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STRIATAL DOPAMINE SYSTEM IN NEUROLOGICAL AND PSYCHIATRIC DISORDERS

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The chase is better than the catch.
Scooter

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ABSTRACT

The striatal dopamine system that regulates motor function and motivation shows interindividual variation and is altered in neurological and psychiatric disorders, such as Parkinson's disease (PD), schizophrenia, and addictions. These effects can be estimated using positron emission tomography (PET) that offers a unique opportunity to unravel the function and structure of the dopaminergic system. However, PET is an expensive and labour-intensive imaging method that exposes subjects to ionizing radiation, limiting the size and thus reliability of PET studies.

The data used in this thesis were retrospective [^{18}F]fluorodopa (n = 220) and [^{11}C]raclopride (n = 437) PET images, which reflect the dopamine synthesis capacity and the availability of type 2 dopamine receptors (D_2R) at baseline, respectively. We investigated the effects of PD, schizophrenia, severe violent behaviour, pathological gambling, and depression on striatal dopaminergic function. Additionally, we estimated the effects of age, sex, and body mass index (BMI). We quantified the effect of scanner type on the PET estimates and compared PET quantification approaches using a subject-specific magnetic resonance image (MRI) versus a common PET template as anatomical information.

Lowered dopamine synthesis and D_2R availability were associated with PD, ageing, and male sex. Both in controls and PD patients, the dopamine synthesis was positively correlated between the regions. This was also the case regarding D_2R availability. The subjects with severe violent behaviour showed relatively low interregional D_2R correlation, although the sample was small. In summary, our findings, together with the other existing literature, indicate that the links between BMI and our dopaminergic estimates are not strong. The scanner had a substantial influence on the PET estimates. Based on our data, the template-based spatial normalisation of PET images may be used with caution.

KEYWORDS: dopamine, positron emission tomography, neurological, psychiatric

TURUN YLIOPISTO
Lääketieteellinen tiedekunta
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TUULIA MALÉN: Tyvitumakkeiden dopamiinijärjestelmä neurologisissa ja psykiatrisissa häiriöissä
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TIIVISTELMÄ

Aivojen tyvitumakkeiden dopamiinitoiminta, joka säätelee motoriikkaa ja motivaatiota, on tavanomaisesta poikkeavaa useissa neurologisissa ja psykiatrisissa häiriöissä, kuten Parkinsonin taudissa, skitsofreniassa ja riippuvuuksissa. Lisäksi dopamiinitoimintaan vaikuttavat yksilölliset tekijät, kuten ikä ja sukupuoli. Vaikutuksia voidaan tutkia positroniemissiotomografialla (PET), joka tarjoaa ainutlaatuisen mahdollisuuden kuvantaa dopamiinijärjestelmän rakennetta ja toimintaa. PET on kuitenkin kallis ja työläs kuvantamismenetelmä, joka altistaa tutkittavan radioaktiiviselle säteilylle. Siksi PET-tutkimusten otokset ovat tyypillisesti pieniä, mikä rajoittaa tulosten luotettavuutta.

Tämän väitöskirjan aineisto koostui retrospektiivisistä [^{18}F]fluorodopa (n = 220) ja [^{11}C]raklopridi (n = 437) PET-kuvauksista, joilla mitattiin lepotilassa dopamiinin tuotantoa ja tyypin 2 dopamiinireseptoreiden (D_2R) tiheyttä tyvitumakkeissa. Tutkimme miten Parkinsonin tauti, skitsofrenia, vakava väkivaltakäyttäytyminen, ongelmapelaaminen ja masennus vaikuttavat tyvitumakkeiden dopamiinitoimintaan. Kartoitimme myös iän, sukupuolen ja painoindeksin vaikutuksia. Arvioimme myös miten käytetty kamera vaikuttaa PET-havaintoihin. Lisäksi vertasimme PET-havaintoja, jotka johdimme käyttäen joko tutkittavan omaa magneettikuvaa tai usean tutkittavan keskiarvoista mallia aivojen rakenteista.

Madaltunut dopamiinin tuotanto ja D_2R-tiheys olivat yhteydessä Parkinsonin tautiin, ikääntymiseen ja miessukupuoleen. Sekä verrokeilla että PD potilailla dopamiinin tuotanto korreloi tyvitumakkeiden välillä positiivisesti. Näin oli myös reseptoreiden osalta. D_2R-tiheys korreloi tyvitumakkeiden välillä verrattain heikosti tutkittavilla, joilla oli taustalla vakavaa väkivaltakäyttäytymistä, joskin otos oli pieni. Aineistomme ja muun tutkimuksen valossa painoindeksin vaikutus ei ole voimakas. Käytetty kamera vaikutti PET-havaintoihin. Keskiarvoista aivorakenteiden anatomiaa PET-aktiivisuuden paikantamisessa kannattaa käyttää harkiten.

AVAINSANAT: Dopamiini, positroniemissiotomografia, neurologinen, psykiatrinen

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Abbreviations

5-HT_{1A}	Serotonin receptor 1A
5-HT_2	Serotonin receptor 2
5-HTT	Serotonin transporter
AADC	L-aromatic amino acid carboxylase
AAL3	Automated anatomical labelling 3 that is an atlas provided by Montreal Neurological Institute
ADHD	Attention-deficit/hyperactivity disorder
BED	Binge eating disorder
BMI	Body mass index, i.e., weight in kilograms per height in meters squared
BP_{ND}	Nondisplaceable binding potential
cAMP	Cyclic adenosine monophosphate
COMT	Catechol O-methyltranferase
CT	Computed tomography
D_1R	Type 1 dopamine receptor
D_2R	Type 2 dopamine receptor
DAT	Dopamine transporter
DSM-5	Diagnostic and statistical manual of mental disorders, fifth edition by American Psychiatric Association
fMRI	Functional magnetic resonance image or imaging
GABA	Gamma aminobutyric acid
GLM	General linear model or modelling
ICD-10	International classification of diseases, 10^{th} revision by World Health Organization
IQR	Inter-quartile range, i.e., the distance of the 25% and 75% quartiles
keV	Kiloelectron-volt
K_i^{ref}	Influx rate constant estimated using occipital cortex as reference region
MAO	Monoamine oxidase
MBq	Megabecquerel
MNI	Montreal Neurological Institute
MOR	μ-opioid receptor
MRI	Magnetic resonance image or imaging

n	Number of observations
PD	Parkinson's disease
PET	Positron emission tomography
PG	Pathological gambling
ROI	Region of interest
SD	Standard deviation
SPECT	Single photon emission computed tomography
SRTM	Simplified reference tissue model
SNRI	Serotonin and noradrenaline reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
VTA	Ventral tegmental area
μ	Expected value (in the context of statistical analysis)

List of Original Publications

This dissertation is based on the following original publications (Studies), which are referred to in the text by their Roman numerals:

I Tuulia Malén, Jouni Tuisku, Marco Bucci, Severi Santavirta, Valtteri Kaasinen, Sakari Kaasalainen, Janne Isojärvi, Jarmo Hietala, Juha Rinne & Lauri Nummenmaa. Striatal dopamine synthesis capacity in Parkinson's disease: Effects of age, sex, and body mass index in a large [^{18}F]fluorodopa PET cohort. *NeuroImage: Clinical*, 2026, 103944. https://doi.org/10.1016/j.nicl.2026.103944

II Tuulia Malén, Tomi Karjalainen, Janne Isojärvi, Aki Vehtari, Paul-Christian Bürkner, Vesa Putkinen, Valtteri Kaasinen, Jarmo Hietala, Pirjo Nuutila, Juha Rinne & Lauri Nummenmaa. Atlas of type 2 dopamine receptors in the human brain: Age and sex dependent variability in a large PET cohort. *NeuroImage*, 2022; 255: 119149. https://doi.org/10.1016/j.neuroimage.2022.119149

III Tuulia Malén, Severi Santavirta, Sven De Maeyer, Jouni Tuisku, Valtteri Kaasinen, Tuomas Kankare, Janne Isojärvi, Juha Rinne, Jarmo Hietala, Pirjo Nuutila & Lauri Nummenmaa. Alterations in type 2 dopamine receptors across neuropsychiatric conditions: A large-scale PET cohort. *NeuroImage: Clinical*, 2024; 103578. https://doi.org/10.1016/j.nicl.2024.103578

1 Introduction

The striatal dopaminergic system, governing motor function and motivation, is altered in several neurological and psychiatric disorders, such as Parkinson's disease (PD), schizophrenia, and addictions (Harsing Jr, 2008). Besides clinical status, striatal dopaminergic function is influenced by age (Darbin, 2012), sex (Zachry et al., 2021), and body mass index (BMI) that is weight in kilograms per height in meters squared (Janssen & Horstmann, 2022).

Positron emission tomography (PET) can quantify molecule-level processes including dopaminergic neuroreceptor density and function in the human brain (Das, 2015). It offers a unique opportunity to unravel the function and structure of the dopaminergic system in health and disease. However, PET is an expensive and labour-intensive method that also exposes subjects to ionising radiation. Consequently, PET studies have typically been limited by small sample sizes. Noise, such as non-systematic variation and measurement inaccuracy in the data, limits the reliability of conclusions drawn from small samples (Andrade, 2020). Furthermore, the scope has usually been restricted to either (1) individual variation in a healthy cohort, or (2) a single clinical condition. Less attention has been paid to whether individual differences and clinical effects are independent, and how clinical cohorts compare to each other.

At the Turku PET Centre, *in vivo* brain PET imaging of the striatal dopamine system has been conducted since the 1980s for the purposes of several studies, using the radioligands [^{18}F]fluorodopa and [^{11}C]raclopride to quantify the striatal dopamine synthesis capacity and the availability of type 2 dopamine receptors (D_2R),

respectively. The imaging and related metadata have been compiled retrospectively into an in-house database Aivo (https://aivo.utu.fi).

Pooled data typically involve heterogeneity, such as variation from involving several scanners in the data acquisition. The magnetic resonance image (MRI), used to localise functional PET data, may be unavailable for some subjects in historical datasets, requiring the anatomical information to be derived from other individuals. The magnitude of the scanner-related variation and the comparativeness of spatial normalisation using the anatomy of the subject versus a group average have not been explicitly quantified before in [^{18}F]fluorodopa and [^{11}C]raclopride PET cohorts.

Overall, retrospective datasets have enormous potential as data pooling allows secondary use of hundreds of PET images and permits the simultaneous investigation of several clinical cohorts along with healthy controls. These data can validate previous findings, answer novel research questions, test different PET preprocessing methods, and create functional brain atlases; these are the aims of this thesis.

2 Review of the Literature

2.1 Dopaminergic system

2.1.1 Neurotransmitter dopamine

Neurotransmitters are divided into (1) peptide neurotransmitters, such as vasopressin, oxytocin, and opioids, including endorphins, and (2) small-molecule neurotransmitters, such as dopamine and serotonin (Purves et al., 2018c). The division is based on the number of amino acids (3–36 in peptides) in the neurotransmitter molecules (Purves et al., 2018c). Small-molecule neurotransmitters are acetylcholine, purines, biogenic amines, and single amino acids, such as gamma aminobutyric acid (GABA) and glutamate (Purves et al., 2018c). Biogenic amines, including serotonin, histamine, adrenaline, noradrenaline, i.e., norepinephrine, and its precursor dopamine, share similar chemical properties and postsynaptic actions (Purves et al., 2018c). They govern many homeostatic and cognitive brain functions, and their dysfunction is involved in several psychiatric disorders (Purves et al., 2018c). Dopamine, adrenaline, and noradrenaline, are also catecholamines, that is a class of monoamines, due to their common precursor amino acid tyrosine (Purves et al., 2018c). Dopamine particularly governs voluntary movement, cognition, and emotions related to reward seeking (Harsing Jr, 2008; Janssen & Horstmann, 2022; Schultz, 1998). Dopamine release is involved in feelings of ‘high’, positive emotions, and alertness (Joutsa et al., 2012).

2.1.2 Dopaminergic signalling

There are about 300,000–400,000 dopaminergic neurons in the human brain (Harsing Jr, 2008). The dopaminergic neurons in the central nervous system mainly originate from three nuclei: substantia nigra, ventral tegmental area (VTA), and arcuate nucleus in hypothalamus (Harsing Jr, 2008). Dopamine is synthetised from tyrosine in the axon terminals of the dopaminergic neurons (Harsing Jr, 2008). Tyrosine is an amino acid gained directly from dietary proteins or through conversion processes in the liver and dopaminergic neurons (Bressan & Crippa, 2005).

When dopaminergic neurons are activated, two enzymes, tyrosine hydroxylase and dopa decarboxylase are transported from the cell body to the nerve terminal cytoplasm (Harsing Jr, 2008). Tyrosine hydroxylase converts tyrosine into L-DOPA, and dopa decarboxylase, also called L-aromatic amino acid carboxylase (AADC), further converts L-DOPA into dopamine (Harsing Jr, 2008). In the presynaptic axon terminals, dopamine is stored in cytoplasm and in the vesicular pools, i.e., vesicles (Harsing Jr, 2008). Unlike in the cytoplasm, dopamine remains protected and stored in the vesicles, until it is released into the synaptic cleft (Harsing Jr, 2008).

Dopamine neurons are regulated by dopamine and other neurotransmitters, such as GABA and glutamate (Harsing Jr, 2008). Dopamine release depends on the (1) physiological stimulus-induced discharge that is action potential, (2) autoreceptor regulation of dopaminergic firing, synthesis, and release, and (3) activation of the non-dopaminergic receptors, such as glutamate and GABA heteroreceptors on the dopaminergic neuron (Harsing Jr, 2008). Once released into the synaptic cleft, dopamine molecules activate postsynaptic dopamine receptors that induce a series of reactions in the following, postsynaptic, neuron. Transmembrane proteins dopamine transporters (DAT) terminate the postsynaptic binding by removing dopamine from the synaptic cleft back to the presynaptic nerve terminal for later reuse (Harsing Jr, 2008).

There are five subtypes (1–5) of dopamine receptors (Harsing Jr, 2008). This thesis focuses on the type 2 dopamine receptor (D_2R) family, that involves the subtypes 2, 3, and 4. The type 1 dopamine receptor (D_1R) family involves the remaining subtypes 1 and 5. The receptor families have overlapping distributions in the brain, however, the ratio of the quantified D_1R and D_2R vary between the regions (Bressan & Crippa, 2005).

Some D_2Rs are postsynaptic on the surface of the target neuron, while others are presynaptic on the surface of the sending dopaminergic neuron (Harsing Jr, 2008). All dopamine receptors are G-protein-coupled, meaning the dopamine receptor activation also activates some G-protein (Harsing Jr, 2008). However, postsynaptic D_2R stimulation mediates inhibition of the target neurons that in the striatum, including caudate nucleus, nucleus accumbens, and putamen, are commonly the inhibitory GABAergic medium spiny neurons (Harsing Jr, 2008; Purves et al., 2018a, 2018b). More specifically, the striatal regions are composed of the cell bodies and surrounding dendrites of the medium spiny neurons that the dopaminergic axons target (Purves et al., 2018a, 2018b). Nevertheless, the postsynaptic D_2R stimulation disinhibits, meaning excites, the striatum.

Dopamine may also exit the synaptic cleft into extracellular space where it activates presynaptic dopamine receptors, autoreceptors, which regulate firing activity of the dopaminergic neurons (Harsing Jr, 2008). Activation of autoreceptors inhibits dopaminergic firing activity in cell bodies, as well as synthesis and release

in nerve terminals (Harsing Jr, 2008). Dopamine is metabolised by the enzymes monoamine oxidase (MAO) and catechol O-methyltranferase (COMT) (Purves et al., 2018c).

D_2Rs show high and low affinity, high-state D_2R being functional via G-protein coupling (Egerton et al., 2009). While D_2R agonists prefer binding to receptors at a high affinity state, antagonists show comparable affinities to high-affinity and low-affinity D_2R (Egerton et al., 2009). D_2R may also internalise, that is become passive, at least as a reaction to elevated dopamine release via psychomotor stimulants, such as the amphetamine class of drugs (Cárdenas et al., 2004; Laruelle, 2000).

Dopamine synthesis capacity is a rather stable individual trait and cannot be enhanced by increasing tyrosine concentrations (Harsing Jr, 2008), while dopamine release and receptor availability are dynamic processes (Janssen & Horstmann, 2022). However, tyrosine hydroxylase can be modulated by substances, such as caffeine, morphine, and antidepressant medication (Harsing Jr, 2008).

Phasic dopamine signalling, i.e., firing or release, is six times more frequent (approximately 30 events per second) than tonic release (approximately 5 events per second) (Volkow et al., 2009). Dopamine concentration is also higher in phasic (millimolar range) than in tonic (nanomolar range) signalling (Grace, 2000), a millimolar having a million times more molecules per litre than a nanomolar.

Tonic activity affects the amplitude of the phasic firing that signals saliency of a given stimulus (Grace, 2016). The more tonically activated dopaminergic neurons, the more prepared the system is to rapidly response to salient stimulus with phasic activation, that is to allow, as an example, an efficient fight or flight response in a threatening environment (Grace, 2016).

Phasic dopamine firing is initiated by a burst of electric spikes, action potentials, in the neuronal axon, which induce fast dopamine release, postsynaptic D_2R binding, and reuptake without dopamine leakage to extracellular space outside the neuron (Grace, 2000). Phasic, such as drug-induced, dopamine release causes rapid fluctuations in the dopamine levels, which is experienced as highlighted saliency of a given stimulus (Grace, 2000; Volkow et al., 2009).

Tonic, steady-state dopamine release is induced by sustained elevation of spontaneous dopamine neuron firing or glutamate-activated dopaminergic nerve terminals (Grace, 2000, 2016). If the concentration is too low to activate the postsynaptic receptors, tonic dopamine escapes from the synaptic cleft to extracellular space and activates the presynaptic D_2Rs that work as autoreceptors, inhibiting phasic dopamine (Grace, 2000). Tonic extracellular dopamine is rather stable and sensitively regulated (Grace, 2000). Projections from the hippocampus and amygdala contribute to how widespread the tonic activity is and thus how prepared the system is for phasic bursts and the following behavioural response (Grace, 2016), which are finally calmed down via autoreceptor binding (Grace,

2000). In healthy dopamine functioning, tonic and phasic firing are in a homeostatic state, while this balance might become disrupted in clinical conditions, such as prolonged drug-abuse (Grace, 2000; Volkow et al., 2009).

