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Insights from *in vivo* Brain PET Imaging

Imran Waggan

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Cover: *The illustration, digitally hand-drawn by Imran Waggan, features **'Dr. James Parkinson' tulips** in front of **Turku Cathedral**. The artwork pays homage to both the individuals living with Parkinson's Disease, the focus of this research, and Turku, the city where the study was conducted. Inspired by the art of Batool Rizvi. (All rights reserved.)*

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ABSTRACT

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the loss of dopaminergic neurons in the substantia nigra and the presence of alpha-synuclein pathology. The resulting dopamine deficiency leads to motor symptoms such as bradykinesia, rigidity and tremor, accompanied by a broad range of non-motor features. The adenosine A_{2A} receptor ($A_{2A}R$), which is co-localized with dopamine D_2 receptors in the striatum, plays a critical role in regulating basal ganglia neurotransmission. Modulation of $A_{2A}Rs$ has been shown to influence motor control making it an important therapeutic target in PD. However, *in vivo* data on how $A_{2A}R$ expression changes with disease progression and dopaminergic medication remain limited. In this thesis, $A_{2A}R$ availability was examined in patients with PD using positron emission tomography (PET) with the selective $A_{2A}R$ radioligand [^{11}C]TMSX. The aims were to (1) assess the effect of short-term cessation of dopaminergic medication on striatal $A_{2A}R$ availability, (2) compare $A_{2A}R$ binding between healthy controls, early- and moderate-stage PD, and (3) explore $A_{2A}R$ expression in cerebral gray and white matter regions. Quantitative PET analyses were performed using reference tissue models to estimate distribution volume ratios across brain regions. The results showed $A_{2A}R$ availability in the putamen and pallidum was comparable between on and after short term cessation of dopaminergic medication. However, the results in caudate were not equal between both states. Furthermore, patients with early-stage PD showed a decrease in caudate and moderate-stage PD exhibited increased $A_{2A}R$ binding in the pallidum compared to healthy controls, indicating progressive receptor alterations with disease severity. Finally, we showed $A_{2A}R$ alterations in cerebral gray and white matter regions, implying that adenosinergic signaling may contribute to extra-striatal and potentially, neuroinflammatory aspects of PD. These findings demonstrate that [^{11}C]TMSX PET imaging can be used to characterize A_{2A} receptor availability *in vivo* and that $A_{2A}R$ expression is dynamically altered by disease progression. The results provide new insights into disease stage dependent changes in $A_{2A}R$ availability in patients with PD.

KEYWORDS: Parkinson's disease, [^{11}C]TMSX, adenosine A_{2A} receptor, PET, dopaminergic medication, basal ganglia, purinergic signaling, neuroinflammation

TURUN YLIOPISTO
Lääketieteellinen tiedekunta
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Kliiniset neurotieteet
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IMRAN WAGGAN: Adenosiini A_{2A} -reseptorit parkinsonin taudissa –
Havaintoja in vivo aivojen PET-kuvantamisesta
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TIIVISTELMÄ

Parkinsonin tauti (PD) on etenevä neurodegeneratiivinen sairaus, jolle on ominaista dopaminergisten neuronien menetys mustatumakkeessa ja alfa-synukleiinin patologian esiintyminen. Tästä johtuva dopamiinin puute aiheuttaa motorisia oireita, kuten bradykinesiaa, jäykkyyttä ja vapinaa, sekä laaja valikoima ei-motorisia oireita. Adenosiini A_{2A} -reseptori ($A_{2A}R$), joita sijaitsee dopamiini D_2 -reseptorien yhteydessä aivojuoviossa (striatumissa), on tärkeässä roolissa tyvitumakkeiden neurotransmissiota säätelevässä toiminnassa. $A_{2A}R$-reseptorien modulaation on osoitettu vaikuttavan motoriseen kontrolliin, mikä tekee siitä tärkeän terapeuttisen kohteen PD:ssä. In vivo -tiedot siitä, miten $A_{2A}R$-ilmentyminen muuttuu taudin etenemisen ja dopaminergisen lääkityksen myötä, ovat kuitenkin edelleen rajallisia. Tässä väitöskirjassa tutkittiin $A_{2A}R$-reseptorien saatavuutta Parkinsonin tautia sairastavilla potilailla käyttämällä positroniemissiotomografiaa (PET) ja selektiivistä $A_{2A}R$-radioligandia [^{11}C]TMSX. Tavoitteena oli (1) arvioida dopaminergisen lääkityksen lyhytaikaisen tauotuksen vaikutusta striatumin $A_{2A}R$-saatavuuteen, (2) verrata $A_{2A}R$-sitoutumista terveillä verrokeilla, varhaisessa ja keskivaikeassa vaiheessa olevilla Parkinsonin tautia sairastavilla potilailla ja (3) tutkia $A_{2A}R$:ien ilmentymistä aivojen harmaassa ja valkeassa aineessa. Kvantitatiiviset PET-analyysit suoritettiin käyttämällä vertailukudosmalleja aivojen alueiden välisten jakautumistilavuussuhteiden arvioimiseksi. Tulokset osoittivat, että $A_{2A}R$:n saatavuus aivokuorukassa (putamen) ja linssitumakkeen pallossa (pallidum) oli vertailukelpoinen dopaminergisen lääkityksen käytön aikana ja sen lyhytaikaisen lopettamisen jälkeen. Häntätumakkeen (caudatus) alueen tulokset eivät kuitenkaan olleet samat molemmissa tiloissa. Lisäksi varhaisvaiheen PD-potilailla havaittiin caudatus-alueen $A_{2A}R$-sitoutumisen vähenemistä ja keskivaikean vaiheen PD-potilailla pallidum-alueen sitoutumisen lisääntymistä verrattuna terveisiin verrokkiryhmiin, mikä viittaa reseptorien progressiivisiin muutoksiin taudin vaikeusasteen myötä. Lopuksi osoitimme $A_{2A}R$-muutoksia aivojen harmaassa ja valkeassa aineessa, mikä viittaa siihen, että adenosiininerginen signalointi voi vaikuttaa PD:n striatumin ulkopuolisiin ja mahdollisesti neuroinflammatorisiin näkökohtiin. Nämä havainnot osoittavat, että [^{11}C]TMSX PET -kuvantamista voidaan käyttää A_{2A}-reseptorin saatavuuden karakterisointiin *in vivo* ja että $A_{2A}R$-ilmentyminen muuttuu dynaamisesti taudin etenemisen myötä. Tulokset antavat uutta tietoa taudin vaiheesta riippuvista muutoksista $A_{2A}R$-saatavuudessa PD-potilailla.

