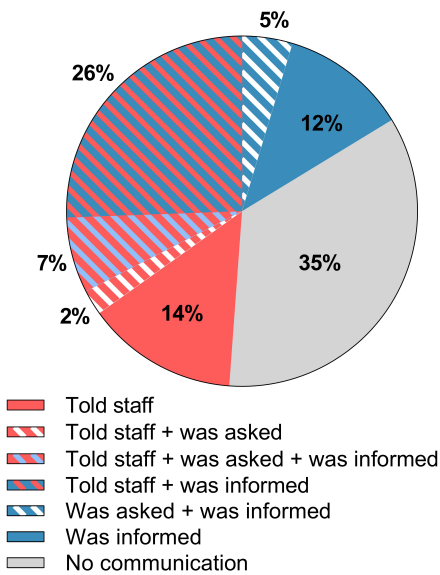

Figure 14. Communication about ICDs in clinical PD care. Based on patient reports, n=43. Overlapping relative frequencies of three types of staff-patient communication about ICDs in PD care.

A second subject of investigation in Study III was the collaboration between clinical PD care and psychiatric care concerning ICDs. According to patient reports, only few of them with strong ICB had been in contact with psychiatric or psychological care for their ICD (12%, 5/43). In the studied medical records, no formal ICD diagnoses were given for ICDs under PD therapy, and 13% of the patients had been in contact with psychiatric care explicitly for an ICD (6/46). Those with psychiatry records included severe ICD cases, such as "strongly depressed due to large debt" or "suicidal ideation related to gambling disorder".

Changes in striatal neuroactivity under ropinirole treatment

An additional objective of Study IV, besides the behavioural analyses, was mapping changes in striatal neuroactivity under different dopaminergic treatments in intact and parkinsonian rats. As mentioned above, the parkinsonian phenotype led to an increased activation of the area denervated by 6-hydroxydopamine lesions in the dorsolateral striatum under all treatments. When comparing the treatment effect on pS6-immunopositive cells in the total striatum, monotherapy with ropinirole decreased the counts by 59% compared with saline treatment, indicating a reduced neuroactivity (-175 cells/mm^2, $p<0.001$). Even compared with levodopa monotherapy, ropinirole induced a similar activity reduction (54%, -145 cells/mm^2, $p<0.001$). Cotreatment with levodopa and ropinirole resulted in a reduction of active cells by 35% in comparison to saline treatment (-105 cells/mm^2, $p=0.040$), with no significant difference to levodopa treatment alone. All treatment effects were independent of the animals' phenotype.

In addition to the overall reduction of pS6-immunopositive cells, ropinirole treatment shifted the neuroactivity between striatal areas (Figure 15). Visible both in individual example sections (15a) and groupwise accumulated 2D histograms (15b), treatment including ropinirole yielded the highest activation confined to central and medial areas of the striatum. In contrast, levodopa monotherapy led to a similar activation pattern as saline treatment, localised mainly in a broad dorsolateral area. The significance of this pattern change was confirmed by statistical mapping of comparative 2D histograms of pS6-immunopositive cell counts. The overall relevance was shown by principal component analysis, which identified the visually detected patterns as two of the main covariance motifs explaining variation in the material (data not shown, see Appendix – Study IV, Figure 8a/a', 8c/c', S2, and S3).