The four major dopaminergic pathways in the human brain are (1) nigrostriatal, (2) mesolimbic, (3) mesocortical, and (4) tuberoinfundibular pathways (Harsing Jr, 2008). The nigrostriatal pathway, referred to as the motor circuit, runs from substantia nigra pars compacta to the dorsal striatum, including caudate nucleus and putamen (Harsing Jr, 2008). The mesolimbic pathway, referred to as the reward pathway, projects from the VTA to the ventral striatum, including the nucleus accumbens (Harsing Jr, 2008). The mesocortical pathway spans from VTA to prefrontal and cingulate cortices (Harsing Jr, 2008). Finally, the tuberoinfundibular pathway, referred to as the neuroendocrine circuit, originates from hypothalamus and ends in pituitary gland (Harsing Jr, 2008). The dopaminergic neurons, signalling and pathways are illustrated in **Figure 1.**

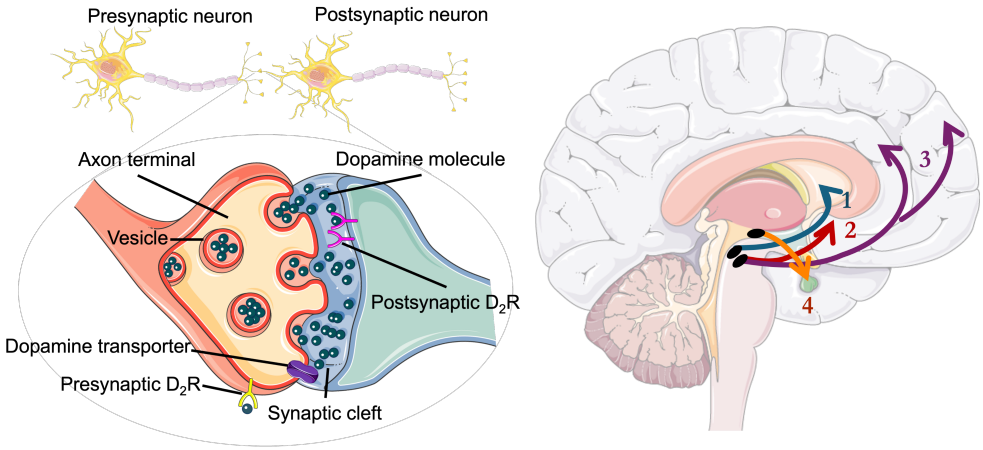

Figure 1. Left: Presynaptic dopaminergic neuron and the target neuron are connected in the synapse zoomed below. Right: The four major dopaminergic pathways. In the sagittal view, the brain view is cut in between the eyes, and forehead is on the right. Created in PowerPoint version 16.105.3 (26020123) using and combining several objects from Servier Medical Art, https://smart.servier.com/citation-sharing/, provided by Servier and licensed under CC BY 4.0 https://creativecommons.org/licenses/by/4.0/.

2.1.3 Functions of the dopamine system

The dopamine system governs reward seeking and harm avoidance (Schultz et al., 1997). Reward is an object, behaviour, situation, or inner state for which the individual assigns a rewarding, positive, appetitive, and motivational value (Schultz et al., 1997). Rewarding stimulus induces (1) approach and consummatory

behaviour, (2) continued consumption that strengthens the association between the reward and its preceding cue, and (3) pleasant emotions (Schultz, 1998). Aversive stimulus does the opposite encouraging avoidance behaviour and unpleasant emotions (Schultz, 1998).

Reward seeking and harm avoidance promote survival and reproduction, which is why these characteristics have generalised in the animal, including human, populations. Although subjective and dynamic in nature (Schultz, 1998), rewards, such as food, sex, and other gained resources, typically show a positive effect on our well-being (Schultz et al., 1997). In contrast, harmful effects such as injury, death, or lost resources, which threaten our well-being, are commonly experienced as aversive (Schultz, 1998).

Predicting the environment by understanding common causes and effects is crucial for successful reward seeking and harm avoidance (Schultz et al., 1997). While seeing the future is impossible, the predictions rely highly on past experiences of rewards and punishments (Schultz et al., 1997). These lessons learnt modify our predictions, promoting approach and avoidance behaviour (Schultz, 1998).

The dopaminergic pathways from substantia nigra and VTA to the striatal caudate nucleus, putamen, and nucleus accumbens, as well as to the frontal cortex play a crucial role in reinforcement learning, regardless of the stimulus type that can be social, nutritional etc. (Schultz et al., 1997).

The dopaminergic neurons show elevated phasic firing to rewards that are better than expected event outcomes (Schultz et al., 1997). The pre-reward cue is associated with the reward, and re-exposure to the cue is sufficient to activate the dopamine pattern, promoting reward seeking (Schultz et al., 1997). Once the cue-reward link is learnt, it is particularly the cue, rather than the reward, that enhances dopamine firing (Schultz et al., 1997). Reduced or paused phasic firing is coupled with outcomes that are less favourable than expected (Schultz et al., 1997). The preceding cue is associated with aversive emotions and becomes avoided in the future (Schultz et al., 1997). Reward prediction error is the discrepancy between the prediction and the outcome, for both better and for worse (Schultz, 1998). Finally, outcomes well-aligned with predictions do not alter the phasic dopaminergic firing (Schultz et al., 1997).

Goal-oriented behaviour, such as reward seeking and harm avoidance, involves (1) motivation, including reward-related emotions, (2) cognition, such as learning, evaluation, decision making, and planning, and (3) motor function, such as voluntary movement and motor control (Wolf, 2012). These processes are regulated by the dopaminergic function, spread around several medial and cortical regions, forming the mesocorticolimbic circuit of the brain (Wolf, 2012).

2.1.4 Functions of the striatal dopamine system

This thesis focuses on the striatum, directly involved in the mesolimbic and nigrostriatal pathways governing motivation and motor function, although clear distinction of the pathways and their functions is not realistic nor meaningful due to the overlap and co-work of the circuits (Bressan & Crippa, 2005).

Despite the overlap, the so-called reward circuit is the mesolimbic pathway, running from VTA to ventral striatum or nucleus accumbens (Harsing Jr, 2008) that possibly has a specific role of coding the *valence* (pleasant or unpleasant) of prediction errors (Berridge & Kringelbach, 2015; Grill et al., 2024), while caudate, otherwise known as the associative striatum, processes the *magnitude* of prediction errors (Grill et al., 2024).

The reward prediction errors induce reinforcement learning that influences decision making, leading to approach or avoidant behaviour (Schultz, 1998; Schultz et al., 1997). The dorsal striatum, that is caudate and putamen, is involved in the decision making (Balleine et al., 2007) and the implementation of action, as it is centrally part of the nigrostriatal motor pathway (Harsing Jr, 2008; Purves et al., 2018b). The dorsal striatum, together with globus pallidus and subthalamic nucleus in the ventral thalamus, regulate the upper motor neurons in the cortex and brainstem (Purves et al., 2018b). Appropriate function of this regulatory network enables smooth voluntary movement, that includes timely implementation of wanted, as well as accurate inhibition and termination of unwanted movement (Purves et al., 2018b). While the cortex is outside the scope of this thesis, the mesocortical pathway is prominently involved in cognitive functions, such as behavioural control (Purves et al., 2018d).

2.2 Individual differences in striatal dopaminergic function

The striatal dopaminergic system governs motivation and motor function that are disturbed in several neurological and psychiatric disorders (Bressan & Crippa, 2005). To determine the role of dopamine in these clinical conditions, it is imperative to characterise dopaminergic variation in healthy populations, explained by factors such as age, sex, and BMI. As the striatal dopamine system is a target of several drugs treating neurological and psychiatric disorders (Bressan & Crippa, 2005; Purves et al., 2018c), understanding the healthy variation, such as sex differences, is also inevitable for personalised pharmacological treatments (Williams et al., 2021; Zachry et al., 2021). Once the normal dopaminergic variation is characterised, comparison of healthy and several clinical cohorts will elucidate the neural correlates of neuropsychiatric disorders.

2.2.1 Effects of age and sex

Normal ageing, involving cognitive and motor decline (Esiri, 2007), is linearly associated with dopaminergic downregulation, consistently demonstrated for dopamine receptors and transporters (Karrer et al., 2017). Evidence of changes in dopamine synthesis capacity is less consistent, which has partially been explained by small sample sizes (Karrer et al., 2017). However, although the quadratic, U-shaped, function explained the relationship of dopamine synthesis and age better than the linear function, age did not, however, explain much of the variation in the dopamine synthesis capacity (Karrer et al., 2017).

The existing literature also points towards sex differences in the dopaminergic function, some being dependent and others independent of hormonal factors (Zachry et al., 2021). Dopamine synthesis declined with age particularly in men who overall had lower synthesis capacity than females (Laakso et al., 2002). With higher dopamine synthesis, females could hypothetically have a higher endogenous dopamine concentration than males, which was supported by a study subtly suggesting lower striatal D_2R affinity in females versus males (Pohjalainen et al., 1998). This is assuming that lower [^{11}C]raclopride-D_2R affinity reflects more endogenous dopamine (Pohjalainen et al., 1998).

2.2.2 Effect of body mass index

Overweight (BMI > 25) and obesity (BMI > 30), are consequences of energy intake that overtime is greater than energy expenditure (Morton et al., 2014). Because humans have evolved in circumstances where acquisition of sufficient energy has been unpredictable and uncertain, it is to be expected that humans find energy-rich food extremely palatable and motivating and why being overweight is so common today in societies where the shortage of food no longer exists (Butler & Eckel, 2018). To ease the global challenge of overweight, attempts have been made to unravel the metabolic and neurobiological risk factors for weight gain.

It has been proposed that similar to addictive behaviour, excessive feeding disturbs the balance of the neural circuits related to motivational drive, reward saliency, conditioned learning, and behavioural control, resulting in superior saliency of energy-rich foods and increased difficulty to abstain from their consumption (Volkow et al., 2011).

Binge eating disorder (BED), characterised by periods of sudden, excessive, and incontrollable food intake promoting overweight, is associated with lowered striatal dopamine synthesis capacity at baseline (Majuri et al., 2017). Palatable foods stimulate the mesolimbic dopamine pathway, increasing the dopaminergic neurotransmission from VTA to nucleus accumbens (Butler & Eckel, 2018). Eating a pleasurable meal increases dopamine release, while lower amplitude of the post-

meal release is associated with blunted feeding-related pleasure, although observed only in caudate and putamen and not in "the reward region" accumbens (Small et al., 2003). However, it has also been argued that dopamine influences particularly the drive for palatable foods, rather than the experience of palatableness that is ultimately a sensory characteristic (Butler & Eckel, 2018). In mice, the lack of D_2R promotes compulsive-like eating (Kim et al., 2025). On the whole, these findings support a dopamine deficiency hypothesis suggesting that blunted dopaminergic function leads to lower reward and compensatory over-consumption of food (Volkow et al., 2011).

Janssen, Horstmann and colleagues (Horstmann et al., 2015; Janssen & Horstmann, 2022) further propose that in overweight and mild obesity, dopamine shows a low tone, with high phasic release and high food reward sensitivity. This is in contrast to more severe obesity which is associated with high tonic yet low phasic release and low food reward sensitivity (Horstmann et al., 2015; Janssen & Horstmann, 2022). However, the limited support from existing literature and the need for analyses specifically testing this idea are highlighted (Janssen & Horstmann, 2022). Furthermore, the negative association between tonic and phasic firing is somewhat discrepant with the idea that high tonic activation enables more efficient phasic responses (Grace, 2016), although tonic dopamine also enables autoreceptor binding that inhibits phasic firing (Grace, 2000).

According to the review by Janssen and Horstmann (Janssen & Horstmann, 2022), there is a link between low striatal dopamine synthesis capacity and high BMI, while dopamine release, receptor availability, and reuptake, are independent of BMI in humans, supported by a meta-analysis concluding unaltered dopamine receptor availability in overweight and obese individuals compared to controls (Pak & Nummenmaa, 2023). Although high BMI does not indicate overeating nor BED, these observations generally suggest that despite lowered dopamine synthesis capacity, the baseline D_2R binding, is not systematically altered in overweight.

Nonetheless, feeding and reward processing involve several interacting classes of neurotransmitter systems. Particularly, dopamine controls reward anticipation, while endogenous opioids regulate reward-induced pleasant feelings, such as post-reward liking (Butler & Eckel, 2018), and these systems stimulate each other in the ventral striatum and caudate (Tuominen et al., 2015). Not only the low dopamine release (Small et al., 2003), but also the low μ-opioid receptor (MOR) availability might dampen the food-induced hedonia, promoting overeating for sufficient satisfaction (Karlsson et al., 2015). In fact, in addition to lowered dopamine synthesis capacity, BED subjects showed widespread reductions of opioid receptors in multiple subcortical and cortical brain regions (Majuri et al., 2017). In obese subjects (number of observations (n) = 25, mean BMI = 41) without BED, the correlation of MOR and D_2R availability in ventral striatum was weaker than in lean subjects

(Tuominen et al., 2015). Thus, the dopamine and opioid systems may also selectively decouple in morbid obesity, possibly altering reward processing (Tuominen et al., 2015). Finally, the influence of sociocultural and psychological factors cannot be detached from feeding behaviour altogether.

2.3 Dopamine in neurological and psychiatric disorders

2.3.1 Parkinson's disease

PD, which is the most common neurodegenerative disease after Alzheimer's disease, is characterised by progressive degeneration of nigrostriatal dopaminergic neurons, leading to initially asymmetric motor symptoms and reduced striatal dopamine synthesis capacity (Kalia & Lang, 2015) even at early stages in the disease (Kaasinen & Vahlberg, 2017), particularly in the putamen (Nurmi et al., 2001). PD also shows non-motor symptoms, such as depression, sleep disturbance and fatigue, as well as olfactory and, particularly in later stages of the disease, autonomic dysfunction, such as urinary incontinence and constipation (Kalia & Lang, 2015). Cognitive disturbance is also associated with PD (Kalia & Lang, 2015).

The prevalence of PD is approximately 1% of people over 60 years of age (Atula, 2023). Male-to-female ratio is 3:2 (Kalia & Lang, 2015). While the onset is typically at the age of 50–70 years (Atula, 2023), the number of patients will expectedly grow with increasing life expectancy (Kalia & Lang, 2015) and ageing of the baby boom generation. The cause of dopaminergic degeneration in PD is unknown (Atula, 2023), although several risk factors, such as a prior head injury and rural living, including agricultural occupation, pesticide exposure, and well water drinking, have been recognised (Kalia & Lang, 2015). Unexpectedly, consumption of tobacco, caffeine and alcohol decrease the risk of PD (Kalia & Lang, 2015). Mutation in GBA, encoding the lysosomal enzyme β-glucocerebrosidase, is the greatest genetic risk factor (Kalia & Lang, 2015).

In Finland, the diagnosis is primarily based on having two of the three most common motor symptoms, i.e., tremors, bradykinesia, and rigidity (Atula, 2023). It has been estimated that when PD is clinically detectable, 50% of the neurons in substantia nigra and 70% of the striatal dopamine have already been lost (Wichmann & DeLong, 2012). No blood tests or conventional brain imaging techniques, such as computed tomography (CT), or MRI clearly identify PD (Atula, 2023). PET or single photon emission computed tomography (SPECT) can be used to confirm asymmetric dopaminergic decline, although it is not required for diagnosis (Atula, 2023).

PD has no cure or preventive treatment today (Atula, 2023), but the symptoms are commonly eased with physical exercise, physiotherapy, and pharmaceuticals

elevating and extending synaptic dopamine levels. Some of the pharmaceuticals are the dopamine-precursor levodopa, which increases dopamine synthesis in the brain, and dopamine agonists, such as pramipexole and apomorphine, as well as MAO and COMT inhibitors selegiline and entacapone (Wichmann & DeLong, 2012).

Early PD, approximately the first four years from symptom onset, has been associated with upregulation of striatal D_2R availability (Rinne et al., 1990), particularly in the putamen (Rinne et al., 1995), possibly compensating for declined dopamine firing (Kaasinen et al., 2021), while partial lesion of the system increases sensitivity of the existing binding sites (Harsing Jr, 2008). Nevertheless, advanced PD shows downregulated striatal D_2R availability with PET (Kaasinen et al., 2021).

2.3.2 Schizophrenia

Schizophrenia is a severe psychiatric disorder associated with several neural changes, such as aberrant neurotransmitter, including the dopaminergic, function (Coyle & Konopaske, 2012), brain volume reduction (approximately 2%), and disturbed interaction between the default mode and task-specific neural networks (Jauhar et al., 2022). The symptoms of schizophrenia are classified as positive, negative, and cognitive or disorganisation symptoms (Coyle & Konopaske, 2012; Jauhar et al., 2022). Positive symptoms include psychotic experiences, such as delusions and hallucinations, and illogical or bizarre speech (Coyle & Konopaske, 2012). Negative symptoms are low motivational drive, blunted mood, impoverished emotion expressions and speech, and social withdrawal (Howes & Kapur, 2009), as well as motor disturbances, such as catatonic rigidity and/or agitation (Coyle & Konopaske, 2012). In comparison, cognitive symptoms consist of disturbed executive functions, memory, decision making, attention, and concentration (Rovasalo, 2025b).

Worldwide, the prevalence for schizophrenia is approximately 1% of the population, with the onset typically in early adulthood (Jauhar et al., 2022; McGrath et al., 2004). Males versus females differ in prevalence (1.4–1.7 males per 1 female) and in typical age of onset that is younger in males versus females (Jauhar et al., 2022; McGrath et al., 2004). The life expectancy of individuals with schizophrenia is reduced by 10 years (Coyle & Konopaske, 2012). In Finland, the diagnostic criteria requires a month-long period of at least two out of the five typical symptoms: (1) delusions, (2) hallucinations, (3) incoherent speech, (4) incoherent behaviour or catatonia, and (5) negative symptoms, in addition to having disturbed social functioning for several months (Rovasalo, 2025b).

Psychotic symptoms have commonly been associated with altered function of the mesocorticolimbic circuit (Bressan & Crippa, 2005), particularly dopaminergic hyperfunction in the midbrain (Howes & Kapur, 2009). It has been argued that

during acute psychosis, elevated phasic firing in the striatum amplifies experienced saliency of innocuous stimuli (Howes & Kapur, 2009), enabling delusional thoughts, such as the person on TV is talking directly to oneself (Lieberman & Long, 2018).

While conventional antipsychotics block the D_2R (Howes & Kapur, 2009), the current view is that individuals with schizophrenia do not show increased striatal D_2R density (Jauhar et al., 2022). Schizophrenia overall is associated with increased presynaptic dopamine (Hietala & Syvälahti, 1996; Howes et al., 2012), particularly in the dorsal, although not in the ventral, striatum (McCutcheon et al., 2018), conflicting with the mesolimbic hypothesis of psychotic symptoms. Altogether, negative and cognitive symptoms, also observed prodromal schizophrenia (Rovasalo, 2025b), have been linked with dopaminergic, particularly D_1R, hypofunction in the cortex (Howes & Kapur, 2009).

There is a great variety in symptoms across individuals (Rovasalo, 2025b). The symptom severity fluctuates even within individuals and some periods may be symptom free (Rovasalo, 2025b). Approximately 5–10% of patients show full recovery and 40–70% partial recovery with alleviated symptoms (Rovasalo, 2025b). Positive symptoms commonly ease over time (Rovasalo, 2025b). However, approximately 20–40% of individuals continue having severe symptoms for decades and are unable to return to work (Rovasalo, 2025b). Early detection and treatment may improve the long-term course of schizophrenia (Rovasalo, 2025b). The treatments combine psychosocial and mainly D_2R-blocking pharmacotherapy, aiming at retained or reacquired everyday autonomy (Coyle & Konopaske, 2012; Rovasalo, 2025b).

It is noteworthy that dopamine is linked generally to psychotic symptoms and not just to schizophrenia (Howes & Kapur, 2009). Furthermore, dopamine dysregulation alone does not account for schizophrenia, but a combination of inherited biological and environmental factors contributes to its onset (Howes & Kapur, 2009). The biological risk factors include several interacting genes and neurotransmitter, such as dopamine, glutamate, GABA, and choline systems (Coyle & Konopaske, 2012). Some of the environmental risk factors are obstetric complications, drug use, and stressful life events, such as traumas and social isolation (Howes & Kapur, 2009).

2.3.3 Antisocial behaviour

Aggressive and antisocial behaviour, including physical, sexual, and emotional violence, can harm oneself and others. Obviously, not all aggression is ‘bad’ or leads to violent behaviour and many times non-violent aggression is adaptive, promoting goal-directed behaviour, such as standing up for one’s rights, to gain resources (Nummenmaa, 2019).