AVAINSANAT: Parkinsonin tauti, [^{11}C]TMSX, adenosiini-A_{2A}-reseptori, PET, dopaminerginen lääkitys, tyvitumakkeet, purinerginen signalointi, neuroinflammaatio

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Abbreviations

2-TCM	Two-Tissue Compartment Model
3D-OP-OSEM	Three-Dimensional Ordinary Poisson Ordered-Subset Expectation Maximization
A_{2A}	Adenosine A2A Receptor
A_{2B}	Adenosine A2B Receptor
ADP	Adenosine Diphosphate
AIS	Axon Initial Segment
ATP	Adenosine Triphosphate
BG	Basal Ganglia
BP_{ND}	Binding Potential Non-Displaceable
CB_1	Cannabinoid CB1 Receptor Complex
CNS	Central Nervous System
COMT	Catechol-O-Methyltransferase
COX	Cyclooxygenase
CSF	Cerebrospinal Fluid
D_2	Dopamine D2 Receptor Complex
DA	Dopamine
DAT	Dopamine Transporter
DVR	Distribution Volume Ratio
FBP	Filtered Back Projection
fMRI	Functional Magnetic Resonance Imaging
GABA	Gamma-Aminobutyric Acid
FOV	Field of View
GP	Globus Pallidus
GPCR	G-Protein Coupled Receptor
HRRT	High Resolution Research Tomograph
IgG	Immunoglobulin G
L-DOPA	Levodopa (L-3,4-dihydroxyphenylalanine)
LID	Levodopa-Induced Dyskinesia
LOR	Line of Response
LRRK2	Leucine-Rich Repeat Kinase 2

MAO-B	Monoamine Oxidase B
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
MSN	Medium Spiny Neuron
OPC	Oligodendrocyte Progenitor Cell
PD	Parkinson's Disease
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
PINK 1	PTEN-Induced Putative Kinase 1
PMT	Photomultiplier Tube
RF	Radiofrequency
ROI	Region of Interest
SNARE	Soluble N-ethylamide Sensitive Factor Attachment Protein Receptors
SNc	Substantia Nigra pars compacta
SNCA	Synuclein Alpha coding gene
SNRI	Serotonin-Norepinephrine Reuptake Inhibitor
SPECT	Single Photon Emission Computed Tomograph
SRTM	Simplified Reference Tissue Model
SSRI	Selective Serotonin Reuptake Inhibitor
STN	Subthalamic Nucleus
TAC	Time-Activity Curve
TGF-β	Transforming Growth Factor Beta
TNF	Tumor Necrosis Factor
UPDRS	Unified Parkinson's Disease Rating Scale
VA	Ventral Anterior Thalamic Nucleus
VL	Ventrolateral Thalamic Nucleus
VTA	Ventral Tegmental Area

List of Original Publications

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

I **Imran Waggan,** Eero Rissanen, Jouni Tuisku, Markus Matilainen, Semi Helin, Riitta Parkkola, Juha O. Rinne, Laura Airas. Effect of dopaminergic medication on adenosine 2A receptor availability in patients with Parkinson's disease. *Parkinsonism and Related Disorders,* 2021; 86: 40-44.

II **Imran Waggan,** Eero Rissanen, Jouni Tuisku, Juho Joutsa, Semi Helin, Riitta Parkkola, Juha O. Rinne, Laura Airas. Adenosine A_{2A} receptor availability in patients with early- and moderate-stage Parkinson's disease. *Journal of Neurology*, 2023; 270: 300-310.

III **Imran Waggan,** Eero Rissanen, Jouni Tuisku, Markus Matilainen, Riitta Parkkola, Juha O. Rinne, Laura Airas. Adenosine A_{2A} receptor availability in cerebral gray and white matter of patients with Parkinson's disease. *Parkinsonism & Related Disorders*, 2023; 113.

1 Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder worldwide. It is characterized by motor features such as bradykinesia, rigidity, postural instability, and resting tremor. It has been hypothesized that the pathogenic mechanism of PD involves the spread of alpha-synuclein from the gut to the brain, potentially leading to the degeneration of dopamine-producing neurons in the substantia nigra (Braak et al., 2003; Braak, De Vos, et al., 2006; Braak & Del Tredici, 2017; Morris et al., 2024). This degeneration disrupts nigrostriatal projections, resulting in a decrease in striatal dopamine levels and an imbalance in basal ganglia output. This disruption lies at the core of the motor symptom sequelae experienced by patients with PD (Kouli et al., 2018).

Intuitively, one of the earliest therapeutic approaches aimed at providing symptomatic relief was to replenish striatal dopamine by administering levodopa (Armstrong & Okun, 2020a). However, over time, use of levodopa may lead to increased sensitivity to fluctuations in levodopa levels resulting in the emergence of levodopa-induced dyskinesias (LID) (Riederer et al., 2025). Moreover, axial symptoms which may be resistant to levodopa emerge over the years, highlighting the broader limitations of dopaminergic therapies (Fabbri et al., 2016).

This clinical challenge prompted researchers to investigate new therapeutic targets for PD. Ideally, these targets should be located within anatomical regions affected by the disease. In this context, purinergic signaling has emerged as a relevant area of interest in which purinergic receptors, activated by extracellular nucleotides and nucleosides such as adenosine and ATP, are widely expressed throughout the brain and are known to modulate neurotransmitter release and neuronal excitability. Of particular relevance are the adenosine A_{2A} receptors, located adjacent to dopamine D_2 receptors in the striatum, which also play a key role in modulating basal ganglia output (Svenningsson et al., 1997). Furthermore, A_{2A} receptor expression is elevated in putaminal indirect medium spiny neurons in patients with advanced-stage PD and levodopa-induced dyskinesia (LID), which has led to the development of A_{2A} receptor antagonists for therapeutic use (Calon et al., 2004; LeWitt et al., 2008; Mori & Shindou, 2003a).

PET imaging of A_{2A} receptors provides a way to quantify receptor availability in the striatal and extra-striatal regions. By enabling the study of receptor changes *in vivo*, PET offers a translational link between preclinical findings and clinical questions. Despite significant advances in understanding purinergic signaling and the role of A_{2A} receptors in PD, several crucial questions remain unanswered. Firstly, since most diagnosed patients are on some form of dopaminergic medication, it becomes crucial to understand how withdrawal from these medications influences the striatal purinergic system, particularly the availability of A_{2A} receptors, and especially for the context of drug studies. Secondly, there remains an unmet need for a single therapy that may help improve both motor and non-motor symptoms during the early and moderate stages of PD, a population that has been largely understudied in the context of purinergic signaling. Finally, animal studies have shown that pharmacological modulation of A_{2A} receptors outside the striatum may alleviate non-motor symptoms, highlighting the importance of examining extra-striatal regions in the human brain as well.

2 Review of the Literature

2.1 Parkinson's Disease

Parkinson's disease (PD), a neurodegenerative disorder of the central nervous system, was first described by an apothecary-surgeon, political activist and paleontologist named Dr James Parkinson in 1817 (Lewis, 2017). He described the condition as 'the shaking palsy' and 'paralysis agitans' in his seminal essay on the disease (Parkinson, 1817). The condition was so well described by Parkinson that Dr. Jean-Martin Charcot, more than 50 years later in 1872, had to add just one more clinical criterion before naming the disease after Parkinson himself (Jean M. Charcot, 1877; Lewis, 2017). That basic clinical criterion, more or less, still holds to this day (Fig 1).