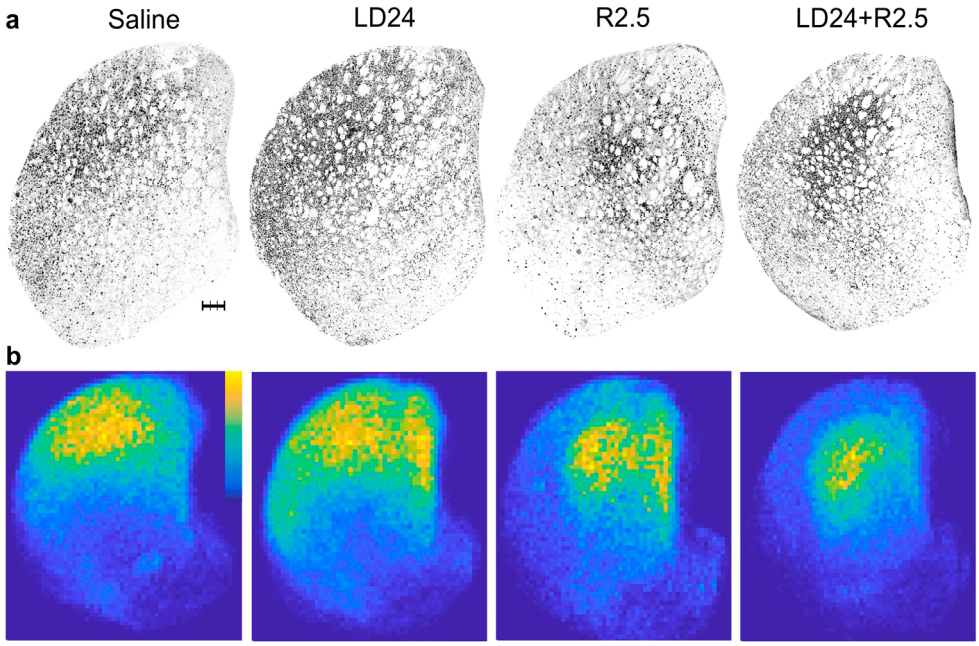

Figure 15. Patterns of striatal neuroactivity under different dopaminergic treatments in intact rats. (a) Representative immunohistochemical stainings of pS6-immunopositive cell distributions in the striatum from one example animal per experimental group. Scalebar = 300 µm. **(b)** Groupwise 2D histograms of pS6-immunopositive cell counts per pixel in the striatum. n(sections/group)=42-56. Colour scale: yellow = highest activity, blue = lowest activity. **LD24**: Levodopa 24 mg/kg/day; **R2.5**: Ropinirole 2.5 mg/kg/day.

Discussion

Main conclusions

- Similar to dopamine agonists, MAO-B inhibitors should be used carefully in patients with a risk for ICDs.
- It remains controversial if levodopa treatment added to other drug classes is a safe alternative in ICD patients. DBS should be considered to enable dopamine agonist dose reduction in ICD patients.
- Screening systematically for ICDs in clinical PD care could lead to a much better detection and management of ICDs as side effects.
- PD patients are likely to benefit from a well-established collaboration between neurology and psychiatry with an easy access to psychiatric care for ICD treatment.
- ICDs seem to affect all patients under antiparkinsonian dopaminergic treatment, independent of an underlying PD neuropathology.
- As the majority of patients that develop ICDs under antiparkinsonian dopaminergic treatment, RLS patients need more attention in clinical care and research.
- Given the clinical and demographic differences between PD, RLS and psychiatric patients, the best approach to avoid ICDs under dopaminergic medication has to be adapted for each individual study population.
- When identifying patients vulnerable to ICDs, the different risk factor profiles for each specific ICD need to be considered.
- Combining the rIGT, the compulsive checking test, and the analysis of stereotypical patterns in active behaviour represents a feasible, relatively simple approach to exploring different ICBs in rats with a PD phenotype.
- Inspired by a distinct neuroactivity profile in the striatum under D2/3 agonist treatment, future efforts should target the specific role of brain regions, receptor types and intracellular pathways in ICDs under dopaminergic medication for improved therapy options.

Implications for clinical Parkinson's care

The collective research effort during the last decades has enabled an evidence-based approach to avoid and manage ICDs during PD therapy [117]. D2/3 agonists are acknowledged as high-risk treatments, which could be confirmed by this thesis in the context of the total Swedish population [104,110-112]. We could also show that today, in the Swedish county Skåne the main strategy to reduce ICDs in clinical PD is to discontinue dopamine agonist treatment or reduce the dose, in line with the latest guidelines [117]. The D2/3 agonists ropinirole and pramipexole have in general been shown to increase the ICD risk equally much, perhaps with a trend towards ropinirole being the safer option [93,94,104,116]. Interestingly, our epidemiological findings indicate that ropinirole was more strongly associated with ICDs than pramipexole, in line with a recent analysis of dopamine agonist serum concentrations in relation to ICDs [122].