Young age and male sex are the key risk factors for violent offending (Nummenmaa, 2019). Globally, 75% of the violence is committed by men, although most men are not violent (Nummenmaa, 2019). Overall, few people are violent, as over a half of the violent acts are committed by 1% of the population (Nummenmaa, 2019). Violence, that does not refer to psychiatric illness, is most often committed by people without psychiatric disorders (Nummenmaa, 2019). However, impulsive aggression is often comorbid with mental disorders, such as depression, and addictions (Seo et al., 2008).

Individuals with aggressive and antisocial behaviour typically share a combination of high sensitivity for provocation, as well as difficulty in behavioural control (Nummenmaa, 2019). Aggressive outbursts have been linked with high activation of the emotion circuits in the midbrain and low activation of the cortical regions accounting for behavioural control (Nummenmaa, 2019; Seo et al., 2008).

Aggression is not caused by any single chemical, but multiple neurotransmitter systems, such as dopamine and serotonin, contribute to its manifestation (Seo et al., 2008). Particularly, hypoactive serotonergic function in concert with hyperactive dopaminergic function in the frontal cortex encourage impulsive forms of aggression (Seo et al., 2008). Dopamine stimulation enhances impulsivity, recognised in several species (Seo et al., 2008). Mice lacking the dopamine metabolising enzymes MAO and COMT show aggressive behaviour (Harsing Jr, 2008), suggesting that hyperdopaminergism promotes aggression realisation. In humans, D_2R antagonists that block D_2R, inhibit aggressive behaviour and the recognition of aggression in others (Seo et al., 2008). Nevertheless, violent offenders with psychopathy showed lower baseline D_2R availability compared to age and sex-matched controls, possibly promoting sensation-seeking (Lukkarinen et al., 2024). Overall, the regions implicated in reward processing and emotion regulation are those involved in aggression commonly in healthy, forensic, and clinical cohorts, including psychiatric populations (Harju et al., 2025).

2.3.4 Pathological gambling

Addictions are characterised by diminishing control over addictive behaviour that is continued despite negative consequences (Castrén, 2023). The purpose of the addictive behaviour changes from seeking pleasure to feeling normal or avoiding withdrawal symptoms, such as nervousness and disturbance of concentration and sleep (Castrén, 2023). Pathological gambling (PG) is a behavioural addiction, classified either as an impulse control disorder or a gambling disorder under substance-related and addiction disorders, depending on the classification of diseases as ICD-10 or DSM-5, respectively (Kaasinen et al., 2009; Moreira et al., 2023).

In Finland, the prevalence of PG is approximately 1.4 %, being higher in males versus females (Castrén, 2023). Common comorbidities are other addictions, such as alcohol or drug abuse, and mood disorders (Castrén, 2023). Additional risk factors are an impulsive or antisocial personality (Castrén, 2023), attention-deficit/hyperactivity disorder (ADHD), and environmental factors, such as social acceptance of gambling (Castrén, 2023). PG causes social, emotional, and financial burden on the individuals, their families, and society (Kaasinen et al., 2009). The compulsiveness of addictive behaviour might not be evident for others, possibly limiting the social support provided. The key component in recovery is motivation for change (Castrén, 2023), while the pharmacological treatments are currently under investigation (Ioannidis et al., 2025).

The aetiology of PG is unknown, yet the onset expectedly involves a combined burden of genetic and environmental factors augmented with disturbances in several neurotransmitter, substantially dopamine, functioning (Kaasinen et al., 2009). Similar to aggression (Seo et al., 2008), PG is apparently linked with a disturbance of emotion regulation and behavioural control (Kaasinen et al., 2009).

As with any other reward-seeking behaviour, PG is learnt through reward prediction errors (Kaasinen et al., 2009). Reward reception, such as winning in a wager, induces a dopamine boost that reinforces the cue-reward link that promotes sensitivity for relevant cues in the environment, encouraging further gambling (Kaasinen et al., 2009; Volkow et al., 2009). The attributed saliency of addictive behaviour exceeds that of natural rewards, creating a vicious cycle of prolonged dependency in vulnerable individuals (Kaasinen et al., 2009; Volkow et al., 2009).

Playing a video game with monetary reward enhances striatal dopamine release and D_2R binding, the effect being strongest in the ventral striatum (Koepp et al., 1998). Elevated dopamine synthesis capacity was reported in individuals with PG (Van Holst et al., 2018), although in samples overlapping with the data of this thesis, there was no clear difference in dopamine synthesis capacity (Majuri et al., 2017) or baseline D_2R availability (Joutsa et al., 2012) between pathological gamblers with a variety of symptom severity, and healthy controls. Nevertheless, the more severe the PG, the higher the dopamine release and pleasure gained in a high-reward task, suggesting enhanced dopaminergic response to gambling in individuals with PG (Joutsa et al., 2012). Another study suggested lower baseline D_2R availability and higher gambling-related dopamine release in the ventral striatum in individuals with PG, although limited to PD patients (Steeves et al., 2009). A review summing up animal and human dopamine release studies, including the study by Steeves and colleagues (Steeves et al., 2009), also suggested that lower baseline D_2R may predispose individuals to pathological gambling, and that the dopamine release of pathological gamblers is particularly sensitive to gambling (Egerton et al., 2009). Finally, dopamine receptor agonists, that enhance the dopaminergic function,

increase the risk for PG and other impulse control disorders (Kaasinen et al., 2009). In conclusion, while enhanced dopamine release during gambling or lower baseline D_2R availability are not clear biomarkers for PG, they probably show some role in the development of addiction.

2.3.5 Depression

Mood disorders are the main cause of prolonged sick leaves in Finland, and in 2023, more than 100 000 people received sickness allowance for mood disorders, depression being the second most common cause after anxiety (Kansaneläkelaitos, 2024). In Finland, it has been estimated that the prevalence of depressive disorders is 5% (Rovasalo, 2025a), the same as it is globally (World Health Organization, 2025). The lifetime prevalence is 17%; although in females it can even reach 33% (Rovasalo, 2025a).

Common symptoms of depression are a general lack of hedonia, motivational drive, and reward experiences (Rovasalo, 2025a), pointing towards dopaminergic dysregulation in depression. Compared to controls, individuals with depression show lower levels of dopamine metabolite homovanillic acid in the cerebrospinal fluid (Reddy et al., 1992), although this finding is not consistent across all studies (Mann et al., 2012). Furthermore, dopaminergic stimulants, such as methylphenidate, show mood-elevating effects (Mann et al., 2012).

Serotonin affects mood and contributes to pleasant feelings about the present moment, while dopamine promotes interest in future possibilities (Bressan & Crippa, 2005; Lieberman & Long, 2018). Particularly, serotonin holds a central role in the current views on depression, as antidepressant drugs, such as selective serotonin reuptake inhibitors (SSRIs), commonly target the serotonin system (Belujon & Grace, 2017; Gershon et al., 2007).

Serotonergic changes, however, interact with the striatal and thalamic dopaminergic function (Penttilä et al., 2004; Tiihonen et al., 1996) and thus, dopamine may be involved in depression indirectly through the serotonergic link (Gershon et al., 2007; Hirvonen et al., 2008). On the one hand, the SSRIs aiming at increased mood through activation of the serotonin system have been argued to deactivate the dopaminergic signalling, promoting anhedonia that involves disturbed pleasure and drive for rewards (Belujon & Grace, 2017). Therefore, the benefits of activating the serotonin system may be counteracted with simultaneous deactivation of the dopamine system, possibly related to limited efficacy of SSRIs (Belujon & Grace, 2017). On the other hand, an SSRI citalopram was reported to decrease dorsal striatal D_2R availability, suggested to reflect increased SSRI-induced dopamine release (Tiihonen et al., 1996). It was further discussed that the blunted dopaminergic response observed in animal studies may have been induced by factors other than the

serotonergic intervention, such as microdialysis, or to be species specific, conflicting with the response in humans (Tiihonen et al., 1996).

Nevertheless, a meta-analysis concluded that in major depressive disorder, DAT availability is lowered, while dopamine synthesis capacity and – whether restricted to SSRI-free patients or not – D_2R availability is unaltered in the striatum (Mizuno et al., 2023). Moreover, the thalamic D_2R was concluded as intact in major depressive disorder (Mizuno et al., 2023). The D_2R availability of medicated subjects were not analysed alone, leaving the role of antidepressants uncertain (Mizuno et al., 2023).

As regards other neuropsychiatric conditions, the pathophysiology of depression likely involves several neural circuits and neurotransmitter systems (Belujon & Grace, 2017; Mann et al., 2012). Furthermore, depression apparently shows several subtypes with different biological, psychological, and social causes, and the set of symptoms vary between individuals (Rantala et al., 2018; Rovasalo, 2025a). These factors challenge pinpointing specific biological markers for depression.

2.4 Pharmacological effects on striatal dopamine

2.4.1 Dopamine-enhancing drugs

Drugs that enhance striatal dopaminergic function, such as dopamine precursor levodopa, dopamine agonists, and MAO inhibitors, effectively treat motor symptoms of PD (Gnegy, 2012; Poewe & Mahlknecht, 2020). However, these drugs also show aversive side effects, such as psychotic symptoms and disturbed impulse control (Poewe & Mahlknecht, 2020), including PG (Atula, 2023) and binge eating (Sáez-Francàs et al., 2016) in PD patients. Approximately one fourth of PD patients experience impulse control disorders (Sáez-Francàs et al., 2016).

Psychomotor stimulants, such as the amphetamine class of drugs, methylphenidate, and cocaine, augment extracellular monoamine, including dopamine, serotonin, and noradrenaline levels (Wolf, 2012). Amphetamine and methamphetamine reverse DAT function, and thus excite the dopamine release to the synaptic cleft (Harsing Jr, 2008; Volkow et al., 2009). Methylphenidate and cocaine inhibit dopamine reuptake by blocking dopamine transporters, prolonging and/or emphasising the dopamine receptor activation (Harsing Jr, 2008; Volkow et al., 2009). Low to moderate doses of psychomotor stimulants induce euphoria and increase talkativeness, vitality, and satiety (Wolf, 2012). High doses of psychomotor stimulants show aversive effects, such as repetitive motor activity (Wolf, 2012). Methamphetamine may also cause cognitive impairment (Wolf, 2012) and amphetamine trigger psychotic symptoms, such as hallucinations and delusions (Bressan & Crippa, 2005).

The conventional antidepressants are SSRIs, such as citalopram and fluoxetine, and serotonin and noradrenaline reuptake inhibitors (SNRIs), such as duloxetine and venlafaxine (Gershon et al., 2007; Socada, 2023a). These drugs enhance serotonin and noradrenaline levels (Gershon et al., 2007; Pittenger, 2012). However, serotonin and noradrenaline systems interact with the mesolimbic dopamine function and the antidepressant effect may be influenced by the indirect dopaminergic changes, such as elevated mesolimbic neurotransmission (Gershon et al., 2007).

Although the dopaminergic system is rarely the main target of current antidepressants, it may have potential to effectively treat depression, particularly via the striatal D_2R activation (Gershon et al., 2007). While the antidepressant bupropion inhibits the reuptake of noradrenaline and its precursor dopamine, possibly without affecting the serotonergic firing or postsynaptic receptors, it does not cause sexual dysfunction, weight gain, or sedation that are common side effects of antidepressants (Stahl et al., 2004). Furthermore, several dopaminergic drugs, such as dopamine agonist pramipexole, have shown antidepressant effects in clinical trials (Gershon et al., 2007).

2.4.2 Dopamine-inhibiting drugs

Antipsychotics that inhibit striatal dopaminergic function, typically via blocking the D_2R, reduce psychotic symptoms (Bressan & Crippa, 2005) and aggressive behaviour (Miczek & Fish, 2005). These D_2R antagonists show side effects, such as blunted motivation, cognitive disturbance, and dysphoria (Bressan & Crippa, 2005), as well as extrapyramidal symptoms dystonia, akathisia, and parkinsonism (Socada, 2023b).

Typical antipsychotics, such as haloperidol, affect both the nigrostriatal and the mesolimbic dopamine pathways (Jackson & Westlind-Danielsson, 1994). Typical antipsychotics are particularly common to cause motor side effects, compared to atypical antipsychotics, such as clozapine, that affect the mesolimbic but not the nigrostriatal pathway (Jackson & Westlind-Danielsson, 1994). This further supports the significance of (1) nigrostriatal pathway in motor functioning and (2) mesolimbic pathway in saliency attribution and psychotic symptoms.

Another difference to predominantly D_2R-blocking typical antipsychotics is that the atypical antipsychotics also block the serotonin receptor 5-HT_2 and D_1R more than D_2R, while increased D_2R antagonist occupancy promotes the extrapyramidal side effects bradykinesia, tremors, and rigidity encountered in PD (Coyle & Konopaske, 2012; Volkow et al., 1996). Thus, the atypical antipsychotics appear promising in reducing motor side effects. However, they show other undesirable side effects, such as type II diabetes and weight gain, and neither class of antipsychotics

effectively treat the negative and cognitive symptoms of schizophrenia (Coyle & Konopaske, 2012).

The main mechanisms of antiobesity medications are reducing appetite and controlling intragastrointestinal function (Gudzune & Kushner, 2024). One of the appetite-reducing options mitigating binge eating is naltrexone-bupropion that stimulates the proopiomelanocortin neurons (Gudzune & Kushner, 2024; Lutz & Asarian, 2017). In addition, naltrexone dampens the saliency attribution of food through inhibition of dopamine neurons and opioids in the mesolimbic reward pathway (Gudzune & Kushner, 2024; Lutz & Asarian, 2017). Bupropion increases synaptic dopamine via transporters rather than postsynaptic receptors (Gudzune & Kushner, 2024; Stahl et al., 2004). While gambling symptom severity is linked with elevated dopamine release and greater feelings of 'high' during gambling (Joutsa et al., 2012) that crucially contribute to development of addiction (Kaasinen et al., 2009), naltrexone, also used to treat substance addictions (Lutz & Asarian, 2017), has shown potential in treating PG, yet its effectiveness requires further validation (Ioannidis et al., 2025).

2.5 Summary of the literature

Striatal dopamine function is altered in several neurological and psychiatric disorders and has a specific role in motor function and motivation. It appears as a continuum, where mesocorticolimbic hypofunction induces motor symptoms, low motivational drive, blunted reward experiences, and anhedonia. In contrast, hyperfunction promotes euphoria, attributions of saliency, psychotic symptoms, and impulsive or incontrollable behaviour, such as PG and aggressive confrontations. Several disorders display these symptoms related to hypo- and hyperactive dopaminergic function. However, specific clinical cohorts have been investigated in isolation and comparative studies in multi-cohort datasets are lacking.

The existing literature also points towards age-related dopaminergic decline and higher dopamine concentration in females versus males. While age is a clear risk factor for some of the disorders, such as younger age for schizophrenia and older age for PD, sex may also predispose individuals to certain neurological and psychiatric conditions with altered striatal dopaminergic function.

Understanding the interindividual and clinical dopaminergic variation is imperative for treatment planning and understanding the neurological and psychiatric aetiology.

3 Aims

The aim of this thesis was to generate standard retrospective cohorts of baseline [^{18}F]fluorodopa (n = 220) and [^{11}C]raclopride (n = 437) PET images, and use those cohorts to:

1. Estimate the effects of age, sex, BMI, and clinical status as PD, schizophrenia, severe violent behaviour, PG, or depression, on the striatal dopaminergic system.
2. Investigate regional coupling in the dopamine system through correlations of (1) dopamine synthesis capacity and (2) D_2R availability between striatal and thalamic regions in healthy and clinical cohorts.
3. Compare PET estimates of dopamine synthesis capacity and D_2R availability from (1) different scanner types in multi-scanner datasets and (2) template versus MRI-based quantification approaches.
4. Generate brain atlases of the dopamine synthesis capacity, and the D_2R availability of healthy and clinical cohorts, and share them via NeuroVault (Gorgolewski et al., 2015).

4 Materials and Methods

4.1 Data

The imaging data consist of baseline [^{18}F]fluorodopa (Study I) and [^{11}C]raclopride (Studies II–III) *in vivo* PET scans of healthy and clinical human cohorts. The PET scans were acquired at the Turku PET Centre between the years 1989–2019 using the scanners (1) Emission Computed Axial Tomograph (ECAT) 931 by CTI PET Systems or Siemens, (2) GE Advance by General Electric, (3) High Resolution Research Tomograph (HRRT) by CTI PET Systems or Siemens, (4) High Resolution Plus (HR+) by CTI PET Systems or Siemens, (5) GE Discovery Volume Computed Tomography (VCT) PET/CT by General Electric, and (6) GE Discovery 690 PET/CT by General Electric. **Table 1** shows the number of subjects per scanner in Studies I–III.

Table 1. Number of observations (n) per scanner in Studies I–III. The number of observations (subjects) in each cohort are further specified as HC = healthy controls, and subjects with Parkinson's disease (PD), schizophrenia (SCH), overweight (OW), pathological gambling (PG), depression (DEP), and severe violent behaviour (VIO). *GE Discovery. The approximate year when the scanner was acquired for the Turku PET Centre is given in parenthesis. Original table summarising the data of the original publications I–III (Malén et al., 2022; Malén et al., 2024; Malén et al., 2026).

Study	n	ECAT 931 (1988)	GE Advance (1996)	HRRT (2003)	HR+ (2003)	*VCT PET/CT (2005)	*690 PET/CT (2010)
I	220	n = 67: 52 HC 15 PD	n = 127: 26 HC 101 PD	n = 26: 16 HC 10 PD	0	0	0
II	156	0 HC	36 HC	76 HC	18 HC	6 HC	20 HC
III	437	n = 110: 50 HC 54 PD 4 SCH 2 OW	n = 134: 69 HC 3 SCH 12 PG 12 DEP 38 OW	n = 97: 81 HC 16 OW	n = 25: 13 HC 6 PD 6 OW	n = 27: 9 HC 10 VIO 8 OW	n = 44: 17 HC 27 OW

We used the following data: the PET imaging data including the information of the scanner type used, and information of the subject age, sex, height, weight, and clinical status as healthy control, PD, schizophrenia, severe violent behaviour, PG, depression, or overweight. These data were retrieved from an in-house imaging data archive Aivo (https://aivo.utu.fi) that is secured by the IT-protocols of the Turku University Hospital. Data from Aivo were supplemented with patient record data used to confirm the clinical status and search for additional information, such as symptom duration at scan. The patient record data were collected from the Finnish health care documentation by researchers with sufficient expertise in medicine and applicable permissions to access the data.

4.2 Subjects

4.2.1 Study I

In Study I, we investigated the dopamine synthesis capacity in healthy and PD cohorts using baseline [^{18}F]fluorodopa PET images. The sample involved 220 subjects with available imaging data and information of age, sex, BMI, and clinical status as healthy control or PD patient. Descriptive statistics of the sample are given in **Table 2**. Information on smoking status, handedness, PD duration, motor symptom severity, and medication use was not systematically available. Among the healthy controls, 11 subjects were non-psychotic first-degree relatives of individuals with schizophrenia. The injected dose generally ranged from 110 to 309 megabecquerels (MBq), while for one subject it was lower (74 MBq, BMI = 19, no K_i^{ref} outliers based on visual inspection), and the information was not available for three scans (no K_i^{ref} outliers based on visual inspection).

Table 2. Descriptive statistics in the sample (n = 220) of Study I. HC = healthy controls, PD = patients with Parkinson's disease, n = number of observations, SD = standard deviation. Modified from the original publication I (Malén et al., 2026).

	Age (years)			**Sex (n)**		**Body mass index (kg/m^2)**		
	Mean	SD	Range	Male	Female	Mean	SD	Range
HC (n = 94)	46	15	20–79	46	48	25	4	18–39
PD (n = 126)	63	10	33–80	78	48	26	4	19–44

4.2.2 Study II

In Study II, we assessed the striatal D_2R availability in healthy controls using baseline [^{11}C]raclopride PET images. The primary sample comprised of 156 subjects with available imaging data and information of age, sex, and BMI. The range of the injected dose in the sample was 183–538 MBq. Descriptive statistics of the sample are shown in **Table 3**. Information on smoking status or handedness was not systematically available.