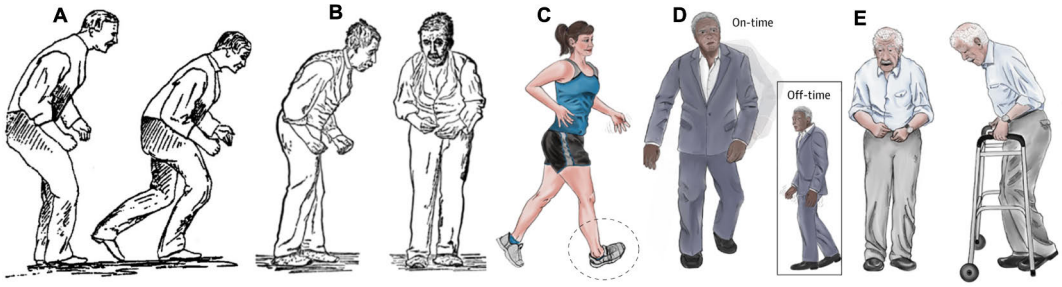

Figure 1. **Historical and modern depictions of motor symptoms in PD. 1A** and **1B** illustrate the stooped posture and rigidity characteristic of PD as documented in early sketches by neurologists Jean-Martin Charcot (1825-1893) and William Gowers (1845-1915) respectively. **1C** shows mild early-stage, motor-predominant, PD **1D** demonstrates the "ON-time" (effective medication) and "OFF-time" (symptom resurgence) states observed in moderate to advanced stage PD patients. **1E** shows advanced stage of the disease, including bradykinesia, rigidity and the reliance on assistive devices. Adapted from (Armstrong & Okun, 2020b), (W. R. Gowers & A. Churchill, 1887) and (J.M. Charcot, 1888). 1C, 1D and 1E used with permission from publisher (License# 5962370666269).

2.1.1 Epidemiology

PD is one of the fastest growing neurological conditions of the 21st century (Steinmetz et al., 2024). Approximately 11.8 million people were living with PD

globally in 2021. The prevalence of PD has more than doubled in the past three decades (Dorsey et al., 2018). The global incidence rate of PD is approximately 8-18 per 100,000 people per year. The incidence rate is age dependent with it being 4-5 per 100,000 people from age 40-59 and increasing to 120 per 100,000 people in population over 80 years of age (Steinmetz et al., 2024). This difference could be attributed to the average age of onset of PD which is approximately 60 years. The age standardized prevalence of PD is 138.6 per 100,000 people (Li et al., 2025). PD is less prevalent in females compared to males, with a female-to-male prevalence ratio of 0.68 (Steinmetz et al., 2024). This higher incidence in males could be attributed to environmental or occupational risk factors (Dorsey & Bloem, 2024).

In Finland, more than 15,000 individuals were living with PD in 2016 with an age adjusted increase in prevalence of around 5.8% since the 90s (Dorsey et al., 2018; Säävuori et al., 2018). By 2040, the prevalence of PD is expected to increase to 12 million people globally (Dorsey & Bloem, 2018). This increase can be attributed to improved living and healthcare standards leading to a growing proportion of elderly populations. Most cases of PD are idiopathic resulting from a confluence of environmental factors and variations in metabolic pathway genes (Ben-Shlomo et al., 2024). Familial PD, including cases involving mutations in genes such as LRRK2 and SNCA (Alpha-Synuclein), represent only a minority (approx. 10 %) of all PD cases.

The risk factors of PD include occupations that are associated with toxicant exposure such as farming or welding, higher intake of dairy products and reduced estrogen in women. In addition, constipation, although considered as one of the prodromal symptoms of PD, is also associated with increased risk for PD. (Bellou et al., 2016; Ben-Shlomo et al., 2024). Caffeine consumption and regular physical activity, higher urate levels and cigarette smoking have been shown to protect against PD (Ben-Shlomo et al., 2024).

2.1.2 Clinical presentation and diagnosis of Parkinson's disease

The earliest and most common symptoms of prodromal PD include constipation, depression, orthostatic hypotension, rapid eye movement (REM) sleep behavioral disorder, excessive daytime sleepiness, hyposmia, urinary dysfunction, and asymmetric shoulder pain. These non-motor symptoms precede for years, sometimes for up to a decade, before typical motor symptoms begin to manifest. The symptoms generally may not be PD specific but do increase the likelihood of a PD diagnosis over time (Armstrong & Okun, 2020a).

PD diagnosis is mainly based on a detailed history and physical examination. To meet the diagnostic criteria for parkinsonism, a patient must exhibit bradykinesia

along with resting tremor, rigidity, or a combination of both (Postuma et al., 2015). The diagnosis, however, is not clinically established as PD, unless patients both lack absolute exclusion criteria and meet at least two of the following supportive criteria:

(1) improvement with levodopa/carbidopa,

(2) resting tremor of a limb

(3) levodopa-induced dyskinesia

(4) evidence of olfactory loss or cardiac sympathetic denervation in ancillary testing.

The severity of PD related disability and impairment is monitored using the Unified Parkinson's Disease Rating Scale (UPDRS), especially in research settings (Fahn, 1987). It is a compound scale designed to encapsulate the many different facets of PD clinical phenotype. **(Table 1)**.

Table 1. Different parts of the Unified Parkinson's Disease Rating Scale (UPDRS) and their key features.

PART	FOCUS	KEY FEATURES
I	Non-motor aspects of daily living	Cognition, mood, behavior and autonomic symptoms like orthostatic hypotension
II	Motor aspects of daily living	Impacts on eating, dressing, hygiene, mobility and speech
III	Motor examination	Assessment of tremor, rigidity, bradykinesia and postural instability
IV	Treatment related motor complications	Dyskinesias, motor fluctuations and freezing of gate
V	Hoehn and Yahr Staging	Stages of disease progression based on functional impairment

If there is uncertainty between the diagnosis of PD and essential tremor, imaging studies, particularly SPECT Dopamine Transporter Imaging (DAT-SPECT), are performed. A significant reduction in dopamine transporter uptake in the striatum suggesting presynaptic dopamine neuronal dysfunction, strongly supports the diagnosis of PD and effectively excludes drug induced parkinsonism and essential tremor. However it does not distinguish PD from atypical parkinsonian disorders such as Parkinson-plus syndromes (Bajaj et al., 2013). Magnetic Resonance Imaging (MRI) is used to rule out structural abnormalities, vascular or atypical parkinsonism (Armstrong & Okun, 2020a). Genetic testing is generally reserved for patients with

early onset PD, typically those diagnosed before the age of 40, regardless of family history or in patients with positive family history if they were diagnosed between ages 40 and 50 (Bloem et al., 2021; Suomalaisen Lääkäriseuran Duodecimin & Suomen Neurologisen yhdistyksen asettama työryhmä, 2022).

2.1.3 Pathogenesis of Parkinson's Disease

The motor symptoms of PD are primarily driven by the degenerative changes in the dopaminergic neurons within the substantia nigra pars compacta (SNpc). These changes are largely attributed to the deposition of aggregated α-synuclein, a pathological hallmark of the disease that is present widely in the central and peripheral nervous system, often preceding its appearance in the substantia nigra (Morris et al., 2024).

2.1.3.1 Anatomy of Affected Regions

It is important to understand the structures involved in the pathology of PD, as 'anatomy creates the boundaries of the physiological space'(Bergman, 2021, p. 38). The degeneration of nigral dopaminergic neurons projecting to the basal ganglia leads to dopamine depletion, disrupting basal ganglia output and causing the motor dysfunction observed in PD patients. Basal ganglia is a collective term for three input nuclei, one intrinsic nuclei and two output nuclei (Lanciego et al., 2012).