Only few studies have focused on the specific effect of MAO-B inhibitors on ICDs, showing an association, but milder than the effect of dopamine agonists [103,177]. Notably, according to our epidemiological drug screening, MAO-B inhibitor treatment was more strongly associated with GD than dopamine agonist treatment. Furthermore, our preclinical study showed that adding levodopa to dopamine agonist treatment did not worsen any ICB further. Even in the total Swedish population, there was no association between ICDs and a combinational therapy consisting of levodopa and a dopamine agonist or MAO-B inhibitor beyond the effect of the drugs levodopa was added to. Levodopa therapy has in general been regarded one of the safest options for avoiding ICDs [104,111,117], but in contrast to our findings, some studies showed an increased ICD risk when levodopa was added to dopamine agonist treatment [102,104,108].

Our analysis of the ICD recognition in clinical PD care pointed out that despite well-informed staff and patients, the communication about ICDs is insufficient to date. Only half of all PD patients mentioned their ICD to the staff and very few were actively asked about it. Even the process of informing the patient about the ICD risk at the start of PD therapy can be improved. These findings highlight that a systematic screening for ICDs during routine clinical care visits could improve the patients' situation substantially. Once an ICD was recognised, ICD management was performed according to evidence-based guidelines. Thus, improving the ICD detection process holds a large potential for treating affected patients more adequately. In particular, patients with risk factors for ICDs such as young age or male sex should be monitored actively for ICDs during their PD therapy. Consulting relatives can be an important source of information in this context, given that not all patients recognise their ICB themselves.

ICDs during PD therapy were almost exclusively handled within PD care, whereas psychiatric care was involved only in a few, severe cases. Considering the variety

of psychiatric symptoms in PD, often more present in patients experiencing ICB, a closer collaboration with psychiatric units could be beneficial. Once manifested, not all ICDs can be reversed simply by changes to a patient's pharmacotherapy. Furthermore, some life domains might be affected so heavily by the ICD, that the consequences outlast the ICD symptoms themselves. In both cases, the support by psychiatric care could improve the patient's quality of life considerably. In Lund, one encouraging example of the cooperation between neurology and psychiatry has been established. At the centre for Huntington's disease, both clinical care and research are performed in an interdisciplinary manner [178].

The screening of PD patients' medical records revealed that ICDs were handled without assigning any specific ICD diagnoses codes. This supports our assumption that many ICD patients were not included in our register studies due to the lack of a formal diagnosis. We detected an incidence of approximately one in 1000, far below the 10-25% reported by other studies [102,104,107,110].

Restless legs patients as the under-recognised, major patient group

As part of this thesis, we performed a comprehensive analysis of all patients receiving antiparkinsonian dopaminergic medication in Sweden. Almost eighty percent were being treated for other indications than PD. This percentage was consistent for the subgroup of patients who developed an ICD, suggesting similar prevalences of ICDs in PD and non-PD patients, in line with previous findings [32,36,102,104]. It can be assumed, that most of the patients without a neurological diagnosis from specialised care received dopaminergic treatment for RLS. Together with the sixteen percent of ICD patients diagnosed with RLS in specialised care, more than half of all ICD cases during antiparkinsonian dopaminergic treatment occurred in RLS patients. Additionally, an RLS diagnosis given in specialised care was a clear risk factor for developing GD and other ICDs compared with other neurological disorders.