Table 3. Descriptive statistics in the sample of Study II, n = number of observations, SD = standard deviation. Modified from the original publication II (Malén et al., 2022).

Sex	**Age (years)**			**Body mass index (kg/m^2)**		
	Mean	SD	Range	Mean	SD	Range
Male (n = 120)	25	5	19–56	24	3	19–38
Female (n = 36)	37	14	20–71	22	3	18–33

4.2.3 Study III

In Study III, we assessed the D_2R availability in healthy and clinical cohorts using baseline [^{11}C]raclopride PET images. The sample consisted of 437 subjects (294 males, 143 females), including healthy controls (n = 239, of whom 116 were involved in Study II), and subjects with PD (n = 60), schizophrenia (n = 7), severe violent behaviour, i.e., prison sentence for violence (n = 10), PG (n = 12), depression (n = 12), and overweight or obesity (n = 97, of whom 40 were involved in Study II, as they were assigned to the overweight cohort due to BMI ≥ 25). The subjects were aged 19–82 years (**Table 4**). BMI range was 18–49 in the 291 subjects (67% of the total sample) for whom we had information available. The range of the injected dose in the sample was 95–570 MBq.

Table 4. Age in years of the cohorts presented separately for males and females in the sample of Study III, n = number of observations, SD = standard deviation, NA = not applicable. Modified from the original publication III (Malén et al., 2024).

	Male (n = 294)				**Female (n = 143)**			
	n	Mean	SD	Range	n	Mean	SD	Range
Healthy controls (n = 239)	174	28	11	19–78	65	41	16	19–82
Parkinson's disease (n = 60)	31	62	12	34–82	29	60	11	41–81
Schizophrenia (n = 7)	3	22	3	19–25	4	36	13	24–53
Severe violent behaviour (n = 10)	10	31	7	24–46	0	NA	NA	NA
Pathological gambling (n = 12)	12	32	8	23–49	0	NA	NA	NA
Depression (n = 12)	3	38	10	25–48	9	41	5	34–50
Overweight (n = 97)	61	29	9	19–56	36	43	13	23–74

4.3 Positron emission tomography

PET is incomparable technology which enables *in vivo* brain imaging at a molecular level by measuring tracer concentration in tissue (Das, 2015). Whereas MRI enlightens anatomical structures and functional MRI (fMRI) detects overall activity, such as blood and oxygen flow, PET can unravel specific neurotransmitter mechanisms and structures, such as the dopamine synthesis capacity and D_2R availability (Das, 2015).

PET scanning involves a radioligand, that is a short-lived radioactive tracer (Das, 2015). Each tracer molecule consists of a molecule with certain biological property that serves for the target of interest, and a positron-emitting radiolabel, radionuclide (Das, 2015). The tracer [^{18}F]fluorodopa, is a fluorine-18, noted as [^{18}F], labelled analogue for L-DOPA that becomes converted into dopamine in tissue via AADC-activity (Oikonen, 2023a). The tracer [^{11}C]raclopride is a carbon-11, noted as [^{11}C], labelled dopamine analogue in the sense that it binds to striatal D_2Rs, particularly the receptor types 2 and 3 (Oikonen, 2023b). During these processes of AADC activity and D_2R binding, the tracer concentration in tissue is recorded with PET (Das, 2015).

The tracer radioactivity is short-lived, as it decays to zero rather quickly, depending on the half-life of the radionuclide. Half-life is the time in which the radioactivity decays to a half from the initially injected radioactivity (Das, 2015). The half-life is 110 minutes for fluorine-18 and 20 minutes for carbon-11 (Das, 2015). As the radioactivity decays through positive beta decay, positively charged positrons are emitted (Das, 2015). After a few millimetres travel from the emission,

the positron encounters a negatively charged electron (Das, 2015). In the following annihilation reaction, the positron and the electron form a pair of 511 keV gamma photons (rays) that travel to opposite directions until they hit the gamma detector in the scanner ring around the brain (Das, 2015). The annihilation events can be localised based on the time recordings of the detector ring (Das, 2015). Finally, the radioactivity counts are transformed into biological measures, such as dopamine synthesis capacity or D_2R availability (Das, 2015). The principles of PET are illustrated in **Figure 2**.

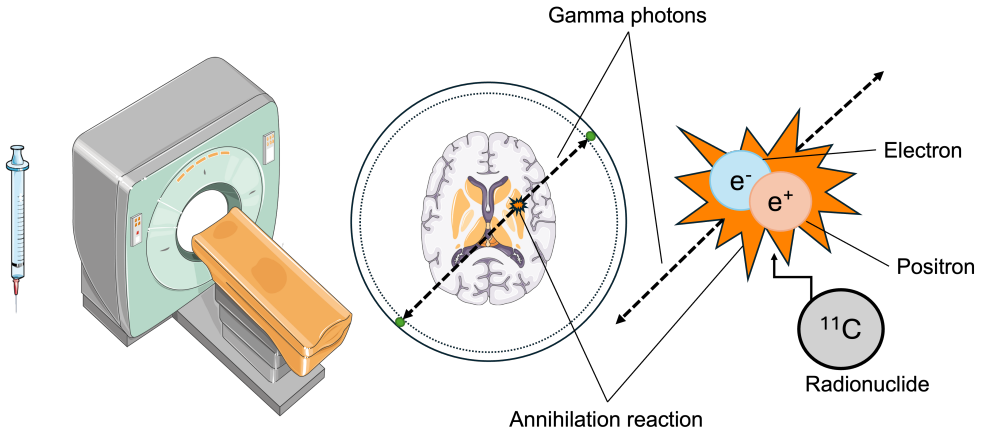

Figure 2. PET imaging is performed after tracer injection. The radionuclide emits a positron that encounters an electron. In the annihilation reaction, a pair of gamma photons travel to opposite directions, finally hitting the gamma detector on the scanner ring. Created in PowerPoint version 16.105.3 (26020123) using and combining several objects from Servier Medical Art, https://smart.servier.com/citation-sharing/, provided by Servier and licensed under CC BY 4.0 https://creativecommons.org/licenses/by/4.0/, and inspired by the Doctoral theses of MD Tatu Kantonen (Kantonen, 2022), and PhD Tomi Karjalainen (Karjalainen, 2019).

4.3.1 Quantification of [^{18}F]fluorodopa uptake

The rate of dopamine synthesis, the dopamine synthesis capacity, can be measured by quantifying the accumulation of [^{18}F]fluorodopa in the striatum (Volkow et al., 1996). In Study I, the [^{18}F]fluorodopa uptake was quantified using the Patlak method where the influx rate constant K_i^{ref} (Gjedde et al., 1991) was estimated using multiple time graphical analysis (Patlak & Blasberg, 1985) in voxel and regional level within 15 to 60 minutes by using occipital cortex as the reference region (Nurmi et al., 2001). The image preprocessing and modelling were conducted using an in-house automated image analysis pipeline Magia (Karjalainen et al., 2020) running on MATLAB (The MathWorks Inc.).

The Patlak-based K_i^{ref} estimate may drop below zero, possibly due to limited signal-to-noise ratio of filtered back projection reconstruction, particularly in regions with low dopamine synthesis capacity. We did not remove observations with negative K_i^{ref} estimates to avoid a positive bias on our estimates. Five subjects (four PD patients and one healthy control) had negative observations in the thalamus and one of the same four PD patients had a negative observation also in the putamen.

The functional information of PET is localised using an anatomical reference that conventionally is the subject's MRI. However, as most subjects did not have their MRI available and as we wanted to maximise the sample size, the spatial normalisation was primarily conducted using a common PET template that was based on the average MRI of 18 healthy controls of the sample, all imaged with HRRT. For validation, however, we compared the K_i^{ref} estimates from MRI and template-based normalisation methods in the sample of subjects with MRI available (n = 45, including 22 healthy controls and 23 PD patients). Most of the images (38/45) were acquired with HRRT, while the remaining (7/45) scans were imaged with GE Advance.

4.3.2 Quantification of [^{11}C]raclopride uptake

In Studies II and III, regional specific binding of [^{11}C]raclopride was quantified as a nondisplaceable binding potential (BP_{ND}), using simplified reference tissue model (SRTM) and cerebellum from the Harvard-Oxford atlas (Jenkinson et al., 2012) as the reference region (Lammertsma & Hume, 1996). BP_{ND} refers to the ratio at equilibrium of specifically bound radioligand to that of nondisplaceable radioligand in tissue (Innis et al., 2007). BP_{ND} is scaled so that 0 means equal binding, 1 reflects 100% more binding (and so forth) in the ROI versus the reference region (Innis et al., 2007). BP_{ND} reflects density of available receptors that are not occupied by endogenous dopamine (Innis et al., 2007). It is estimated that 38% of the D_2R antagonist, such as [^{11}C]raclopride, binding is sensitive to competition by endogenous dopamine (Egerton et al., 2009). BP_{ND} is also affected by the affinity of the radioligand and the receptor (Innis et al., 2007). As a D_2R antagonist, the radioligand [^{11}C]raclopride binds to both low-affinity and high-affinity striatal D_2Rs, particularly to the receptor subtypes 2 and 3, enabling their precise quantification without high affinity to D_1Rs or cortical D_2Rs (Egerton et al., 2009; Oikonen, 2023b). The image preprocessing and modelling were again performed with Magia (Karjalainen et al., 2020).

Study II: Primarily, the images were spatially normalised using the subject-specific MRI. Additionally, we derived alternative BP_{ND} estimates spatially normalising the images using a common PET template. This allowed us to compare the BP_{ND} estimates produced by the two methods. The comparison was done in the

sample that could be quantified with both methods (n = 189), including scans from GE Advance (n = 37), HRRT (n = 96), HR+ (n = 18), GE Discovery VCT PET/CT (n = 17), and GE Discovery 690 PET/CT (n = 21). The validation sample was larger than the primary sample (n = 156), as subjects excluded from the primary sample due to missing information, such as BMI or injected dose, could be included here in the simple comparison of BP_{ND} estimates.

Study III: The spatial normalisation was primarily done with the template-based method because of missing MRIs and successful validation of the template-based method in Study II. The PET template used in Studies II and III was based on an average MRI of 187 (+2) subjects. In Study III, the BP_{ND} estimates from the two spatial normalisation methods were again compared in those cases with both methods applicable. The validation sample consisted of 249 subjects, including 142 healthy controls, five PD patients, 10 subjects with severe violent behaviour, 12 subjects with PG, and 80 subjects with overweight. The scans were imaged with GE Advance (n = 59), HRRT (n = 96), HR+ (n = 23), GE Discovery CT PET/CT (n = 27), and GE Discovery 690 PET/CT (n = 44).

4.3.3 Regions of interest

Due to reliable quantification of striatal dopamine synthesis capacity (Egerton et al., 2010; Volkow et al., 1996) and baseline D_2R availability (Alakurtti et al., 2015; Hietala et al., 1999; Hirvonen et al., 2003), the data in Studies I–III were analysed in the following regions of interest (ROI): striatal caudate nucleus (caudate), nucleus accumbens (accumbens), and putamen, as well as extrastriatal, yet proximal thalamus that possibly shows slightly less reliable quantification of the synthesis capacity (Egerton et al., 2010; Volkow et al., 1996) and D_2R availability (Alakurtti et al., 2015; Hirvonen et al., 2003) compared to the striatum. The ROIs are visualised on a brain map in **Figure 3**.

When the spatial normalisation was done with the subject-specific MRI, anatomical ROIs were extracted using FreeSurfer (Fischl, 2012; https://surfer.nmr.mgh.harvard.edu/). When the template-based method was used instead, the bilateral ROIs were defined using the Harvard-Oxford atlas (Jenkinson et al., 2012), which was transformed into a subject native space using the in-house PET templates.

In Studies I and III, we used the mean of the left and right hemisphere PET estimates in our statistical analyses. Data supporting the validity of the mean hemispheric estimates are presented in the original publications (Studies I, III). In Study II, we used hemisphere-specific BP_{ND} estimates in our statistical analyses.

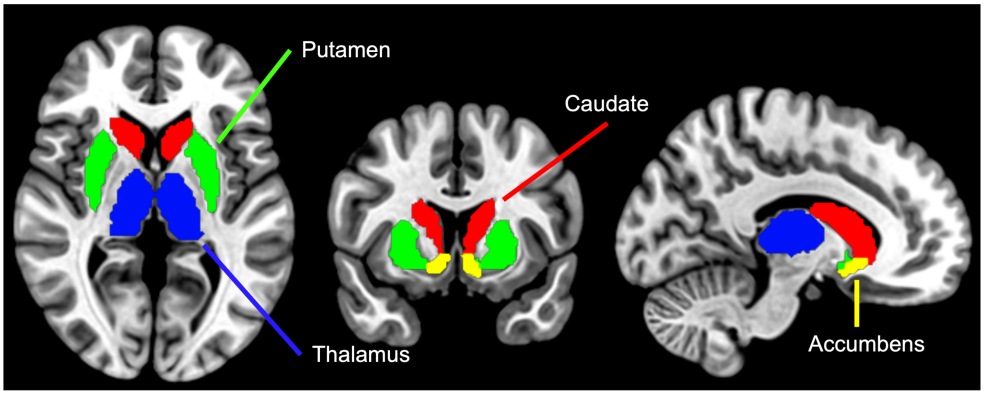

Figure 3. Regions of interest used in Studies I–III, based on AAL3 atlas downloaded from: https://www.oxcns.org/aal3.html (Rolls et al., 2020); putamen in green, thalamus in blue, caudate in red, and ventral striatum (accumbens) in yellow, overlaid on the MNI152 template (Mazziotta et al., 2001). Original figure created using MRIcroGL (Rorden, 2025) and PowerPoint version 16.105.3 (26020123).

4.4 Statistical analysis

In Studies I–III, the main analysis method was general linear (regression) modelling (GLM) without (Study I) or with (Studies II, III) mixed effects. Bayesian approach was applied to carry out the GLM. Additionally, we used correlation analysis to descriptively assess the interregional PET estimate (K_i^{ref} or BP_{ND}) coupling profiles, and to compare the two alternative spatial normalisation methods. The statistical analyses were applied in RStudio (Posit team, 2023), built on programming language R (R Core Team, 2025).

4.4.1 Correlation analyses

To assess the dopaminergic coupling profiles, we analysed the interregional correlation of (1) the dopamine synthesis capacity (two-sided Pearson in Study I) and (2) the D_2R availability (one-sided Spearman in Study III), separately in healthy and clinical cohorts.

We also compared the PET estimates from the two alternative spatial normalisation methods using correlation: one-sided Pearson and Spearman in Study I using [^{18}F]fluorodopa data of healthy and PD cohorts, and one-sided Spearman in Study III using [^{11}C]raclopride data of healthy and clinical cohorts. In Study II, we visually inspected the correlations in [^{11}C]raclopride data of healthy controls. For the consistency of the thesis, (one-sided Pearson) correlations were estimated also in the [^{11}C]raclopride data of healthy controls in Study II, although it was not performed in the original publication II.

We used Shapiro-Wilk testing and sample sizes to decide whether Pearson or Spearman correlation was used. Our prior assumptions, described in the original publications I and III, determined whether the correlations were analysed as one-sided or two-sided. We carried out the normality testing (Shapiro-Wilk) and the correlation analyses with R packages stats (R Core Team, 2025) and corrplot (Wei, 2021), respectively.

4.4.2 Bayesian general linear models

To model the demographic and clinical effects on regional PET data, we used GLM with fixed and random effects. Random effects are varying intercepts and/or slopes, making it mixed effects modelling (Harrison et al., 2018). Mixed effects modelling enables (1) adjustment of grouping structure in the dependent variable when the within-group variation is smaller than the between-group variation, and (2) utilisation of shrinkage toward the mean, meaning the random effects are pooled toward each other, which is useful particularly when the average effect is considered more reliable than the single effects (Harrison et al., 2018).

We conducted the modelling in a Bayesian fashion, as it enables (1) estimation of the entire parameter (such as regression coefficient) probability distribution, instead of describing the probability of the given sample conditional on a fixed parameter value, (2) utilisation of prior knowledge in the modelling via prior probability distributions, and (3) modelling without multiple comparison corrections, unlike the conventional frequentist framework (Gelman et al., 2012). Although the work of Gelman and colleagues (Gelman et al., 2012) focuses on why corrections are not needed in hierarchical Bayesian modelling, altogether the Bayesian framework can be applied without *p*-values, typically corrected for multiple comparisons. We conducted the Bayesian GLM modelling using the R package brms (Bürkner, 2017, 2018, 2021), utilising RStan (Stan Development Team, 2023), while the details and codes to perform the modelling are provided in the supplementary materials of the original publications (I – III).

4.4.2.1 Study I

In Study I, we investigated the effects of age, sex, BMI, and PD on dopamine synthesis capacity, estimated as [^{18}F]fluorodopa K_i^{ref}. In separate regional models, we estimated the fixed, population-level, main effects that were slopes of age, sex as difference between males and females, BMI, and PD as difference between PD patients and healthy controls, on K_i^{ref}.

Despite calibration and standardisation, different PET scanners may induce variation in the data, because the scanners differ in their properties, such as

sensitivity and resolution, which may affect the acquired K_i^{ref} estimate. To address this potential variation in the same regional models, we also estimated the fixed main effect of scanner on K_i^{ref}, as we wanted to estimate the scanner effect, as well as the effects of age, sex, BMI, and PD independently of the scanner type used. We used standardised continuous predictors (age and BMI) and regional K_i^{ref} in the modelling. Log-transformation was not used due to a few negative K_i^{ref} estimates, while negative values cannot be log-transformed.

GLM was applied here as non-mixed, as we did not involve random effects in the modelling. The number of scanners (n = 3), and ROIs (n = 4) in the data were small considering that when modelled as a random effect, such as a random intercept for scanners, the variable levels (e.g. ECAT 931, HRRT, GE Advance) represent a random sample of all possible scanners whose intercepts follow a common distribution (Harrison et al., 2018). The recommended minimum of random factor levels is five (Harrison et al., 2018). Furthermore, if the ROI-specific intercepts (or slopes) are regarded as somewhat independent, and not as a random sample from a common distribution, estimating the effects of interest independently in separate regional models may be a good idea.

We set normal prior with expected value (μ) of 0, and standard deviation (SD) of 1 for the regression coefficients (for age, sex, BMI, clinical status of the subject as PD patient or healthy control, and scanner). For the remaining parameters, we used the default priors of brms, described as weakly informative (Bürkner, 2017).

Using alternative priors suggesting negative effects of male sex, BMI, and PD, did not essentially change our findings. We also assessed the possible non-linearity of the age and BMI effects, as well as interaction of age and sex. More details on these additional analyses are given in the original publication I.

4.4.2.2 Study II

In Study II, we investigated the effects of age, sex, and BMI on D_2R availability, estimated as [^{11}C]raclopride BP_{ND}, in healthy individuals. The effects of age, sex and BMI on regional BP_{ND} were estimated separately in the left and right hemisphere using interaction terms. As interactions are reciprocal, the interaction of sex and hemisphere also allows the assessment of lateralisation separately in males and females, which is not further discussed here but in the original publication II (Malén et al., 2022).

BP_{ND} estimates were log-transformed, as the log-transformation allows direct estimation of the relative, such as 10%, rather than absolute change in BP_{ND} across predictor levels. Relative versus absolute change is more intuitive regarding BP_{ND} that is a ratio that describes receptor availability, and is not a direct measure of

receptor density (Innis et al., 2007). For the sake of conciseness, we simply refer to the linear effects on a logarithmic scale as linear.