The three input nuclei of the basal ganglia primarily comprise of the striatum, subthalamic nucleus and the substantia nigra pars compacta (SNc)/ventral tegmentum area with striatum being the largest of the three (Lanciego et al., 2012). Striatum has two parts i.e. the caudate and the putamen. Both structures receive input from the cerebral cortex, hippocampus, amygdala, dopaminergic input from the SNc, serotonergic input from the midbrain raphe nuclei and cholinergic input from the pedunculopontine nucleus (Bobillier et al., 1976; Gerfen, 1984; Ragsdale & Graybiel, 1988; Reiner et al., 2010). The cellular architecture of the striatum (both caudate and putamen) is predominantly composed of gamma-aminobutyric acid (GABA)-ergic medium spiny neurons (MSNs), forming more than 90% of the structure. Functionally, MSNs can be segregated into two distinct populations expressing either D_1 or D_2 dopamine receptors. The dopamine D_1 receptor MSNs also express dynorphin and substance P (neuroactive peptides). Similarly, dopamine D_2 receptor MSNs also produce the neuropeptide, enkephalin (Durieux et al., 2011).

The rest of the striatum is comprised of GABAergic medium aspiny interneurons, parvalbumin expressing fast-spiking interneurons (FSI) and giant aspiny cholinergic interneurons (Kawaguchi et al., 1995). The parvalbumin expressing FSIs provide lateral inhibition within the striatum (Prensa et al., 1999).

Cholinergic interneurons release acetylcholine and their distribution mimics that of the dopaminergic markers within the striatum. The uniformity of the striatal cellular architecture suggests that all the functionally distinct neuronal input from various regions of the brain is being subjected to identical computation (Bergman, 2021).

Subthalamic nucleus (STN), another input nucleus of the basal ganglia, receives efferent connections from frontal cortex, thalamus, SNc and several brainstem nuclei (Castle et al., 2005; Rommelfanger & Wichmann, 2010). It sends glutamatergic projections to both output nuclei and external segment of the globus pallidus (Castle et al., 2005). SNc, on the other hand, receives input from the striatum, STN, frontal cortex, raphe nucleus and other brainstem structures. SNc transmits dopaminergic efferents via the nigrostriatal and mesocortical pathways.

Globus pallidus externa (GPe) is the sole intrinsic nucleus of the basal ganglia. Afferent connections to the GPe include GABAergic input from the striatum as well as glutamate mediated excitatory input from the subthalamic nucleus. GPe provides inhibitory connections to both the input and output nuclei which makes it a vital regulator of basal ganglia circuitry. It also provides a direct connection to the frontal regions of the cerebral cortex (Saunders et al., 2015)

Finally, the output nuclei of the BG, globus pallidus interna (GPi) and substantia nigra pars reticulata (SNr), receive GABAergic input from the striatum and GPe as well as glutamatergic input from the STN. Output from SNr and GPi innervate thalamic motor nuclei, pedunculopontine nucleus, and superior colliculus.

2.1.3.2 Models of the Basal Ganglia Circuitry

The direct/indirect pathway model (rate model) was introduced in the late 80s which suggests that input from the cerebral cortex to the basal ganglia is processed via two distinct population of MSNs (Spix & Gittis, 2020). Neurons with Dopamine D_1 receptors and substance P make up the direct pathway inhibiting the basal ganglia output nuclei. Conversely, neurons with D_2 receptors and enkephalin represent the indirect pathway which disinhibits the output nuclei through excitatory input via STN (Albin et al., 1989; Bergman et al., 1990a; Gerfen et al., 1990). Briefly, the promotion or inhibition of a particular behavior was determined by whether the direct or the indirect pathway was dominant, respectively. Since both pathways are primarily thought to be driven by dopamine, a lack of it would lead to hypokinetic symptoms such as those experienced in PD and an increase would lead to hyperkinetic symptoms e.g. symptoms of levodopa induced dyskinesia (LID) (Bergman, 2021).

Although the direct/indirect pathway model (Fig 2A) explains the outcome of dysregulation of dopaminergic input to the striatum, it fails to factor in the complex circuitry of the basal ganglia described earlier. A more comprehensive model of the basal ganglia circuitry suggests that MSNs of the direct pathway also provide input to the globus pallidus externa which, not only projects backwards to the striatum but also provides input to the cortex (Fig 2B). In addition, STN receives projections from the cortical and subcortical areas while providing connections to the GPe and output

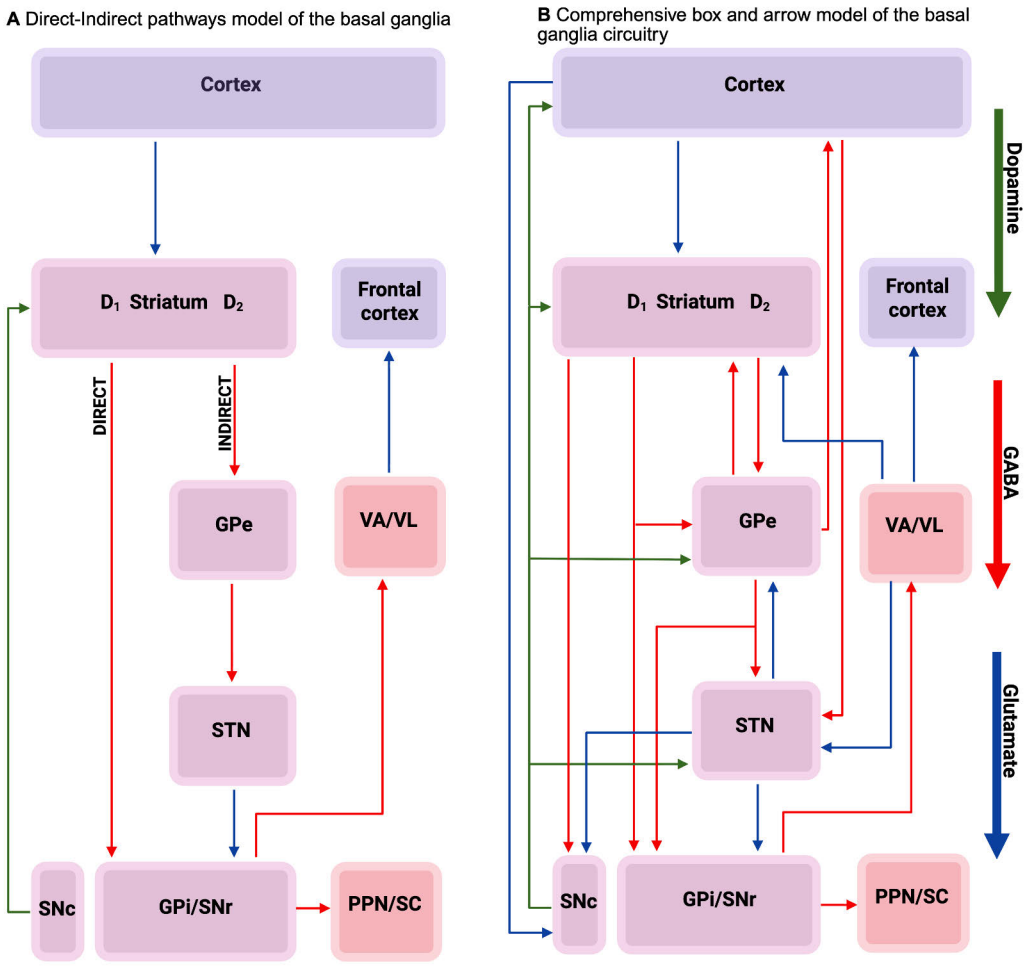

Figure 2. Rate **(A)** and comprehensive **(B)** models of basal ganglia circuitry, illustrating the direct and indirect pathways involved in motor control. Key structures: **Cortex** (cortical input), **D_1/D_2** (dopamine receptor-expressing neurons in the striatum), **Striatum** (input nucleus of the basal ganglia), **GPe** (external globus pallidus), **STN** (subthalamic nucleus), **GPi/SNr** (internal globus pallidus/substantia nigra pars reticulata), **SNc** (substantia nigra pars compacta), **VA/VL** (ventral anterior and ventrolateral thalamic nuclei), and **PPN/SC** (pedunculopontine nucleus/superior colliculus). Arrows denote neurotransmitters. Modified from (Bergman, 2021; Plotkin & Goldberg, 2019). (Created with BioRender.com)

nuclei of the basal ganglia (Plotkin & Goldberg, 2019). Based on this model, it is difficult to intuit the outcome of a particular input but, simultaneously, it underscores the complexity of the basal ganglia circuitry.