Addressing ICDs in RLS patients can involve other challenges than in PD. On the one side, dopaminergic drugs doses in RLS are in general lower than in PD, and can often be kept unchanged during the whole treatment period [119]. Thus, avoiding high-dose dopamine agonist use can be achieved more easily. However, even dopamine agonist treatment at low dosage seems sufficient to induce ICDs in RLS patients with prevalences similar to PD populations. On the other side, RLS patients are typically treated in a primary care setting without regular follow-up appointments to discuss possible side effects of the medication prescribed. Moreover, as shown in this thesis, the knowledge about ICDs during PD therapy is well-established for patients and staff in clinical PD care today. Most likely, RLS patients and staff in

primary care are less well informed about the ICD risk associated with dopaminergic medication. As mentioned more in detail in the next chapter, even demographic factors vary substantially between RLS and PD patients.

In this thesis, behavioural changes studied in rats suggested no impact of the neuropathology in PD on the development of ICDs under dopaminergic treatment. Rats with a PD phenotype were as susceptible to dopamine agonist-induced ICB as healthy controls. Therefore, it can be expected that non-PD populations are as much at risk to develop ICDs under dopaminergic medication as PD patients. Nevertheless, in the same experiment we could show hyperactivity of neurons in the denervated striatal area compared with the total striatum under all treatments in rats with a PD phenotype. While not manifested in behavioural differences, this suggests changes in dopamine signalling under PD conditions that could influence ICD development in ways yet unknown.

Demography and psychiatric comorbidity as risk indicators in different patient groups

The findings in this thesis emphasise that each subgroup of patients under dopaminergic medication needs to be assessed separately regarding their risk factors for ICDs. Younger age was a clear risk factor for ICDs in PD, in line with previous findings [113,114]. Interestingly, we could confirm an equally strong association between younger age and ICDs in RLS patients, shown in one other study before [61]. One could argue that not younger onset age, but the necessity for high-dose dopaminergic treatment in later stages of PD due to the long disease progression constitutes the risk factor for ICDs in PD patients. In RLS patients, however, doses are often kept stable over many years and young age itself is likely to be the ICD risk factor [119].

Regarding the sex distribution, about two-thirds of all PD patients were male, with the opposite distribution, two-thirds female, in RLS patients. Notably, we found male sex to be an ICD risk factor in PD patients, consistent with the common consensus [113,114], but not in RLS patients, where female sex has previously been suggested as a risk factor for ICDs [61]. Considering therefore that more women than men develop ICDs in RLS, clinical manifestations of ICDs may vary between PD and RLS patients. It has been shown that women are more likely to develop compulsive buying and eating compared with other ICDs [25,104,114]. Another interesting observation in this context was that RLS patients with a GD were still female in two-thirds of all cases. This contrasts with the typical majority of men developing GD in general [179], 78% in our study.

Psychiatric comorbidities such as depression, anxiety and substance use disorders, have been shown to be associated with ICDs in PD patients [106,109,112,180]. This thesis confirms severe psychiatric comorbidity both as a risk factor before an ICD developed and as a consequence after the ICD had been diagnosed. Mood and especially anxiety disorders were common prior to all ICDs. An additional risk factor for GD was an alcohol use disorder and patients with substance use disorders were at higher risk for developing other ICDs. Our findings suggest that specific ICDs might be predicted by different profiles of psychiatric comorbidity. A comprehensive investigation of psychiatric comorbidities as risk factors for each individual ICD might enable an easier detection of vulnerable patients. Psychiatric comorbidity has rarely been investigated in RLS patients with ICDs, including one study reporting increased stress and depression [124].

Notably, we found a dramatic increase in antipsychotic prescriptions for ICD patients after their diagnosis, possibly in an attempt to treat the ICD. Considering that there is no evidence for antipsychotics being effective for treating ICDs, this finding underlines the need for the development of specific drugs targeting impulsive and compulsive traits directly.

Antipsychotics are often prescribed to patients with severe psychiatric disorders and psychotic symptoms have been found to be associated with ICDs in PD patients [180]. Thus, psychiatric patients treated with an antipsychotic constitute an especially vulnerable population for developing ICDs under dopaminergic treatment. Indeed, we could show that patients with schizophrenia and other psychotic disorders had high GD rates even without aripiprazole therapy. We could also confirm aripiprazole treatment as an additional risk factor for GD, as shown before in other studies [135,138]. In comparison to patients under antiparkinsonian dopaminergic treatment, psychiatric patients have been pointed out to develop a more severe form of GD [181]. Based on these findings, it seems crucial to screen this already vulnerable patient group for additional ICD risk factors before choosing aripiprazole as the antipsychotic treatment.