To estimate the effects of age, sex, BMI and hemisphere, we used regionally varying random slopes (random slopes for ROIs). In addition, subjects, scanners, and ROIs, were all modelled as random intercepts, allowing the intercept to vary by subject, scanner, and ROI. We also applied a random intercept for the combination of scanners and ROIs, to allow regionally varying scanner effects. For the residual variances, we applied the same structure of the random intercepts, except for subject, as we did not expect the residuals to vary by subject. Thus, the residuals were allowed to vary by scanner, ROI, and ROI within each scanner. We used normal distributions ($\mu = 0$, SD = 1) as priors for all regression coefficients and half-normal distributions ($\mu = 0$, SD = 1) as priors for all SD parameters of the random effects. On all other parameters, default priors of brms were used.

While the number of scanners (n = 5) and ROIs (n = 4) were still small, we modelled these predictors as random effects. This is because we wanted to utilise the shrinkage towards the mean, particularly shrinkage of possibly the least reliable thalamic effects.

4.4.2.3 Study III

In Study III, we compared the D_2R availability in healthy controls and in individuals with PD, schizophrenia, severe violent behaviour, PG, depression, and overweight. In one primary model, we analysed the cohort differences in regional log-BP_{ND}, while adjusting for age, sex, and scanner. Specifically, we applied the cohort, standardised age, and sex as fixed main effects. We applied random slopes for these effects, allowing them to vary by region, similarly as in the Study II where we allowed the regionally varying effects of interest. We also applied random intercepts for subjects, scanners, ROIs, and scanner-ROI combinations, similarly as in Study II. This means that we allowed the BP_{ND} intercept to vary by subject, region, scanner, and region within each scanner. Also identical to Study II, for the residual variances, we applied random intercepts for scanners, ROIs, and the scanner-ROI combinations, but not for subjects as individual differences were not expected in the residuals.

In the absence of appropriate priors for Bayesian statistical inference from independent data, we gave a normal prior ($\mu = 0$, SD = 1) for the fixed effects of age, sex, and cohort. For the SDs of the random effects, we set the same normal prior. As SD is always positive, the brms package automatically restricts this prior to positive values, making it a half-normal distribution (Bürkner, 2017, 2018, 2021). For the rest of the modelling parameters, we used the default priors of brms (Bürkner, 2017).

5 Results

5.1 Study I: Dopamine synthesis in Parkinson's disease and healthy cohorts

The whole-brain mean and ROI-specific coefficient of variation maps for dopamine synthesis capacity, estimated as [^{18}F]fluorodopa K_i^{ref}, are shown in **Figure 4**. The regional K_i^{ref} descriptives, presented separately for healthy and PD cohorts, are given in **Table 5**. The maps demonstrate lower K_i^{ref} estimates in PD patients versus healthy controls and greater variation in thalamic versus striatal estimates across the subjects in both cohorts. The empty spots visible in the thalamic coefficients of K_i^{ref} variation stem from the few negative observations. The three-dimensional whole-brain maps of mean K_i^{ref} estimates, presented separately for healthy controls and PD patients, are available in NeuroVault (https://identifiers.org/neurovault.collection:21998).

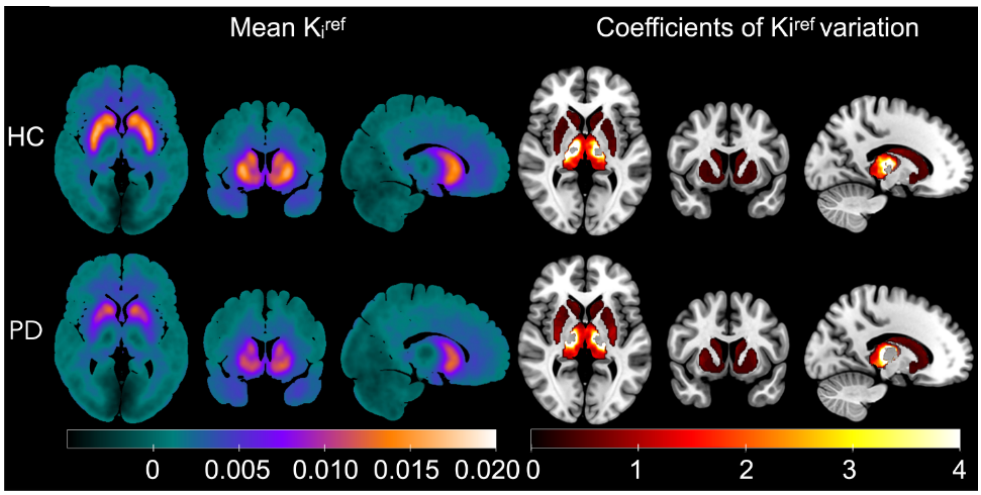

Figure 4. Maps of [^{18}F]fluorodopa influx rate constant (K_i^{ref}) estimates. Left: mean K_i^{ref} maps. Right: coefficient of K_i^{ref} variation (standard deviation / mean) maps within the regions of interest using the Harvard-Oxford atlas (Jenkinson et al., 2012) masks. HC = healthy controls (n = 94), PD = Parkinson's disease patients (n = 126), n = number of observations. The maps are overlaid on the MNI152 template (Mazziotta et al., 2001). Created using SPM12 (Functional Imaging Laboratory, 2018), MATLAB (The MathWorks Inc.), MRIcroGL (Rorden, 2025), and Keynote version 12.2.1 (7035.0.161). Modified from the original publication I (Malén et al., 2026).

Table 5. The regional [^{18}F]fluorodopa influx rate constant (K_i^{ref}) means, standard deviations (SD), and ranges, presented separately for healthy (HC, n = 94) and Parkinson's disease (PD, n = 126) cohorts, n = number of observations. Original table.

	Mean		**SD**		**Range**	
	HC	PD	HC	PD	HC	PD
Caudate	0.0104	0.0077	0.0025	0.0021	0.0044–0.0191	0.00006–0.0130
Accumbens	0.0119	0.0105	0.0028	0.0027	0.0057–0.0218	0.0002–0.0188
Putamen	0.0128	0.0079	0.0025	0.0026	0.0087–0.0218	-0.0001–0.0148
Thalamus	0.0020	0.0018	0.0008	0.0008	-0.0005–0.0042	-0.0009–0.0035

5.1.1 Regional effects of Parkinson's disease, age, sex, and body mass index

Bayesian GLM was used to estimate the effects of PD, age, sex, and BMI on regional dopamine synthesis capacity, estimated as K_i^{ref} (**Table 6** and **Figure 5**). Based on the modelling, the K_i^{ref} estimates were lower in PD patients compared to healthy controls across the striatal ROIs, where the estimates also declined consistently with increasing age and were higher in females versus males. There was subtle support for positive association between BMI and striatal K_i^{ref} estimates, while only in the caudate, did the 95% posterior interval not cross zero. In the putamen and accumbens, the 80% posterior interval did not overlap with zero. We did not observe a BMI effect in the thalamus.

Table 6. Posterior medians for the effects (regression coefficients) of age, sex, BMI, and Parkinson's disease (PD) on regional original-scale [^{18}F]fluorodopa influx rate constant (K_i^{ref}), *95% posterior interval did not cross zero. Parenthesis: For the continuous effects of age and BMI, the regression coefficient is given as a percentage of mean regional K_i^{ref} across the sample, and for the categorical effects of sex, and PD, as a percentage of mean regional K_i^{ref} in the reference category that is females and healthy controls, respectively. Modified from the original publication I (Malén et al., 2026).

	PD patients	**Age**	**Sex**	**Body mass index**
	Vs controls	Per 15 years	Males vs females	Per 4 units (kg/m^2)
Caudate	-0.002* (21%)	-0.0008* (9%)	-0.0007* (8%)	0.0003* (3%)
Accumbens	-0.002* (13%)	-0.0004* (4%)	-0.0007* (6%)	0.0003 (3%)
Putamen	-0.005* (41%)	-0.0005* (5%)	-0.0007* (7%)	0.0002 (2%)
Thalamus	-0.0003* (15%)	-0.0002* (8%)	-0.0002* (11%)	< 0.0001 (0.4%)

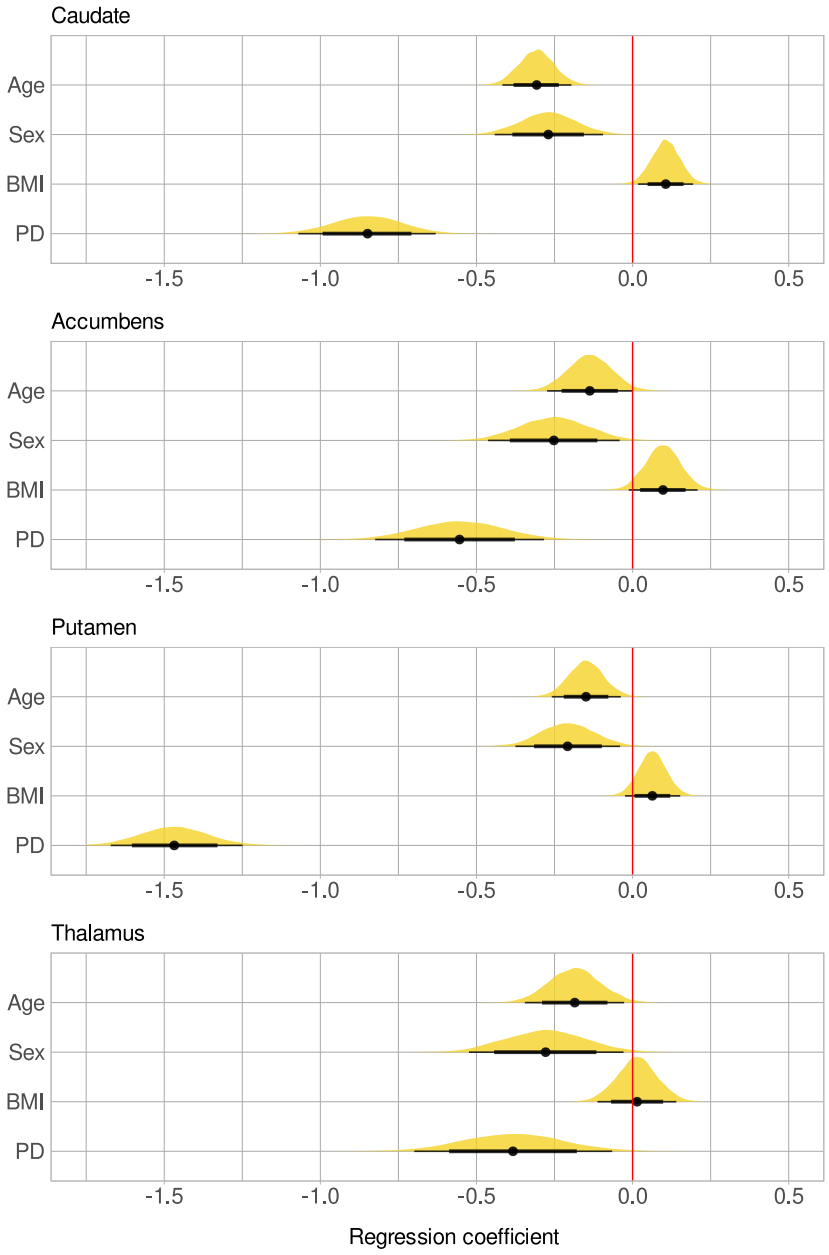

Figure 5. Posterior distributions for the effects (regression coefficients) of age, sex (males versus females), body mass index (BMI), and PD (Parkinson's disease patients versus controls) on regional [^{18}F]fluorodopa influx rate constant (K_i^{ref}). The figure shows posterior medians (point) and intervals (95% thin and 80% thick line) on a standardised scale. Created using R packages ggplot2 (Wickham, 2016), tidybayes (Kay, 2023b), and ggdist (Kay, 2023a) in RStudio (Posit team, 2023) running on R (R Core Team, 2025). Modified from the original publication I (Malén et al., 2026).

5.1.2 Interregional correlations

Interregional K_i^{ref} Pearson correlations were estimated separately for healthy controls and PD patients within each scanner (**Figure 6**). Particularly with the newer scanners HRRT and GE Advance, K_i^{ref} estimates were positively correlated across the ROIs in both cohorts.

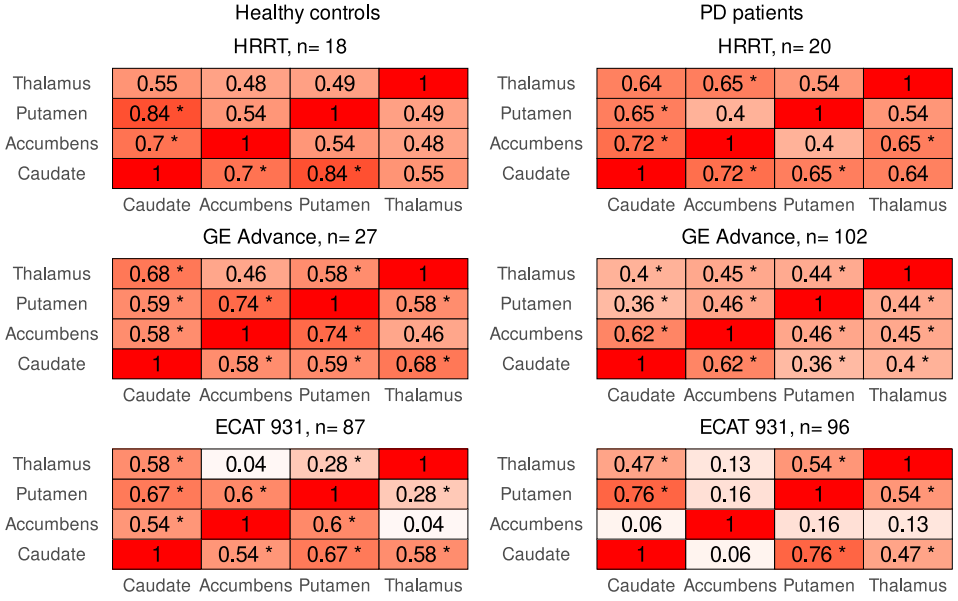

Figure 6. Interregional [^{18}F]fluorodopa influx rate constant (K_i^{ref}) Pearson correlations with number of observations (n), *uncorrected *p*-value < 0.01. Created using R package corrplot (Wei, 2021) in RStudio (Posit team, 2023) running on R (R Core Team, 2025). Modified from the original publication I (Malén et al., 2026).

5.1.3 Variation from scanner type

The scanners ECAT 931, GE Advance, and HRRT showed differences in the acquired K_i^{ref} estimates, as demonstrated in **Figure 7**. In addition, the Bayesian GLM pointed towards a substantial effect of the scanner, that is K_i^{ref} estimates in ECAT 931 < in GE Advance < in HRRT, suggesting higher K_i^{ref} estimates with newer scanners. The effect sizes from the GLM are demonstrated in **Table 7** and **Figure 8**.

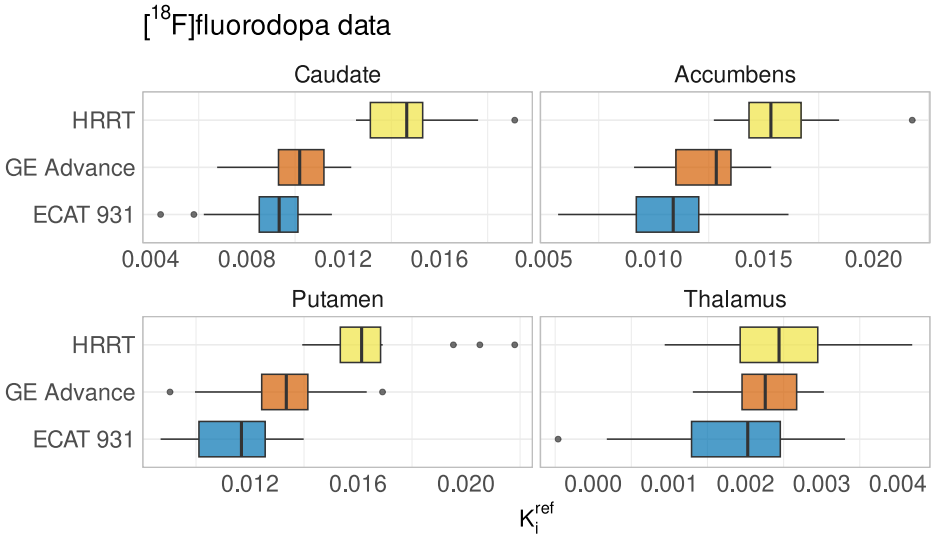

Figure 7. Regional [^{18}F]fluorodopa influx rate constant (K_i^{ref}) estimates from each scanner type, ECAT 931 (n = 52), GE Advance (n = 26), and HRRT (n = 16) in a sample of 94 healthy controls in Study I, n = number of observations. Each boxplot shows the median (middle line), and 25% (lower hinge) and 75% (upper hinge) quartiles. The lower whisker extends from the hinge to the smallest value at most 1.5 * IQR of the hinge. The upper whisker extends from the hinge to the largest value no further than 1.5 * IQR from the hinge. IQR = Inter-quartile range, meaning the distance between the 25% and 75% quartiles. Original figure created using R package ggplot2 (Wickham, 2016) in RStudio (Posit team, 2023) running on R (R Core Team, 2025).

Table 7. Posterior medians for the effects of GE Advance and HRRT on regional original-scale [^{18}F]fluorodopa influx rate constant (K_i^{ref}), compared to the reference scanner ECAT 931, *95% posterior interval did not cross zero. In parenthesis, the posterior median is given as a percentage of the mean regional K_i^{ref} in the reference category ECAT 931. Modified from the original publication I (Malén et al., 2026).