Action selection model suggests that the BG nuclei typically act as adjudicators of inputs from the cortex. The actions or movements that need to be selected are processed via the direct pathway while the ones not selected are inhibited through the indirect pathway. This ensures that a single action is selected from a multitude of inputs to the basal ganglia from the cerebral cortex (Denny-Brown, 1966; Mink, 1996). The model is too simplistic and does not consider the notion that our movements are the result of simultaneous activation and suppression of several muscles (Bergman, 2021).

Other notable models are the actor/critic reinforcement learning model (also applied in machine learning), multiple-critics multi objective optimization model and the Kahneman's system 1 of brain's state to action loops (Joel et al., 2002; Urfalı et al., 2020; Kahneman, 2011; Bergman, 2021). These models largely account for the complex circuitry of the basal ganglia and expand on the physiological role it plays in the human brain.

2.1.3.3 Molecular mechanisms underlying Parkinson's Disease

Alpha- synuclein is a 140-amino acid protein highly expressed at presynaptic terminals, where it exists mainly as a soluble monomer but can also form *a*-helical multimers on lipid membranes (Vekrellis et al., 2011). It regulates synaptic vesicle trafficking and neurotransmitter release by clustering vesicles, assembling soluble N-ethylamide sensitive factor attachment protein receptors (SNARE) complexes and maintain vesicle pools (Sharma & Burré, 2023). Aggregation of alpha-synuclein initiates a cascade of different pathogenic mechanisms involving different organelles, such as mitochondria, which ultimately result in the dopaminergic neuronal loss observed in PD patients. Mitochondrial dysfunction plays a major role in PD pathology as it not only leads to a decrease in the production of ATP but also ramps up the production of toxic reactive oxygen species. This enables the formation of alpha-synuclein oligomers and insoluble fibrils (Picca et al., 2021). In addition, decreased mitochondrial performance disrupts cellular calcium levels which, consequently, interferes with axonal transport, vesicle recycling and neurotransmitter release. Dysregulation of calcium homeostasis maintained by mitochondria is especially toxic to the nigral dopaminergic neurons as it serves the function of a pacemaker to facilitate the sustained release of dopamine (Nicoletti et al., 2021; Yadava & Nicholls, 2007). Furthermore, dopaminergic neurons have higher ATP demands, compared to other neuronal population and astrocytes, which requires optimal mitochondrial function and, therefore, are particularly prone to

mitochondrial impairment (Eldeeb et al., 2022). Familial PD genes PINK 1 and PRKN serve a function in mitochondrial quality control while Gly2019Ser mutation of the LRRK2 disrupts mitophagy, a process that tags damaged mitochondria for autophagy, which also signifies the key role of mitochondrial dysfunction in PD pathogenesis (Singh & Ganley, 2021).

Disruption of the autophagy-lysosomal system in PD leads to a buildup of misfolded alpha-synuclein protein in the brain. Normally, these proteins are degraded and cleared by lysosomes. However, the dysfunction of the ubiquitin-proteosome system and mitochondria impairs the capacity of lysosomes to perform their role effectively leading to an increase in the cellular levels of alpha-synuclein and their subsequent aggregation (Horowitz et al., 2022; Navarro-Romero et al., 2020). LRRK2 overactivation, most common cause of autosomal dominant PD, also decreases the functional capacity of lysosomes (Kluss et al., 2019).

Neuroinflammation also contributes significantly to the degeneration of dopaminergic neurons in PD. Components of both the innate and adaptive arms of the immune system are involved in the neuroinflammatory process. Microglia, the resident macrophages of the brain and part of the innate immune system, are present abundantly in the SNc and the striatum (Imamura et al., 2003). In PD and in other neurodegenerative diseases, these microglia express HLA-DR, a class II major histocompatibility complex protein involved in presenting antigens to the cells of the adaptive immune system, normally absent in healthy brains. HLA-DR positive or activated microglia increase proportionally with the neuronal degeneration in the nigrostriatal neurons (McGeer et al., 1988; Walker & Lue, 2015). Increased levels of reactive oxygen species, tumor necrosis factor (TNF), interleukin 1β and transforming growth factor-β (TGF- β) in the SNc, striatum and cerebrospinal fluid (CSF) could partially be attributed to the activated microglia (Harms et al., 2021). Microglial activation in PD has also been demonstrated in the putamen, midbrain (including substantia nigra) and frontal cortex using translocator protein (TSPO) targeted PET imaging with radioligands such as [^{18}F]-DPA714 and PBR06, particularly in early stages of the disease (Al-Abdulrasul et al., 2025; Gerhard et al., 2006; Kouli et al., 2023; Lavisse et al., 2021). Extracellular alpha-synuclein fibrils have been shown to activate microglia in early onset PD and in turn, microglia can also interact with alpha-synuclein to enhance their propagation and aggregation, as shown *in vitro* and in animal models (Joers et al., 2017; Schapansky et al., 2015).

$CD3^+$ cells of the adaptive immune system have also been found to cross the blood brain barrier in patients with PD (McGeer et al., 1988). Similarly, $CD4^+$ and $CD8^+$ cells have been found to be elevated in the SNc of patients with PD as compared to healthy volunteers (Brochard et al., 2009). $CD4^+$ T cells from patients with PD have also been found to recognize alpha-synuclein peptides indicating that adaptive immune system plays a more direct role in the overall disease process

(Sulzer et al., 2017). Peripheral number of $CD4^+$ T cells and B cells are reduced in in patients with PD (C. H. Stevens et al., 2012). Conversely, deposits of immunoglobulin G (IgG), an antibody produced by B cells, have been found on dopaminergic neurons while the FcγRI, a high affinity activating IgG receptor, has been located on activated microglia which indicates a role of the B-cell led humoral immune system (part of adaptive immunity) in neuroinflammation (C. F. Orr et al., 2005).

Neuroinflammatory cascade is ultimately spearheaded by cytokines, the chemical messengers of the innate and adaptive immune system. TNF-α and IFNγ led signaling are important cytokinetic pathways in PD pathophysiology. TNF-α signaling leads to increased microglial activation which in turn results in an increase in the release of proinflammatory cytokines (including TNF-α). This creates a positive feedback loop that promotes chronic neuroinflammation (Brás et al., 2020). Elevated TNF-α levels have also been found in the CSF and substantia nigra of patients with PD which further highlights the key role played by TNF-α mediated signaling (Eidson et al., 2017; McCoy et al., 2011; Mogi et al., 1994). Similarly, increased levels of IFNγ, another cytokine, have been reported in the midbrain of patients with PD alongside alpha-synuclein. In healthy brains there was a negative correlation between IFNγ and SNCA (alpha-synuclein gene) while in patients with PD, the negative correlation shifted to a strong positive association (Liscovitch & French, 2014). LRRK2, a gene involved in familial PD, is also an IFNγ target gene, signifying the importance of this cytokine in PD pathology (Gardet et al., 2010).