New tests for impulsive-compulsive behaviour in a rat model with Parkinson's phenotype

As outlined in previous chapters, Study IV was based on an extensive characterisation of motor and non-motor behaviours in rats under dopaminergic treatment. While it led to interesting new insights into the specific behavioural effects of ropinirole in contrast to levodopa, it also confirmed the feasibility of the tests applied to study ICB under dopaminergic therapy in parkinsonian rats. To our knowledge, three behavioural tests for ICB were introduced to a parkinsonian rat model for the first time: the rIGT, the compulsive checking test, and the tracking of

stereotypical patterns in active behaviours. The extend of dopaminergic denervation induced by mild, bilateral 6-hydroxydopamine lesions in the dorsolateral striatum in this study did not interfere with the animals' ability to perform in the chosen tests.

The operant form of the rIGT, the rat gambling task, has been established as an option to study gambling-like behaviour in rats under PD treatment previously [139,145,146]. Nevertheless, it requires a long training period for the animals before being able to perform the test. In our study, we found the rIGT to be an easily applicable, maze-based alternative to study decision making in a reward context with much shorter pre-training. The compulsive checking test, developed as a model for obsessive-compulsive disorder under quinpirole treatment [152], proved to be a feasible technique to detect ICB in a PD context with high throughput and a simple arena set up. Similarly, tracking stereotypical, active behaviours yielded satisfactory results when screening for ICB under PD treatment and did not require an elaborate laboratory design. Taken together, we believe that we have started to establish a new, adequate selection of behavioural tests to assess the spectrum of ICBs in a rat model for PD.

Future perspectives

Avoiding dopamine agonist treatment has been established as the optimal strategy to reduce ICDs in PD [117]. Given that dopamine agonist discontinuation or dose reduction are not always possible, further options have been suggested, such as switching to an agonist with less D2/3 selectivity, often rotigotine, or applying DBS. Even other advanced therapies like intestinal pumps for levodopa administration have shown promising, yet still controversial results regarding ICD reduction [182-184]. Considering non-PD populations under dopaminergic treatment in particular, identifying the least risky form of dopamine agonist administration regarding ICDs might be the best approach in the future. Slower, continuous administration, achieved by an oral prolonged release design, pumps, or depots, seems to be favourable compared with the immediate release option for pramipexole but not for aripiprazole [110,185].

To date, there seems to be little collaboration between clinical PD care and psychiatric care. PD presents with a variety of disease- and treatment-related psychiatric symptoms and affected patients would likely receive better care in an interdisciplinary approach. Perhaps, including psychiatric staff in each PD care unit could make this form of collaboration possible on a routine basis.

As pointed out in earlier chapters, RLS patients constitute the majority of patients under dopaminergic treatment with neurological indication. The gap of knowledge about this population compared with PD patients is substantial and large-scale epidemiological and clinical studies are urgently needed. Moreover, the effect of aripiprazole on ICDs in psychiatric patients needs to be investigated more in detail.

Looking even further ahead into future research, the issue of ICDs under dopaminergic medication should be addressed from a neurobiological perspective. Understanding the brain regions and intracellular signalling involved could enable the development of more specific dopamine agonists with less severe side effects. In addition, this could contribute to the discovery of drugs targeting ICB specifically, a significant opportunity to improve the treatment of many psychiatric disorders [140,186]. Based on the shift in striatal neuroactivity that we detected under ropinirole treatment, investigating downstream pathways of D2/3 receptors can be a promising approach. In particular, the upregulation of glycogen synthase kinase-3β in the β-arrestin pathway has been shown in association to ICB under dopaminergic treatment [90].

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