	GE Advance vs ECAT 931	**HRRT vs ECAT 931**
Caudate	0.002* (22%)	0.005* (56%)
Accumbens	0.002* (20%)	0.005* (50%)
Putamen	0.003* (25%)	0.004* (39%)
Thalamus	0.0006* (39%)	0.0008* (50%)

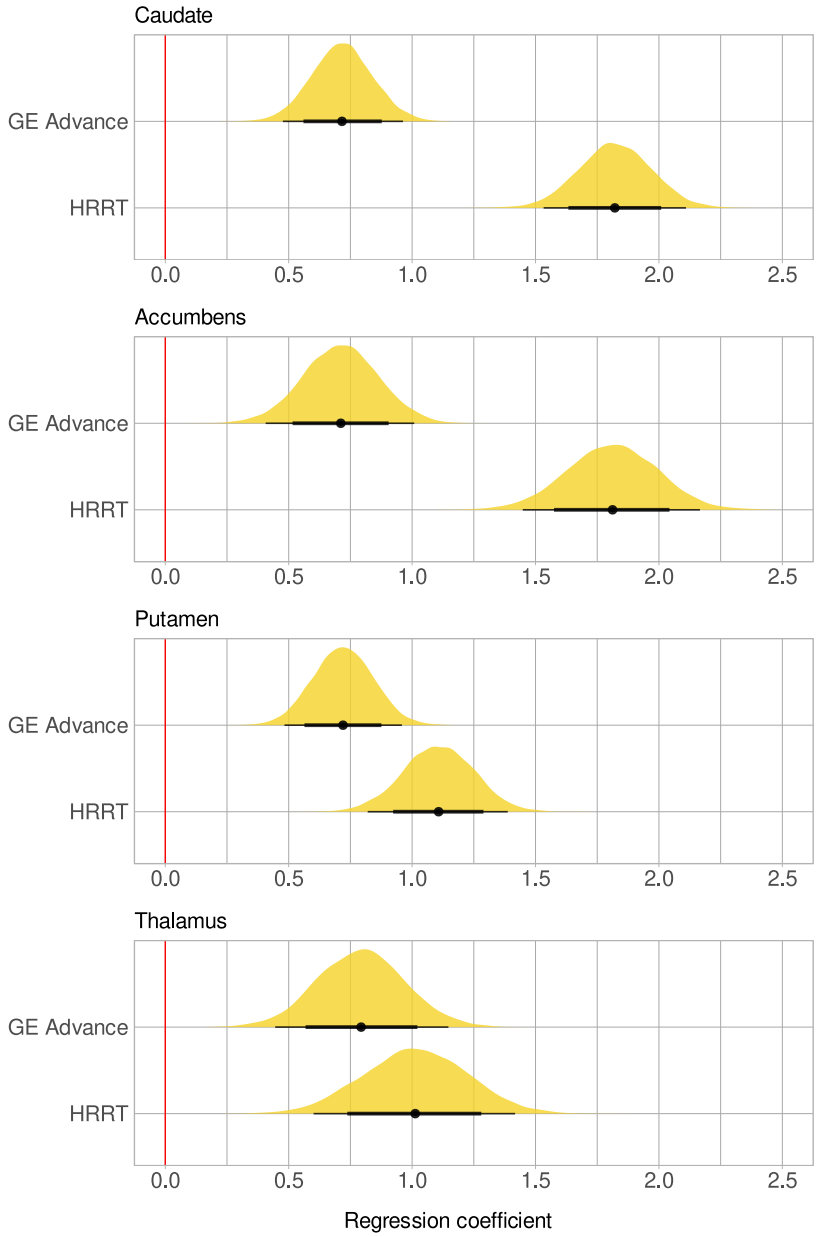

Figure 8. Posterior distributions for the effects of GE Advance and HRRT versus ECAT 931 on [^{18}F]fluorodopa influx rate constant (K_i^{ref}). The figure shows posterior medians (point) and intervals (95% thin and 80% thick line) on a standardised scale. Created using R packages ggplot2 (Wickham, 2016), tidybayes (Kay, 2023b), and ggdist (Kay, 2023a) in RStudio (Posit team, 2023) running on R (R Core Team, 2025). Modified from the original publication I (Malén et al., 2026).

5.1.4 Variation from the normalisation method

We compared the K_i^{ref} estimates from two spatial normalisation methods using either common PET template or subject-specific MRI for those subjects for whom both methods could be applied (n = 45, including 22 healthy controls and 23 PD patients). The preprocessing methods produced the most comparable K_i^{ref} estimates in the caudate and putamen. The one-sided Pearson correlation between the K_i^{ref} estimates of the two alternative methods was 0.57 (p-value < 0.001) in the caudate, 0.13 (p-value = 0.19) in the accumbens, 0.79 (p-value < 0.001) in the putamen, and 0.46 (p-value < 0.001) in the thalamus. The one-sided Spearman rank-order correlation between the K_i^{ref} estimates of the two alternative methods was 0.69 (p-value < 0.001) in the caudate, 0.40 (p-value = 0.003) in the accumbens, 0.79 (p-value < 0.001) in the putamen, and 0.45 (p-value = 0.001) in the thalamus. Using Bonferroni correction, the statistical significance level of 0.05 would result in a new threshold of 0.0125, that is 0.05 / 4 tests, one in each ROI. Considering both the Pearson and Spearman correlations, as well as the corrected threshold for statistical significance (p-value < 0.0125), the estimates showed statistically significant positive correlation in the caudate, putamen, and thalamus. **Figure 9** illustrates the comparativeness of the estimates across the cohorts.

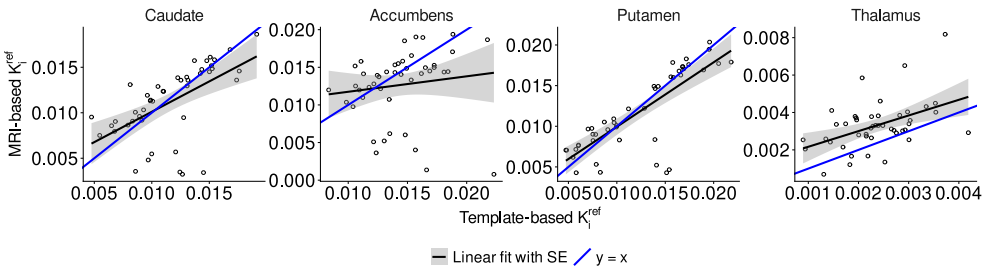

Figure 9. [^{18}F]fluorodopa influx rate constant (K_i^{ref}) estimates from the two spatial normalisation methods in 45 subjects, including 22 healthy controls and 23 Parkinson's disease patients, SE = 0.95 confidence band. Created using R package ggplot2 (Wickham, 2016) and scales (Wickham, 2022) in RStudio (Posit team, 2023) running on R (R Core Team, 2025). Modified from the original publication I (Malén et al., 2026).

The template-based normalisation method worked rather well for most subjects. Nevertheless, as there appeared to be noise in the estimates, the MRI-based normalisation is recommended as the primary method. The template-based normalisation may be worth using when MRI is not available for a given subject and when the impact of noise can sufficiently be decreased with a large sample size.

5.2 Study II: Type 2 dopamine receptor availability in a healthy cohort

The whole-brain map of mean D_2R availability, estimated as [^{11}C]raclopride BP_{ND} of healthy controls (n = 156), is illustrated in **Figure 10**. The binding was the highest in the striatum and practically non-existent in the cortex. The three-dimensional map is available in NeuroVault (https://identifiers.org/neurovault.collection:12099). The regional BP_{ND} descriptives in the sample are given in **Table 8**.

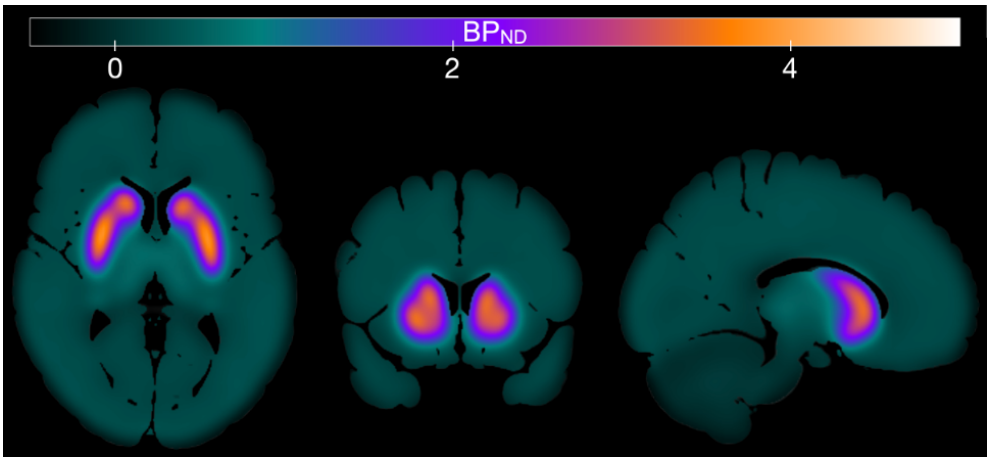

Figure 10. Mean [^{11}C]raclopride nondisplaceable binding potential (BP_{ND}) map across the sample, overlaid on the MNI152 template (Mazziotta et al., 2001). Created using SPM12 (Functional Imaging Laboratory, 2018), MATLAB (The MathWorks Inc.), MRIcroGL (Rorden, 2025), and Keynote version 12.2.1 (7035.0.161). Modified from the original publication II (Malén et al., 2022).

Table 8. The regional [^{11}C]raclopride nondisplaceable binding potential (BP_{ND}) means, standard deviations (SD), and ranges in 156 healthy subjects. Original table.

	Mean		**SD**		**Range**	
	Left	Right	Left	Right	Left	Right
Caudate	2.64	2.69	0.55	0.56	1.48–4.12	1.56–3.85
Accumbens	2.33	2.16	0.53	0.51	1.03–3.49	1.03–3.34
Putamen	3.49	3.48	0.62	0.64	2.13–5.04	2.18–5.11
Thalamus	0.47	0.48	0.10	0.10	0.28–0.71	0.28–0.69

5.2.1 Regional effects of age, sex, and body mass index

There was a consistent age-related decline in striatal D_2R binding. In the putamen and caudate, 10 years of ageing was associated with a 5% decrease in binding. In the accumbens, the approximate decrease was 3% per 10 years. In the thalamus, most of the probability mass supported a negative age effect, although the 95% posterior interval for both hemispheres overlapped with zero, indicating uncertainty in the effects.

Females had approximately 7–8% higher D_2R binding than males bilaterally in putamen. There was support for higher D_2R binding in females versus males also in the other ROIs, although the 95% posterior intervals overlapped with zero. The left accumbens was an exception showing no sex-difference. Our data suggested a positive association between BMI and BP_{ND}, particularly in putamen and thalamus. However, the 95% posterior intervals overlapped with zero, except in the right thalamus with an approximate 1% increase in BP_{ND} per one unit increase in BMI. Overall, the effects of age, sex, and BMI, illustrated in **Table 9** and **Figure 11**, were essentially the same in both hemispheres, except for the sex-difference in the left versus right accumbens.

Table 9. The effects (regression coefficients) of age, sex, and BMI on regional [^{11}C]raclopride nondisplaceable binding potential (BP_{ND}). The effect is given as a percentual change based on the posterior medians, *95% posterior interval did not cross zero.

	Age		**Sex**		**Body mass index**	
	Per 10 years		Males vs females		Per 3 units (kg/m^2)	
	Left	Right	Left	Right	Left	Right
Putamen	-5%*	-6%*	-7%*	-8%*	+2%	+2%
Caudate	-6%*	-6%*	-5%	-6%	+1%	+1%
Accumbens	-3%*	-3%	-1%	-7%	+1%	+1%
Thalamus	-2%	-2%	-5%	-3%	+2%	+3%*

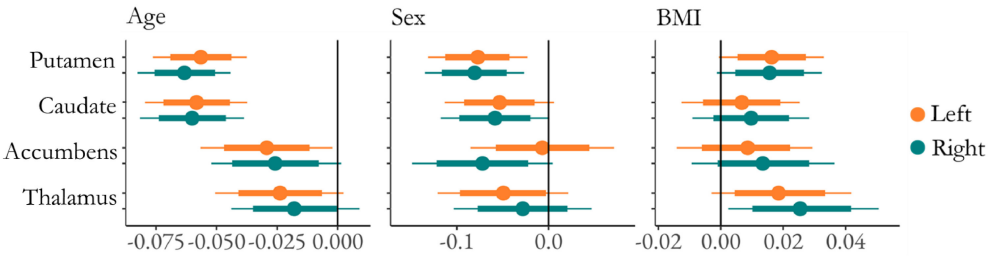

Figure 11. Posterior intervals for the effects of age (standardised), sex (females versus males) and body mass index (BMI, standardised) on striatal and thalamic [^{11}C]raclopride nondisplaceable binding potential (BP_{ND}), presented separately for the left and right hemisphere. The figure shows medians (circles), 95% (thin line), and 80% (thick line) posterior intervals of the regression coefficients on a logarithmic scale. Reproduced from the original publication II (Malén et al., 2022).

5.2.2 Variation from normalisation method

We validated the alternative template-based normalisation approach by comparing the estimates in a sample that could be analysed with both methods, i.e., the subjects with available MRIs (n = 189). The observations from the two methods are visualised in **Figure 12**. In the left hemisphere, the one-sided Pearson correlation of the BP_{ND} estimates of the two alternative methods was 0.94 (p-value < 0.001) in the caudate, 0.89 (p-value < 0.001) in the accumbens, 0.97 (p-value < 0.001) in the putamen, and 0.92 (p-value < 0.001) in the thalamus. In the right hemisphere, the comparable values were caudate 0.93 (p-value < 0.001), accumbens 0.92 (p-value < 0.001), putamen 0.97 (p-value < 0.001), and thalamus 0.93 (p-value < 0.001).

The two methods produced highly comparable BP_{ND} estimates across the ROIs, suggesting that template-based normalisation yields comparable [^{11}C]raclopride BP_{ND} estimates. For the accumbens, the template-based estimates were, however, generally higher than the MRI-based estimates. In contrast, the thalamic estimates were on average lower with the template-based method.

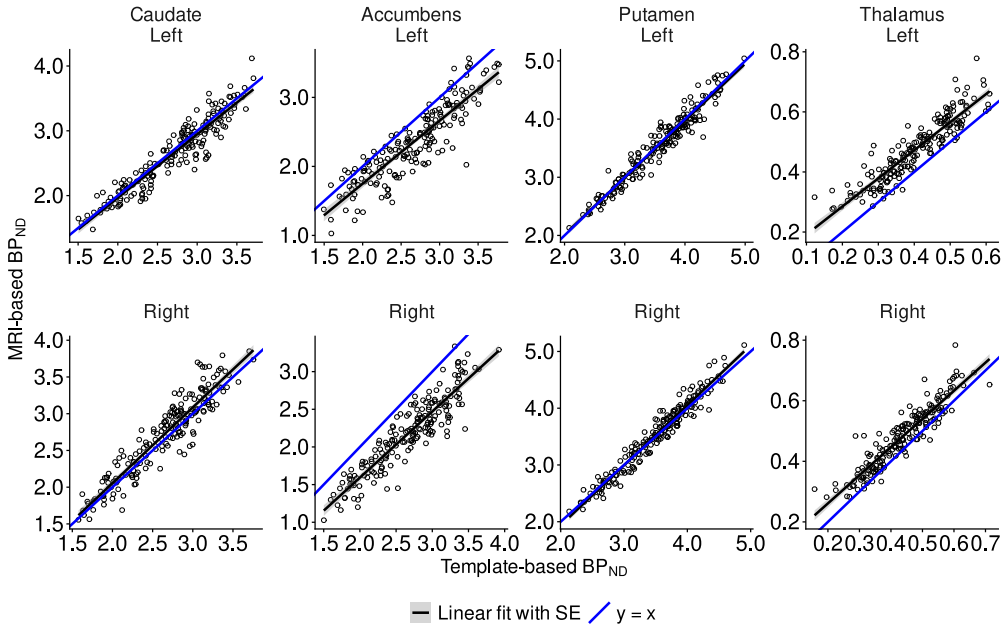

Figure 12. [^{11}C]raclopride nondisplaceable binding potential (BP_{ND}) estimates from the two spatial normalisation methods in 189 healthy controls, SE = 0.95 confidence band. Created using R package ggplot2 (Wickham, 2016) in RStudio (Posit team, 2023) running on R (R Core Team, 2025). Modified from the original publication II (Malén et al., 2022).

5.3 Study III: Type 2 dopamine receptor availability in a mixed cohort

Whole-brain mean and ROI-specific coefficient of variation maps for D_2R availability, estimated as [^{11}C]raclopride BP_{ND}, across the cohorts are shown in **Figure 13**. The regional BP_{ND} descriptives, presented separately in each cohort, are given in **Table 10**. The cohorts show broadly similar receptor distribution, and PD patients show the greatest variation in the striatal and thalamic D_2R availability. Across the cohorts, the variation appears greatest in thalamus. The three-dimensional brain maps of mean D_2R availability of healthy and clinical cohorts are available in NeuroVault (https://identifiers.org/neurovault.collection:12799).

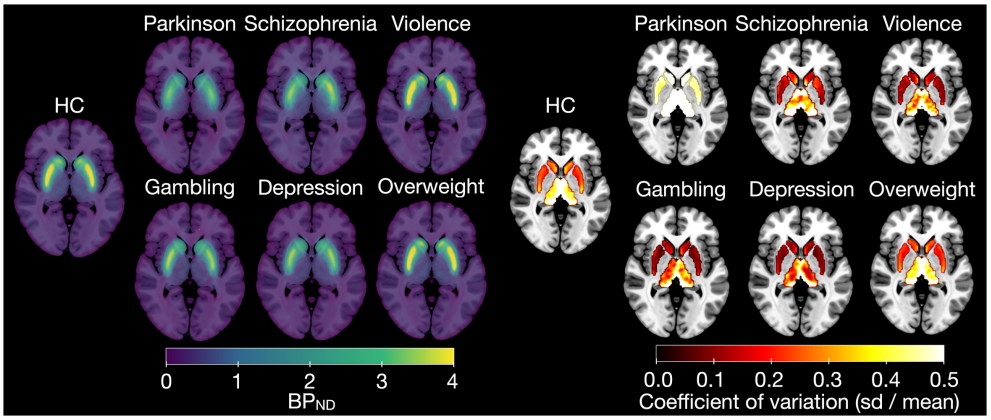

Figure 13. [^{11}C]raclopride nondisplaceable binding potential (BP_{ND}) maps in healthy controls (HC, n = 239), and subjects with Parkinson's disease (Parkinson, n = 60), schizophrenia (n= 7), severe violent behaviour (violence, n = 10), pathological gambling (gambling, n = 12), depression (n = 12), and overweight (n = 97), n = number of observations. Left: mean BP_{ND} maps. Right: coefficient of BP_{ND} variation (standard deviation / mean) maps within the regions of interest using the Harvard-Oxford atlas (Jenkinson et al., 2012) masks. The maps are overlaid on the MNI152 template (Mazziotta et al., 2001). Created using SPM12 (Functional Imaging Laboratory, 2018), MATLAB (The MathWorks Inc.), MRIcroGL (Rorden, 2025), and Keynote version 12.2.1 (7035.0.161). Modified from the original publication III (Malén et al., 2024).

Table 10. The regional [^{11}C]raclopride nondisplaceable binding potential (BP_{ND}) means, standard deviations (SD) in parenthesis, and ranges, respectively, in healthy and clinical cohorts, n = number of observations.

	Caudate	**Accumbens**	**Putamen**	**Thalamus**
Healthy controls (n = 239)	2.34 (0.66) 1.00–3.73	2.35 (0.63) 1.07–3.83	3.16 (0.71) 1.89–4.94	0.39 (0.11) 0.05–0.61
Parkinson's disease (n = 60)	1.25 (0.59) 0.05–3.61	1.40 (0.55) 0.52–3.53	2.45 (0.74) 0.96–5.54	0.30 (0.27) 0.03–1.66
Schizophrenia (n = 7)	1.78 (0.25) 1.42–2.13	1.85 (0.45) 1.45–2.73	2.59 (0.24) 2.30–2.93	0.37 (0.08) 0.23–0.48
Severe violent behaviour (n = 10)	2.41 (0.21) 2.15–2.79	2.46 (0.27) 2.10–2.95	3.38 (0.23) 3.01–3.72	0.33 (0.05) 0.25–0.39
Pathological gambling (n = 12)	1.88 (0.22) 1.32–2.13	1.89 (0.23) 1.52–2.25	2.60 (0.17) 2.20–2.88	0.36 (0.05) 0.24–0.43
Depression (n = 12)	1.90 (0.18) 1.59–2.16	1.90 (0.19) 1.55–2.16	2.62 (0.20) 2.27–2.89	0.35 (0.07) 0.15–0.44
Overweight (n = 97)	2.44 (0.56) 1.10–3.48	2.41 (0.53) 1.30–3.47	3.27 (0.65) 1.94–4.53	0.38 (0.10) 0.11–0.66

5.3.1 Regional comparison of the cohorts

Using GLM, we compared the regional [^{11}C]raclopride BP_{ND} estimates of the cohorts, while adjusting for the effects of age, sex, and scanner on BP_{ND}. Compared to the other cohorts, PD patients had approximately 10–20% lower binding in the caudate, accumbens and thalamus, while in the putamen, the BP_{ND} was approximately 10% higher in PD patients versus other cohorts. Schizophrenia, severe violent behaviour, PG, depression, or overweight did not show clear differences in regional BP_{ND} when compared with healthy controls or other clinical cohorts. The findings are given in **Figure 14**.