Epidemiological evidence also gives us insight on the impact of inflammation in PD. Studies suggest that the use of non-steroidal anti-inflammatory diseases (NSAIDs), specifically aspirin is associated with a decrease in the risk of PD in men (Hernán et al., 2006). Ibuprofen and acetaminophen have also been observed to protect dopaminergic neurons in preclinical studies while meloxicam and sodium salicylate reduce neurotoxicity in MPTP mouse models (Casper et al., 2000; Ferger et al., 1999; Sairam et al., 2003). In humans too, ibuprofen has been linked to a reduced risk of PD but the affect was not observed with other NSAIDs such as aspirin (H. Chen et al., 2005). The protective effect of certain NSAIDs like ibuprofen could potentially be attributed to the inhibition of cyclooxygenase (COX) 1 and COX2 which reduce the oxidative stress particularly on the dopaminergic neurons (Asanuma et al., 2001).

Gastrointestinal dysfunction has also been implicated in the pathogenesis of PD (Fang et al., 2020). The earliest indications of gut involvement came from the Braak hypothesis, which suggests that alpha-synuclein accumulation may originate in the enteric nervous system and the olfactory bulb (dual-hit hypothesis). From the gut, it is proposed to spread via the vagus nerve to the dorsal motor nucleus (Stage 1), ascending through the brainstem (Stage 2) to reach the substantia nigra in Stage 3,

eventually affecting the mesocortex in Stage 4. (Braak, de Vos, et al., 2006; Braak et al., 2003; Braak & Del Tredici, 2017). The trigger for the misfolding of alpha synuclein in the gastrointestinal tract is possibly linked to bacterial amyloid cross-seeding, a process in which amyloid proteins produced by gut bacteria act as templates that induce misfolding and aggregation of host proteins such as alpha-synuclein, resulting from gut microbiome dysfunction (Halimi et al., 2025). Multiple studies have shown fluctuation in the gut bacterial composition. This includes changes in *Prevotellacea, Bifidobacterium*, *Akkermansia,* and *Lactobacillus* in patients with PD (Boertien et al., 2019). In addition, a positive correlation between clinical phenotype i.e. motor symptoms and *Enterobacteriaceae* has also been observed. In the same study, an abundance of bacterium *Prevotellaceae* was considered protective against PD (Scheperjans et al., 2015). In addition, dysbiosis, characterized by an imbalance in gut microbiome composition, has been implicated in promoting colonic inflammation and gut barrier permeability which eventually contributes to neurodegeneration (Bullich et al., 2019). This is also in line with evidence that suggests that patients with inflammatory bowel disease (IBD) have approximately 30% higher risk of acquiring PD compared to normal population (Zhu et al., 2019). Interestingly, coffee drinking, which has been epidemiologically associated with a lower risk of PD, not only promotes gut motility but also changes the composition of gut microbiome to decrease intestinal inflammation (Derkinderen et al., 2014). This is one of several potential mechanisms through which caffeine may exert its neuroprotective effects.

2.1.4 Therapeutic interventions in Parkinson's Disease

The treatment of PD is highly individualized depending on the patient's clinical phenotype. There are currently no medications to slow or prevent the progression of PD in patients in early stages, however, the use of Selegiline, Rasagiline, Ropinirole, vitamin D, mediterranean diet and exercise have yielded encouraging results (Fox et al., 2018; Trinh et al., 2026). Medications used to treat motor symptoms in patients at different stages of the disease are summarized in Table 2. Briefly in the earliest stage of the disease, levodopa/carbidopa or one of the non-ergot dopamine agonists are given as the primary treatment of choice. In Finland, patients younger than 60-65 years of age are started on a dopamine agonist or MAO-B inhibitor to alleviate symptoms. However, older adults (age>60–65years) or younger patients with severe symptoms can be started on Levodopa/Carbidopa from the outset (Pekkonen et al., 2015; Suomalaisen Lääkäriseuran Duodecimin & Suomen Neurologisen yhdistyksen asettama työryhmä, 2022).

The progression from moderate to more advanced stages of the disease comes with added complication of treatment induced motor fluctuations. These include

the early morning off phenomenon (re-emergence of motor symptoms) which results from the diminished dopamine efficacy. Patients also experience sudden shifts between asymptomatic (ON) and symptomatic (OFF) state, termed as 'ON-OFF' phenomenon (Fig 1D). Levodopa induced dyskinesias are also common in the advanced stages of the disease and are usually treated by reducing or altering levodopa dosage, adding a dopamine agonist or with NMDA receptor antagonists.

Non-motor symptoms pose an equally difficult challenge for patients with PD to cope with. In some instances, these symptoms might have a more significant effect on the quality of life (Schapira et al., 2017). Apart from the prodromal symptoms associated with idiopathic PD, patients may also experience impaired color vision, visual hallucinations, pain, anxiety, depression, early cognitive dysfunction, dementia, sleep disturbances and bladder hyper-reflexia (Schapira et al., 2017). A number of these non-motor symptoms could be managed by readjusting the dose of levodopa, as they may stem from low levels of dopamine (van Wamelen et al., 2022). Some, however, might be related to higher dopamine levels e.g. euphoria and agitation and in these instances adjusting levodopa dose, its timing and supplementing with adjunct medication could benefit the patient (Ray Chaudhuri et al., 2018). Serotonin selective reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs) could be used in the management of depression in PD. For dementia in PD, cholinesterase inhibitors e.g. rivastigmine are used to improve cognitive function (Seppi et al., 2019).

Autonomic symptoms including bladder dysfunction, constipation and sialorrhea, pose a significant burden on the daily life of patients with PD. Bladder dysfunction is initially treated by optimizing dopamine dose but if the symptoms persist, anticholinergics such as solifenacin or a β3-adrenoceptor agonist (mirabegron) can be used (Cho et al., 2021; Foltynie et al., 2024). Orthostatic hypotension in patients with PD is treated conservatively in the beginning by reducing blood pressure lowering drugs or increasing salt and water intake. If the condition persists domperidone, midodrine, fludrocortisone or droxidopa can be added to the treatment regimen (Fanciulli et al., 2020). Sleep disturbances are also fairly prevalent in PD (Menza et al., 2010). Dopamine agonists and anticholinergics are frequently implicated in daytime sleepiness which may be alleviated by reducing or adjusting the dose. Caffeine can also be used to treat somnolence (Postuma et al., 2017). Insomnia, on the other hand, can be temporarily treated with non-benzodiazepine cyclopyrrolones or prolonged release melatonin in some cases (Ahn et al., 2020).

Patients who enter the complex phase of the disease experiencing debilitating dyskinesias and extended 'OFF' episodes are considered for non-oral or invasive therapies. Briefly, the non-oral therapies include subcutaneously injectable formulations of apomorphine (Olanow et al., 2014; Thijssen et al., 2022). Invasive

therapies primarily consist of levodopa/carbidopa intestinal gel, subcutaneous infusion of foslevodopa/foscarbidopa or deep brain stimulation of the subthalamic nucleus, ventrolateral thalamus and globus pallidus internus (Antonini et al., 2021; Odekerken et al., 2013; Rukavina et al., 2025; Weaver et al., 2009). Additionally, these structures can also be lesioned through different techniques using magnetic resonance guided ultrasound surgery or radiofrequency thermocoagulation to achieve symptomatic control (Alvarez et al., 2005; Bond et al., 2018; Martínez-Fernández et al., 2020).