		Caudate	Accumbens	Putamen	Thalamus
Parkinson	Healthy controls	0.79 **	0.85 **	1.07 **	0.82 **
	Schizophrenia	0.83 **	0.91 *	1.1 *	0.81 **
	Violence	0.82 **	0.89 **	1.12 **	0.85 *
	Gambling	0.8 **	0.88 **	1.1 **	0.78 **
	Depression	0.78 **	0.85 **	1.07 *	0.81 **
	Overweight	0.78 **	0.85 **	1.07 *	0.81 **
Schizophrenia	Healthy controls	0.95	0.94	0.98	1.02
	Violence	1	0.97	1.01	1.05
	Gambling	0.97	0.96	1	0.97
	Depression	0.94	0.93	0.97	1
	Overweight	0.95	0.93	0.97	1.01
Violence	Healthy controls	0.95	0.96	0.96	0.97
	Gambling	0.98	0.99	0.99	0.93
	Depression	0.95	0.96	0.96	0.95
	Overweight	0.95	0.96	0.96	0.96
Gambling	Healthy controls	0.95	0.93	0.97	1.01
	Depression	0.97	0.97	0.97	1.03
	Overweight	0.97	0.97	0.97	1.04
Depression	Healthy controls	1.01	1.01	1.01	1.02
	Overweight	1	1	1	1.01
Overweight	Healthy controls	1	1	1.01	1.01

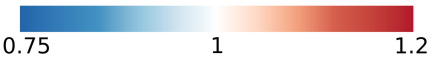

Figure 14. Summary of the [^{11}C]raclopride nondisplaceable binding potential (BP_{ND}) comparisons across the cohorts. The values represent the BP_{ND} ratio of the reference cohort on the left and the cohort on the right, calculated based on original-scale posterior medians. Asterisks represent comparisons were 80% (*) and 95% (**) posterior interval did not cross zero. Reproduced from the original publication III (Malén et al., 2024).

5.3.2 Interregional correlation

Interregional BP_{ND} Spearman correlations are shown separately in the subject cohorts in **Figure 15**. Despite the regional BP_{ND} changes, PD patients showed high between-region BP_{ND} correlation, comparably with healthy controls. Subjects with severe violent behaviour showed the weakest correlation between the regions. While the [^{18}F]fluorodopa data suggested that the interregional correlation may be lower

with older versus newer scanners, all subjects with severe violent behaviour were scanned with one of the newest scanners in the data, the GE Discovery VCT PET/CT. Across the cohorts, the correlations with thalamus were overall the lowest.

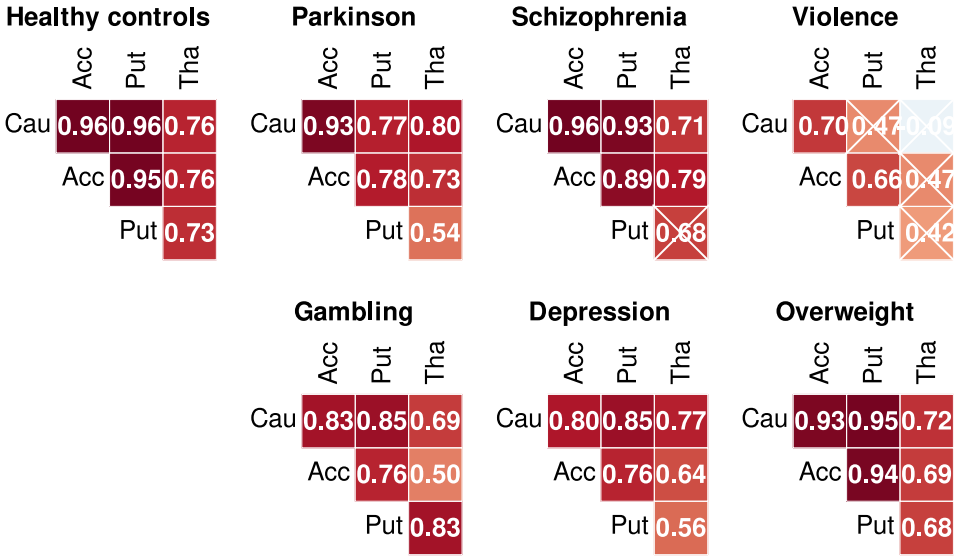

Figure 15. Cohort-specific interregional original-scale BP_{ND} correlations (one-sided Spearman, uncorrected *p*-value > 0.05 marked with a cross), cau = caudate, acc = accumbens, put = putamen, tha = thalamus. The higher the *p*-value, the less support for non-zero correlation. Created using R package corrplot (Wei, 2021) in RStudio (Posit team, 2023) running on R (R Core Team, 2025). Modified from the original publication III (Malén et al., 2024).

5.3.3 Variation from scanner type

PET scans with [^{11}C]raclopride (used in Studies II and III) were acquired using six different PET scanner types: ECAT 931, GE Advance, HRRT, HR+, GE Discovery VCT PET/CT, and GE Discovery 690 PET/CT. The acquired BP_{ND} estimates show differences across the scanners, visualised in **Figure 16**.

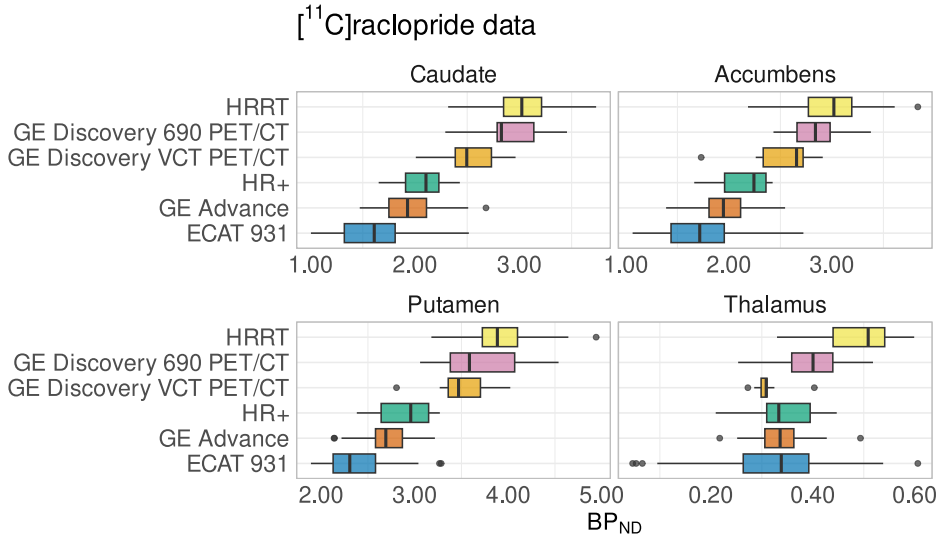

Figure 16. Regional [^{11}C]raclopride nondisplaceable binding potential (BP_{ND}) estimates from each scanner type, HRRT (n = 81), GE Discovery 690 PET/CT (n = 17), GE Discovery VCT PET/CT (n = 9), HR+ (n = 13), GE Advance (n = 69), ECAT 931 (n = 50) in a sample of 239 healthy controls, n = number of observations. Each boxplot shows the median (middle line), and 25% (lower hinge) and 75% (upper hinge) quartiles. The lower whisker extends from the hinge to the smallest value at most 1.5 * IQR of the hinge. The upper whisker extends from the hinge to the largest value no further than 1.5 * IQR from the hinge. IQR = Inter-quartile range, meaning the distance between the 25% and 75% quartiles. Original figure created using R package ggplot2 (Wickham, 2016) in RStudio (Posit team, 2023) running on R (R Core Team, 2025).

5.3.4 Variation from normalisation method

We assessed the Spearman correlation of the BP_{ND} estimates from the two spatial normalisation methods in 249 subjects for whom both methods could be applied. The sample included healthy controls (n = 142), and subjects with PD (n = 5), severe violent behaviour (n = 10), PG (n = 12), and overweight (n = 80). This time, we used the mean of the left and right regional BP_{ND} in contrast to hemisphere-specific estimates in Study II. The correlation was 0.88 (p-value < 0.001) for the caudate, 0.89 (p-value < 0.001) for the accumbens, 0.92 (p-value < 0.001) for the putamen, and 0.78 (p-value < 0.001) for the thalamus. The Bonferroni-corrected statistical threshold is 0.05 / 4 (number of tests, one for each ROI) = 0.0125. Using the Bonferroni correction, all the correlations would be considered statistically significant.

Overall, the alternative BP_{ND} estimates showed the highest agreement in the striatum where the quantification of [^{11}C]raclopride uptake is the most reliable (Alakurtti et al., 2015). Despite a few outlier observations, the methods produce

consistent estimates also in the thalamus. However, the MRI-based estimates are systematically higher than the template-based estimates, particularly in the caudate, putamen, and thalamus. The observations are visualised in **Figure 17**.

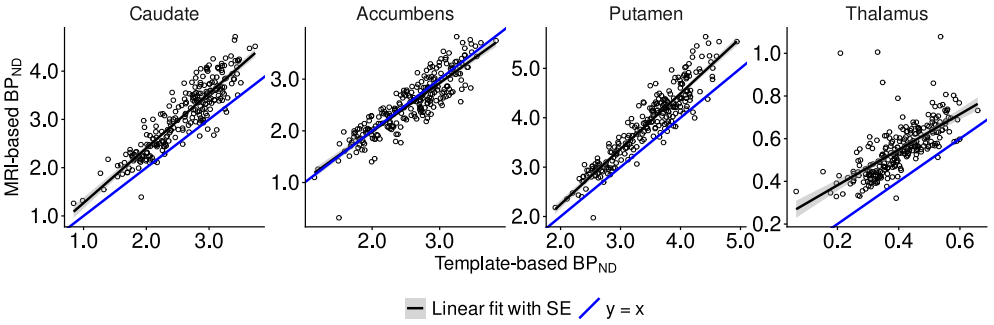

Figure 17. [^{11}C]raclopride nondisplaceable binding potential (BP_{ND}) estimates from the two spatial normalisation methods in 249 subjects, including healthy controls (n = 142), and subjects with Parkinson's disease (n = 5), severe violent behaviour (n = 10), pathological gambling (n = 12), and overweight (n = 80), n = number of observations, SE = 0.95 confidence band. Created using R package ggplot2 (Wickham, 2016) in RStudio (Posit team, 2023) running on R (R Core Team, 2025). Modified from the original publication III (Malén et al., 2024).

6 Discussion

6.1 Individual differences in the striatal dopamine function

6.1.1 Effects of age and sex

Our findings were that there is a decline with increasing age in striatal dopamine synthesis capacity (4–9% of sample mean per 15 years) and D_2R availability (2–6% per 10 years), and that irrespective of age, both measures are higher in females versus males: the synthesis capacity 6–8% from the female sample mean, and D_2R 7–8% in the putamen where the effect was clearest. In the thalamus, the dopamine synthesis capacity decreased by approximately 8% per 15 years and 11% in males versus females. The age and sex effects on thalamic D_2R showed uncertainty, while still pointing towards a decrease with age and higher female versus male D_2R availability. Our additional analyses in the original publications I and II suggested that the decline in dopamine synthesis capacity begins only in later adulthood, approximately at the age of 50, while the age range in the sample was 20–80 years. However, the D_2R availability decreased steadily starting from early adulthood in a sample of subjects aged 19–71 years, although the D_2R data was mainly representative of adults aged 40 and below.

Differing from our findings, a meta-analysis of over 200 subjects by Karrer and colleagues (Karrer et al., 2017) concluded that the dopamine synthesis capacity is independent of age. The possible nonlinear age effect on dopamine synthesis capacity, that is, emergence of the effect only in later adulthood observed in Study I, may have been overlooked in the meta-analysis using correlation-based age effects of the original studies (Karrer et al., 2017). However, their supplemental analysis of the association between age and standardised kinetic synthesis estimate using raw data points of over 200 subjects preferred a U-shaped curve over a linear fit, even though the association was not clear (Karrer et al., 2017). The discrepancy between the findings of Study I and the meta-analysis by Karrer and colleagues (Karrer et al., 2017) may be influenced by the different ageing profiles of the individuals, which can at least be observed in cognition (Josefsson et al., 2012).

In line with our data, the age-related decline in dopamine function involves a steady downregulation of the striatal D_2R (8% per 10 years), particularly the D_2R density (Pohjalainen et al., 1998), as well as D_1R and DAT (Karrer et al., 2017). Age-related decline in striatal D_2R availability, that in our data was approximately 5% per 10 years, also received support in a recent large-scale longitudinal study (Lundgren et al., 2025). Thalamic D_2R has been estimated to decrease with age by approximately 5% per 10 years (Inoue et al., 2001; Kaasinen et al., 2002) and to be statistically non-significantly higher in females versus males in [^{11}C]FLB 457 PET data (Kaasinen et al., 2001). These thalamic D_2R findings are not necessarily discrepant with ours, as our effects pointed towards the same directions (negative age effect, females > males), while we observed uncertainty in the effects. The dopaminergic changes with age potentially contribute to both the mild cognitive decline (Karrer et al., 2017; Lundgren et al., 2025) and motor deficiency (Darbin, 2012), commonly observed among the elderly (Esiri, 2007).

Two studies from the Turku PET Centre, potentially using overlapping data with our Studies I–III, concluded there was a higher dopamine synthesis capacity in 12 females versus 23 males (Laakso et al., 2002) and after correcting for multiple comparisons, no clear sex differences in D_2R affinity nor D_2R density in 21 females versus 33 males (Pohjalainen et al., 1998). Similarly, no sex difference was observed in D_2R density nor affinity in an independent sample of 10 females and 10 males (Farde et al., 1995). Based on our analyses, both dopamine synthesis capacity in 96 females and 124 males involving healthy controls and PD patients, and D_2R availability in 36 females and 120 males were higher in females versus males. Higher D_2R availability in females was also supported by independent data of 20 individuals from each sex (Fazio et al., 2017).

The study of Laakso and colleagues (Laakso et al., 2002) reports males versus females showing steeper reduction in dopamine synthesis capacity in subjects aged 20–60 years. Furthermore, the study by Pohjalainen and colleagues (Pohjalainen et al., 1998) covering an age range of 19–82 years, observed that the age-related decline in striatal D_2R was specific to males. Our supplementary analysis provided in the original publication II similarly pointed towards steeper striatal and thalamic D_2R decline in males, although the 95% posterior intervals crossed zero. In extrastriatal regions, including thalamus, as well as frontal and temporal cortices, the age-related reduction in D_2R availability is estimated to be largely comparable in males and females (Inoue et al., 2001; Kaasinen et al., 2002). While sex steroid changes have been suggested to affect the binding characteristics of endogenous dopamine in ageing females (Kaasinen et al., 2001), serum oestradiol or progesterone levels did not associate with the D_2R availability in females (Kaasinen et al., 2002), leaving the mechanism behind the possible sex-age interaction on D_2R unresolved.

Sex differences in the striatal dopamine function may contribute to vulnerability for certain pathologies. Females showing higher dopamine synthesis capacity and striatal D_2R availability might thus be predisposed to pathology associated with elevated postsynaptic D_2R binding, such as psychotic symptoms. Schizophrenia is not more common in females versus males, yet it is not the only disorder with psychotic symptoms and several mechanisms influence the onset of schizophrenia (Howes & Kapur, 2009).

Conversely, lower synthesis and potential steeper reduction of D_2R level in males may predispose them to PD (Loke et al., 2015) that involves a dopaminergic loss and is more common in males versus females (Kalia & Lang, 2015). Lower D_2R availability of males may also predispose them to behaviour associated with low D_2R, such as high impulsivity (Clark et al., 2012), sensation seeking and antisocial behaviour (Lukkarinen et al., 2024), pathological gambling (Steeves et al., 2009), as well as substance abuse (Volkow et al., 2009); possibly to receive sufficient reward signalling (Lukkarinen et al., 2024).

As the serotonergic and dopaminergic systems may show an inverse link, where the upregulation of one is associated with the downregulation of the other, the higher dopamine synthesis and D_2R observed in females may blunt their serotonergic system contributing negatively to hedonic experiences (Belujon & Grace, 2017). The sex differences in the serotonergic system are not fully established. However, higher serotonin receptor 5-HT_{1A} and lower serotonin transporter 5-HTT availabilities have been observed in females versus males (Jovanovic et al., 2008).

In addition to the baseline, the event-related function, such as the dopaminergic firing during gambling, may also show sex differences (Zachry et al., 2021). As a result, males may be particularly prone to attribute gambling as highly salient, promoting PG. Finally, many variables, involving biological and environmental factors, some of which are protective, and others risks, determine the onset of neurological and psychiatric disorders. However, while dopamine is one of the key neurotransmitters affecting our well-being, the individual-differences in its functioning may well have a significant weight in the interplay of the contributing factors.

6.1.2 Effect of body mass index

Our data suggested that both the striatal dopamine synthesis capacity and D_2R availability show subtle positive associations with BMI. In the caudate, the synthesis capacity increased approximately by 3% of the sample mean per 4 units increase in BMI (Study I). In the thalamus, the D_2R availability increased by 3% per 3 units increase in BMI (Study II). For the other regions, the 95% posterior intervals overlapped with zero.

A recent qualitative review (Janssen & Horstmann, 2022) supported negative association of BMI and dopamine synthesis in striatal subregions, based on three studies with the sample sizes of 60 (Lee et al., 2018), 16 (Wallace et al., 2014), and 15 (Wilcox et al., 2010). We utilised these findings in our additional statistical analysis by placing a higher probability for a negative rather than a positive association between BMI and dopamine synthesis capacity (Study I). Even with such an alternative prior, our sample of two hundred subjects showed moderate support for a positive association between dopamine synthesis capacity and BMI in the striatal regions, whereas no link in the thalamus. In Study II, we assessed both linear and non-linear associations between BMI (range = 18–38) and D_2R availability, finding subtle support for a positive linear association between the measures. As an alternative we compared the baseline intercepts of individuals with overweight (BMI ≥ 25) and the control group in Study III and did not detect differences. Individuals with overweight also showed positive interregional correlation of D_2R availability across the striatum, comparably to controls. Our findings accord with a previous review (Janssen & Horstmann, 2022), as well as Bayesian and frequentist meta-analyses (Pak & Nummenmaa, 2023), which found no clear connections between altered D_2R availability and obesity.

Overall, we saw subtle support for a positive association between BMI and our dopaminergic measures, that in the light of other literature (Janssen & Horstmann, 2022; Pak & Nummenmaa, 2023), is not highly convincing and thus, BMI is not a clear contributor to striatal baseline dopamine synthesis capacity nor D_2R. Our findings as regards baseline PET scans, however, do not exclude the existence of links between weight and event-related dopaminergic function.

6.1.3 Interregional coupling in healthy individuals

Healthy subjects showed strong dopaminergic correlation patterns regarding both the dopamine synthesis capacity (Study I) and the D_2R availability (Study III). This coupling was particularly strong between the striatal regions, suggesting a synchronised function within the striatum. The weakest correlations were most notably manifested with the thalamus, where the estimates might be less reliable than in the striatum (Hirvonen et al., 2003; Volkow et al., 1996).

6.2 Striatal dopamine function across disorders

Our results highlight that PD is consistently linked with regional alterations in dopamine synthesis capacity and D_2R availability. Severe violent behaviour, on the other hand, might link to disturbed correlation between the regional D_2R

availabilities. In subjects with schizophrenia, PG, or depression, we did not observe alterations in baseline regional or interregional coupling of D_2R availability.