Table 2. Overview of pharmacological therapies for the motor symptoms of PD. Modified from (Foltynie et al., 2024) and (Fox et al., 2018).

THERAPEUTIC APPROACH	DRUGS	MECHANISM OF ACTION	STAGE OF USE
Dopamine precursors	Levodopa, Carbidopa	Replenishes dopamine levels in the brain	All stages; primary treatment of choice
Dopamine agonists	Pramipexole, Ropinirole, Rotigotine, Apomorphine	Stimulates dopamine receptors directly	Early to moderate stages or adjunct in advanced stages (apomorphine).
MAO-B inhibitors	Selegiline, Rasagiline	Inhibits breakdown of dopamine by monoamine oxidase-B	Early to moderate stages as monotherapy
COMT inhibitors	Entacapone, Tolcapone, Opicapone	Inhibits breakdown of levodopa by catechol-O-methyltransferase	Adjunct to levodopa in advanced stages for treatment of motor fluctuations
Anticholinergics	Trihexyphenidyl, Benztropine	Reduces cholinergic activity to balance dopamine-acetylcholine	Early stages for tremor control if unresponsive to levodopa replacement
Amantadine	Amantadine	NMDA receptor antagonist	Moderate to advanced stage to treat dyskinesia
Clozapine	Clozapine	Low D_2 receptor antagonist and 5-HT_{2A} antagonist	Moderate to advanced stage to treat psychosis
Adenosine A_{2A} antagonists	Istradefylline	Blocks adenosine A_{2A} receptors to tone-down overactive indirect pathway	Adjunct therapy for advanced stages for improving 'OFF' times *(Approved for use in the US and Japan)*

Abbreviations: MAO-B: Monoamine Oxidase-B, COMT: Catechol-O-Methyltransferase.

2.2 Adenosine signaling and A_{2A} receptors

Adenosine, a purine ribonucleoside, is an essential component of many cellular structures and is widely distributed throughout the body. It also forms adenosine diphosphate (ADP) and adenosine triphosphate (ATP), by the process of phosphorylation, which serve as the main source of energy to sustain cellular functions. In brain adenosine and ATP also act as neuromodulators and not neurotransmitters as they are neither stored in the nerve terminals nor released in the synaptic cleft (Burnstock, 2007; Pinna et al., 2018). Neurons are typically bathed in extracellular adenosine, the concentration of which, under physiological conditions, is tightly controlled. This extracellular adenosine is produced through multiple routes e.g. by the breakdown of ATP, catabolism of cellular structures or co-release with other neurotransmitters (Borea et al., 2018). Rather than producing fast point-to-point synaptic transmission, adenosine accumulates in the extracellular space and signals through G protein coupled receptors to broadly modulate neuronal excitability and synaptic strength across large brain networks (Yahiro et al., 2025). Under pathological conditions or after a neuronal injury extracellular adenosine levels can increase by about 100 times that of normal levels (Dale et al., 2000).

Extracellular adenosine is involved in maintaining physiological plasticity via their action on P1 purinergic receptors. These G-protein coupled receptors play a minor role in homeostasis but are crucial for allostasis, the brain's response to correct imbalance resulting from stressors (Blum & Lopes, 2021). The P1 receptors are classified into four subtypes of adenosine receptors (ARs) including A_1, A_{2A}, A_{2B} and A_3 receptors (Vincenzi et al., 2023). Adenosine A_1 and A_{2A} receptors are more widespread in the brain while the A_{2B} and A_3 receptors have relatively limited presence. Similarly, the A_1 subtype has the highest affinity (70nM) for adenosine followed by the A_{2A} (150nM), A_{2B} (5100nM) and A_3 (6500nM) (Dunwiddie & Masino, 2001). Apart from the brain, A_1 and A_{2A} receptors are also expressed in the heart, lungs, kidneys and immune cells. A_{2A} receptors are also expressed on vascular endothelial cells, where they regulate vascular tone (Johnston-Cox et al., 2012; Sheth et al., 2014).

2.2.1 Adenosine A_{2A} receptors in the brain

Adenosine A_{2A} is a class A rhodopsin-type G_s protein coupled receptor (GPCR). The GPCR is embedded in the seven transmembrane helices spanning the lipid bilayer of the plasma membrane. The transmembrane 7 helix (TM7) in the GPCR enables stronger coupling in the G_s-A_{2A} conformation (Picard et al., 2025). Binding of adenosine to A_{2A} receptor leads to activation of adenylate cyclase via the α-subunit of the GPCR. This leads to an increase in cAMP levels and activation of protein kinase A which results in the downstream effects of A_{2A} receptor activation.

(Alexander et al., 2021). A_{2A} receptors are primarily expressed in the striatum and the external segment of the globus pallidus externa. They are also expressed in nucleus accumbens, olfactory tubercles and nucleus of the solitary tract (Fig 3). Within the striatum and the GPe, they are expressed both pre and post synaptically on the GABA-ergic medium spiny neurons (MSN) (Rosin et al., 2003). The mRNA for A_{2A} receptors was found to be specific for the D_2 and pre-proenkephalin expressing MSNs representing the indirect pathway (Kase, 2001; Martinez-Mir et al., 1991; Svenningsson et al., 1997). However they were not present on the MSNs with D_1 receptor and substance P (Bogenpohl et al., 2012). Within the striatum and GPe, A_{2A} receptors make hetero-receptors complexes with A_1 and D_2 receptors. These complexes allow for allosteric interactions between the two heteroreceptors enabling functional selectivity. Activation of A_{2A} receptors reduces the sensitivity of D_2 receptors to dopamine, as A_{2A} stimulation exerts an antagonistic allosteric effect on D_2 receptor signalling. Conversely, blockade of A_{2A} receptors enhances D_2 receptor sensitivity, thereby facilitating dopaminergic transmission (Mori et al., 1996; Prasad et al., 2021). There also has been evidence of G_q coupled A_{2A}-CB_1 heteromer, where CB1 refers to the cannabinoid receptor type 1, in the somatodendritic compartment and the nerve terminals of the striatal GABAergic MSNs within the indirect pathway (Moreno et al., 2018). A_{2A}-CB_1 heteromers may also be expressed within the striatal cholinergic interneurons or astrocytes (Moreno et al., 2018). Post-synaptically A_{2A}-CB_1 heteromers may combine with D_2 receptor