6.2.1 Clearest regional alterations in Parkinson's disease

Regional dopamine synthesis capacity in the striatum and thalamus was substantially lower in PD patients versus healthy controls, by approximately 13–41% of the regional mean in the healthy cohort (Study I). While the PD-related decline in the striatal dopamine synthesis is undebated (Kaasinen & Vahlberg, 2017), our findings highlight that the magnitude of the PD effect measurably exceeds the effects of age, sex, and BMI.

Moreover, the D_2R downregulation of PD patients compared to the other cohorts was salient. Approximately, the decrease in PD patients versus healthy controls was 21% in the caudate, 15% in the accumbens, and 18% in the thalamus, as observed in Study III. Unexpectedly in the putamen, the GLM suggested circa 7% higher D_2R availability in PD patients than controls. In the raw BP_{ND} estimates in the putamen, there were a few exceptionally high PD observations, greater than the ones of healthy controls, which might have contributed to the model estimate of a higher binding in PD patients versus healthy controls. In early PD, approximately for the first four years from symptom onset, there is an upregulation of D_2R availability detectable in a [^{11}C]raclopride PET scan, which could be explained by (1) compensation to diminished dopamine (Kaasinen et al., 2021) and/or (2) diminished endogenous dopamine competition with the tracer (Cumming et al., 2002; Ginovart, 2005). However, a study in patients with early PD comparing the uptake of reversible binding [^{11}C]raclopride with that of irreversibly binding [^{11}C]NMSP (N-methylspiperone) showed that the increase in uptake of D_2R in the putamen contralateral to predominant symptoms, is similar for both tracers (Kaasinen et al., 2000). This suggests that the deficiency of endogenous dopamine does not explain the increase seen in the uptake of [^{11}C]raclopride, but supports the compensatory mechanism (Kaasinen et al., 2000). Our findings are not adjusted for different disease stages, as the disease duration information was not available for all patients. Altogether, the degeneration in PD is not limited to the nigrostriatal motor pathway but also covers the mesolimbic dopamine circuit.

The positive interregional correlation of dopamine synthesis capacity (Study I) and the D_2R (Study III) were comparable in healthy controls and patients with PD. To our knowledge, these interregional correlation patterns within striatal and thalamic regions of comparable healthy and PD cohorts have not been established previously. High correlation coefficients indicated that individuals with relatively low dopamine synthesis or receptor availability in one region also show low synthesis or receptor availability in the remaining regions, respectively. These

findings, thus, suggest that PD is associated with a relatively uniform reduction in dopamine synthesis capacity and D_2R across the striatal subregions. However, because detailed information on the disease stage was not systematically available, it is possible that early PD shows considerably more regionally selective vulnerability.

6.2.2 Interregional changes in antisocial behaviour

Although the thalamus showed the lowest interregional correlation with the other ROIs in all cohorts, this decoupling was most salient in the subjects with severe violent behaviour, who also had the lowest regional coupling within the striatum. Aberrant coupling in this striatal dopamine network might reflect altered communication and weakened links between the regional nodes. Alternatively, the weakened correlation of D_2R availability between different regions might also be explained by selective alteration of one specific dopaminergic region, while other regions are unaffected (without interaction between regions), nevertheless this hypothesis was not supported by the regional analysis where the binding in subjects with severe violent behaviour did not clearly differ from healthy controls in any of the regions. However, another study from the site, analysing data of the same violent offenders as Study III, concluded that the D_2R availability of the offenders versus controls was lower in the caudate and putamen (Lukkarinen et al., 2024). While the healthy controls in the study by Lukkarinen and others (Lukkarinen et al., 2024) were possibly also involved in our analyses, the control group in Study III consisted of samples of several research projects and was, thus, different than the one used in the study by Lukkarinen and colleagues (Lukkarinen et al., 2024).

The sample size for violent offenders was small which might limit the generalisability of our findings, although some of the other cohorts showing stronger correlation pattern were also small. Our findings nevertheless suggest different dopaminergic correlation profiles between motor symptoms and violent aggression. The D_2R coupling of the regions, as well as the regional changes should be further examined in antisociality.

6.2.3 Unaltered baseline levels of type 2 dopamine receptor in schizophrenia, pathological gambling, and depression

Schizophrenia, PG, and depression did not show clear alterations in regional nor interregional coupling of D_2R availability when compared with healthy controls or the other clinical cohorts. Although limited in cohort sizes, our results are aligned with previous findings in that the striatal and thalamic baseline D_2R is not a central

contributor to schizophrenia (Howes et al., 2012) or depression (Mizuno et al., 2023). However, our findings do not support the blunted baseline D_2R availability in individuals with PG suggested by some works (Egerton et al., 2009; Steeves et al., 2009).

The antipsychotic effect of D_2R blocking agents point towards acute dopaminergic disturbance during psychotic symptoms. However, a SPECT study noticed an elevated baseline D_2R occupancy by endogenous dopamine in individuals with schizophrenia (Abi-Dargham et al., 2000), suggesting increased dopamine concentration in schizophrenia even when psychotic symptoms are not present. The possibility of exceptional agonist-induced D_2R internalisation, instead of dopamine release, is discussed in a review of displacement studies (Ginovart, 2005), while there is also evidence pointing toward unaltered D_2R internalisation in schizophrenia (Weinstein et al., 2018). Finally, a review and a meta-analysis concluded that compared to the presynaptic dopamine synthesis and release, the link between striatal D_2R and schizophrenia is negligible and possibly related to antipsychotic treatment (Hietala & Syvälahti, 1996; Howes et al., 2012).

Individuals with PG show an unaltered baseline D_2R availability in the striatum (Study III), although a higher gambling-related dopamine release in pathological gamblers with more severe symptoms (Joutsa et al., 2012) support an event-related dopaminergic disturbance in PG. Aligned with our findings and acknowledging the heterogenous symptom profiles of individuals with depression (Belujon & Grace, 2017), the baseline D_2R in the striatum does not appear as a biomarker for depression (Mizuno et al., 2023).

6.3 Newer scanners give higher estimates

Based on our data involving six different although calibrated PET cameras (Studies I–III), the scanners introduced variation in the data, which should be adjusted for when analysing PET estimates from different devices. Descriptively, newer scanners produced higher estimates, except for high-resolution HRRT that showed higher estimates than some of the newer scanner types. In Study I, investigating the dopamine synthesis capacity, we explicitly quantified the scanner effect. Based on GLM, the K_i^{ref} estimates were approximately 20–39% (of the ECAT 931 mean) higher in GE Advance versus ECAT 931, and 39–56% (of the ECAT 931 mean) higher in HRRT versus ECAT 931, which proportionally even exceed the effect of PD.

In Studies I–III, we adjusted for the effect of the scanner in the statistical analyses. There are also other methods, such as data harmonisation by scanner prior to statistical analyses (Fortin et al., 2017; Lövdal et al., 2025). Regardless of the adjustment method used, if the subject-related data is highly dependent on the

device, such as all patients scanned with one device and healthy controls with another, careful consideration on how to adjust for the scanner is required to avoid confounds (Fortin et al., 2017). All things considered, the Studies I–III indicate that even with the scanner-related variation in the PET estimates, data pooling enables versatile large-scale PET analyses establishing both replicative and novel findings in a highly generalisable manner.

6.4 Preferred normalisation with subject-specific versus template-based anatomical reference

When individual-level structural MRI is not available, template-based normalisation provides [^{18}F]fluorodopa K_i^{ref} and [^{11}C]raclopride BP_{ND} estimates largely comparable with those from MRI-based method for most subjects. However, the template-based method should be used with caution.

Generally, the consistency of the [^{18}F]fluorodopa K_i^{ref} estimates from the two methods was difficult to determine, as (1) the PET template was based on 18 subjects, and (2) the validation sample consisted of 45 subjects. The limited template sample may explain the cases where the methods showed poor agreement of the K_i^{ref} estimate. The (Spearman) correlations of the regional [^{18}F]fluorodopa estimates from the two methods varied from 0.40 in accumbens to 0.79 in putamen.

The PET template used to spatially normalise the [^{11}C]raclopride data was based on a larger sample, almost two hundred subjects. The [^{11}C]raclopride data was used to compare the methods in both the hemispheric (Study II) and the mean of the left and right (Study III) BP_{ND} estimates. Although the estimates from the two methods were highly correlated, their levels were not fully consistent. Based on the hemisphere-specific data of healthy controls in Study II, the template-based estimates were higher in the accumbens and lower in the thalamus, compared to the MRI-based estimates. In Study III, the mean of the left and right estimates of a mixed-cohort suggested lower template-based estimates in the caudate, putamen and thalamus. In sum, the correlations of the regional [^{11}C]raclopride BP_{ND} estimates from the two methods ranged from 0.89 in the left accumbens to 0.97 in the left and right putamen (healthy controls in Study II), and from 0.78 in the thalamus to 0.92 in the putamen (mixed cohort in Study III).

Whenever there is subject-level anatomical information available, it is expected to be more accurate than a template averaging information across people with brains varying in shape and size. Thus, the MRI-based normalisation should remain the preferred approach. Nonetheless, the template-based normalisation may be worth applying to avoid large data loss due to missing MRIs, particularly when the sample size is sufficient to cover the possible noise in the data. However, whenever both MRI and template-based estimates are available, their agreement should be evaluated

to ensure the robustness of the findings. The whole-brain maps of MRI-based (https://identifiers.org/neurovault.collection:12099) and template-based (https://identifiers.org/neurovault.collection:12799) D_2R availability may offer reference for future studies on the issue.

6.5 Limitations and future directions

The main limitation of Studies I–III is the unavoidable characteristics of pooled retrospective data including several different research projects. The retrospective datasets spanned three decades and multiple PET scanners, introducing technical heterogeneity despite statistical adjustment. The statistical analyses in Studies I and III were primarily based on template rather than MRI-normalised PET estimates, which may have added noise to the measurements. We also did not have complete documentation about the reconstruction algorithms that have been used for all the studies and thus, these could not be accounted for. It is possible that several different reconstruction algorithms have been used for some of the scanners, however, the reconstruction algorithms are typically stable for a particular scanner at the Turku PET Centre. In future studies, the sample differences can be better harmonised and estimated by conducting a pharmacokinetic modelling, that is a PET quantification, and a statistical analysis of the effects of interest in a single model (Matheson et al., 2025), in comparison to handling them separately. Such a method may also reduce the need for extending the conventional sample sizes (Matheson et al., 2025).

Our data were not fully balanced. For investigating the dopamine synthesis capacity using [^{18}F]fluorodopa PET data (Study I), we included only healthy controls and PD patients that clearly had a large sample size ($n > 90$) and excluded some of the other available but smaller cohorts, such as those with depression and schizophrenia. However, in the assessment of the D_2R availability using [^{11}C]raclopride PET data (Study III), we aimed at comparing as many clinical cohorts as possible and compromised with less stringent criteria for the sample size. Although the sample was generally large, the number of subjects, age, sex, and scanner distribution were imbalanced in some of the studied cohorts. Thus, (1) the statistical analysis of the regional cohort differences that adjusted for the age, sex, and scanner related variation in the data, may have left some cohort differences undetected (McElreath, 2020), and (2) our findings of the interregional coupling mainly indicate that in the healthy control, PD, and overweight cohorts, where we had largest number of subjects, the between-region correlation is strong. Larger samples are required to validate the striatothalamic D_2R coupling in the other cohorts with limited sample sizes. In Study II, the sample showed a relatively high sex-ratio (120 males and 36 females) and different age ranges across sexes. We repeated the primary analysis with a more balanced subset of the data including subjects aged 40

and under, which is reported in the original publication II. Future studies with large balanced data could further clarify possible sex differences in dopaminergic ageing and also in specific neurological and psychiatric cohorts (Williams et al., 2021).

Clinical information, such as disease duration, medication status, and symptom severity was not systematically available. Not all subjects were drug-naïve and some of the healthy controls were first-degree relatives of patients with schizophrenia. However, the general protocols at the Turku PET Centre were (1) medication withdrawal prior to the scan, and (2) subjects with (other than the investigated) neurological or psychiatric diagnoses being excluded from brain PET studies. In Study III, we could not exclude the possibility of overweight in the other cohorts, possibly underestimating cohort differences with the overweight cohort. However, patient categorisation was systematically based on their enrolment criteria in the original studies, except for the healthy controls with known BMI ≥ 25 who were reassigned from healthy controls to the overweight cohort to avoid the BMI overlap between these groups. The regional cohort comparisons and interregional coupling of D_2R availability in subjects with schizophrenia, antisocial behaviour, PG, and depression require validation with larger and more sensitive data.

Another limitation is the interpretation of [^{11}C]raclopride BP_{ND} estimates. From a single baseline [^{11}C]raclopride PET image, we can neither differentiate pre- and postsynaptic binding, nor determine the level of endogenous dopamine competing with the radioligand (Innis et al., 2007; Lippert et al., 2019). We used [^{11}C]raclopride and BP_{ND} to measure striatal D_2R availability in Studies II and III. BP_{ND} being a product of receptor density and affinity of unoccupied receptors, the level of binding reflects (1) the D_2R density, (2) the D_2R affinity and (3) the D_2R occupancy by endogenous dopamine (Cumming et al., 2002; Ginovart, 2005; Innis et al., 2007; Laruelle, 2000; Volkow et al., 2009). In a single baseline PET scan, it is not possible to resolve the exact molecule-level mechanism for altered receptor availability, as it is not possible to differentiate dopamine competition, receptor density, and tracer-receptor affinity (Slifstein & Laruelle, 2001). However, we expect the BP_{ND} to dominantly measure the D_2R density as: (1) the binding affinity between dopamine and D_2R is assumed constant (Innis et al., 2007), (2) only less than half of the D_2R antagonist, such as [^{11}C]raclopride, binding is vulnerable to competition by endogenous dopamine (Egerton et al., 2009), and (3) we used baseline scans including no interventions boosting dopamine firing. Other settings, involving one scan with high and another scan with low specific activity, have enabled the differentiation between receptor density and affinity, such as particularly higher putamen D_2R density in early PD (Rinne et al., 1995), decreasing D_2R density with ageing, and possibly higher D_2R affinity of females versus males (Pohjalainen et al., 1998).

An unaltered D_2R level at baseline does not mean the dopaminergic response to certain stimuli would be similar across the studied cohorts. As an example, the dopaminergic response to gambling correlated with symptom severity (Joutsa et al., 2012). Similar process may underlie overeating, as excessive feeding disharmonises the neuronal pathways related to motivation and reward, leading to enhanced saliency of food (Volkow et al., 2011), while stimulus-induced phasic firing governs the assigned saliency of stimuli (Grace, 2016). Investigating such event-related, stimulus-driven, effects in standardised activation paradigms, which could not be incorporated in the current analysis, would further enlighten the role of dopamine in the studied cohorts.

Overall, neuropsychiatric comorbidity is high, challenging the studies on specific neural mechanisms of single disorders (Kaasinen et al., 2009), and we could not adjust for possible comorbidities in the sample. Affective symptoms, such as anhedonia, are common in several neuropsychiatric disorders like depression, PD, schizophrenia, and addictions (Bressan & Crippa, 2005), such as PG (Kaasinen et al., 2009). Furthermore, the distinction between the roles of single neurotransmitters is unrealistic due to their interactive nature, therefore the concert of multiple neurotransmitters is in practicality unfeasible to study and interpret. Dopamine system is particularly closely associated with serotonin, glutamate, and opioid systems (Bressan & Crippa, 2005). Comorbidity of depression, impulsive aggression, and addictions is suggested to stem from deficient serotonergic activity further linked to hyperactive dopamine (Seo et al., 2008), while glutamate receptors modulate the dopamine burst firing in the nigrostriatal and mesolimbic pathways (Jackson & Westlind-Danielsson, 1994). Both dopamine and opioid systems are central to reward processing (Butler & Eckel, 2018). The serotonergic system has been linked with mood disorders, impulsivity, aggression, eating disorders, and alcohol use disorder (Mann et al., 2012), strikingly overlapping with the pathology associated with the dopaminergic function.

Consequently, careful consideration is required when making conclusions of how single neurotransmitters, not to mention their single subunits, such as D_2R, affect human functioning and specific conditions. Some of the selective effects of dopamine targeting drugs might be mediated by other neurotransmitter systems, such as the serotonin system (Jackson & Westlind-Danielsson, 1994). Hence, the interactive neurotransmitters offer a fruitful, yet challenging circumstances for treatment development (Stahl, 2018).

In addition to studies with more specific clinical characterisations, investigations of how dopamine synthesis and D_2R relate to specific behavioural symptoms would complement our findings of dopaminergic links with specific diagnoses. Finally, we encourage future studies to also address D_2R alterations in the cortex using other radioligands such as [^{11}C]FLB457.

7 Conclusions

Both the dopamine synthesis capacity and the D_2R availability are positively correlated across striatal and thalamic regions in healthy individuals. However, the regional dopaminergic function in striatum is dependent on age and sex. Our findings suggested that both the dopamine synthesis capacity and the D_2R (1) decline throughout age, although dopamine synthesis capacity declines later than D_2R, (2) are higher in females versus males, and (3) increase as a function of BMI. Although thalamic findings were uncertain, they were mainly consistent with the overall pattern in the striatum. In general, these effects may contribute to age and sex dependent prevalence in neurological and psychiatric conditions involving altered dopamine expression and function. Our results regarding unaltered D_2R in the overweight subjects suggests that the D_2R availability in the striatum and thalamus is not a central contributor of general weight gain.

Overall, this large multi-cohort dataset suggests that the dopaminergic changes observed in neurological and psychiatric pathology are multifaceted, involving region-specific and between-region mechanisms. PD significantly reduces striatal dopamine synthesis capacity, and the influence is greater than the independent effects of age, sex, and BMI. As with the healthy controls, PD patients show high interregional correlation of (1) striatal dopamine synthesis capacity and (2) D_2R level. Our results, thus, suggest that in striatum and thalamus, motor symptoms are linked to regional D_2R levels, rather than interregional decoupling of D_2R availability. Lowered correlation between the regions might, however, be characteristic for severe violent behaviour, although the finding requires validation with a larger sample. We observed neither regional D_2R alterations nor aberrant regional coupling in schizophrenia, PG, or depression, however, the findings may be influenced by limited sample sizes.

Methodologically, the scanner had a substantial influence on the PET estimates, which emphasises the need to adjust for scanner effects in multi-scanner datasets. Finally, when MRI is unavailable, template-based normalisation may be used with caution to prevent major data loss, though normalisation using subject-specific MRI should remain the preferred approach.

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Original Publications

Malén T, Tuisku J, Bucci M, Santavirta S, Kaasinen V, Kaasalainen S, Isojärvi J, Hietala J, Rinne J & Nummenmaa L (2026)
Striatal dopamine synthesis capacity in Parkinson's disease: Effects of age, sex, and body mass index in a large [^{18}F]fluorodopa PET cohort.
NeuroImage: Clinical

I

Malén T, Karjalainen T, Isojärvi J, Vehtari A, Bürkner P-C, Putkinen V, Kaasinen V, Hietala J, Nuutila P, Rinne J & Nummenmaa L (2022) Atlas of type 2 dopamine receptors in the human brain: Age and sex dependent variability in a large PET cohort.
NeuroImage

II

Malén T, Santavirta S, De Maeyer S, Tuisku J, Kaasinen V, Kankare T, Isojärvi J, Rinne J, Hietala J, Nuutila P & Nummenmaa L (2024) Alterations in type 2 dopamine receptors across neuropsychiatric conditions: A large-scale PET cohort.
NeuroImage: Clinical

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