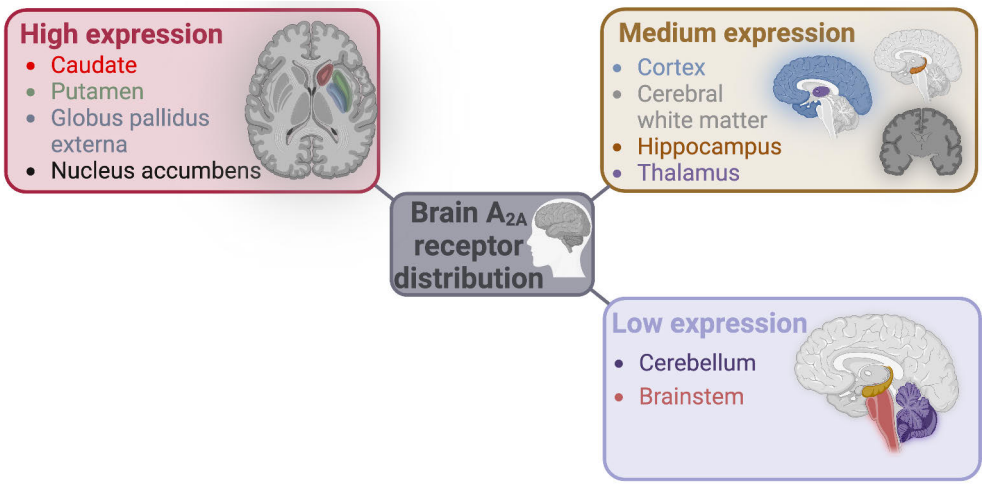

Figure 3. Adenosine A_{2A} receptor distribution in the brain. A_{2A} receptors show high expression in the striatum (caudate, putamen, nucleus accumbens) and external globus pallidus (GPe), regions involved in motor control and basal ganglia signaling. Medium expression is observed in the cortex, hippocampus, thalamus, and cerebral white matter, where A_{2A} receptors contribute to cognitive functions, plasticity, and synaptic modulation. Low expression is present in the cerebellum and brain stem structures. Data from (Mori, 2020). (Created with BioRender.com)

to form heteromeric complexes such as A_{2A}-CB_1-D_2 receptor heteromultimer (Bonaventura et al., 2014; Navarro et al., 2010). Striatal A_{2A} receptors activity is also correlated with docosahexaenoic acid (DHA), an essential component of the lipid bilayer of the plasma membrane. Notably, DHA chains (lipids), surpass partial agonists in the activation of striatal A_{2A} receptors (Mizumura et al., 2020).

Adenosine A_{2A} receptors are also expressed on striatal astrocytes alongside dopamine D_2 receptors (Amato et al., 2024; Pelassa et al., 2019). Within the astrocytes the cross-interaction between these two receptors or the activation of A_{2A} receptors may increase glutamatergic transmission (Kanno & Nishizaki, 2012; Pelassa et al., 2019). A_{2A} receptors are also found on the myelinated axonal initial segment (AIS) of layer V excitatory cortical pyramidal cells, their nodes of Ranvier and in the cerebellar white matter. AIS A_{2A} receptor activation increases the excitability of neurons by increasing cAMP levels whereas their activation on the nodes of Ranvier slows down signal conduction (Lezmy et al., 2021). This suggests that glial A_{2A} receptors contribute to the modulation of conduction speed within white matter. Moreover, A_{2A} receptors are also expressed on oligodendrocyte precursor cells (OPCs) where their activation also increases cAMP levels triggering the differentiation of OPCs into mature oligodendrocytes promoting myelination (Coppi et al., 2013; B. Stevens et al., 2002). A_{2A} receptors expressed on microglia are important in regulating their morphology and physiological functions. Retraction of microglial processes, which is an important hallmark of neuronal inflammation, is, in part, driven by upregulation of A_{2A} receptors (A. G. Orr et al., 2009). A_{2A} receptors expressed on microglia within the spinal cord are also crucial in modulating hypoxia driven plasticity mechanisms (Marciante et al., 2024). Microglial A_{2A} receptors are also involved in postnatal synaptic pruning of the retinogeniculate pathway (Miao et al., 2021). Neuronal A_{2A} receptor inactivity also promotes postnatal pruning of GABAergic synapses as postsynaptic A_{2A} receptors monitor the activity of presynaptic terminals and initiate their removal after a certain period of dormancy (Gomez-Castro et al., 2021).

2.2.2 Adenosine A_{2A} receptors and Parkinson's Disease

As mentioned before, A_{2A} receptors are found predominantly on the postsynaptic GABAergic MSNs in the caudate, putamen and on the nerve terminals in GPe where they modulate motor functions via the indirect pathway. This 'dual excitatory modulation' of the striatopallidal MSNs is important as the imbalance between the direct (GO) and the indirect (NO-GO) pathway is the pathogenic basis of motor symptoms in PD (Mori & Shindou, 2003a). Moreover, it is the therapeutic regulation of the output of indirect pathway that leads to improvement in motor function in patients with PD by suppressing STN and GPi mediated thalamic inhibition

(Bergman et al., 1990b; Obeso et al., 2008; Neumann et al., 2018). The direct pathway, on the other hand, is more associated with the emergence of debilitating dyskinesia. Increase in the A_{2A} receptor mRNA levels was observed in the putamen of PD patients with dyskinesia (Calon et al., 2004). Moreover, increased A_{2A} receptor binding was observed in the GPe in PD patients regardless of whether they suffered from dyskinesia or not (Calon et al., 2004). PET studies showed a similar pattern of increased A_{2A} receptor expression in the striatum of patients with dyskinetic PD (Mishina et al., 2011; Ramlackhansingh et al., 2011). A_{2A} receptor availability was decreased in putamen of the more affected side of the brain in drug naïve patients with PD. However, after the initiation of dopaminergic therapy, the availability of A_{2A} receptors increased in bilateral putamen (Mishina et al., 2011) (Table 3). This increased A_{2A} receptor expression, in addition to altering the striatal output, also contributes to synaptic dysfunction and accelerates neurodegeneration (Blum & Lopes, 2021). Furthermore, the increase in the availability of A_{2A} receptors and the decrease in D_2 receptors indicates that the former exert a greater influence in modulating the output of the indirect pathway in PD (Mori, 2020).

To mitigate the effects of disrupted A_{2A} receptor signaling, their antagonists showed promise in alleviating motor symptoms in preclinical animal models of PD (Mori & Shindou, 2003). The A_{2A} receptor antagonists in combination with levodopa reduce the hyper-excitability of the indirect pathway and restore the direct pathway output via D_1 receptor stimulation, facilitating motor symptom control (Mori, 2020). Discovery of this novel mechanism of symptomatic control led to the development of several A_{2A} receptor antagonists such as Istradefylline, Tozadenant and Preladenant (Shook & Jackson, 2011). Only Istradefylline was approved for use in patients with PD, first in Japan and then by the FDA in the US (LeWitt et al., 2020). It was observed that the use of Istradefylline reduced 'OFF' time (period of worsened motor symptoms) and improved postural abnormalities in patients with PD when used in conjunction with Levodopa without affecting dyskinesia (LeWitt et al., 2008; Takahashi et al., 2022). Furthermore, prioritizing the use of Istradefylline before using other levodopa adjunct medications reduced progressive levodopa daily dose increases, which may reduce levodopa induced complications in the later stages of the disease (N. Hattori et al., 2023). The potential of Istradefylline's use in PD extends beyond just motor symptom control. Its use has been shown to reduce the symptoms of anhedonia and apathy in patients with PD without worsening motor symptoms (Nagayama et al., 2019). This contrasts with SSRIs and SNRIs which may exacerbate motor symptoms (Matić et al., 2024). In addition, Istradefylline also reduced the oculomotor deficit, hence improving smooth pursuit eye movements in patients with PD (Fujita et al., 2023).

Table 3. Summary of PET and Radioligand Binding Studies Investigating A_{2A} Receptor Availability in Parkinson's Disease and Related Models.

STUDY	STUDY TYPE	STUDY POPULATION	TRACER	DISEASE STAGE	ON OR OFF MEDICATION	BINDING (CONTROL)	BINDING (DISEASE GROUP)	MAIN FINDINGS
(Calon et al., 2004)	Post-mortem	9 HC (68±3), 7 PD patients without LID 80±3) and 7 PD patients with LID (77±2)	[^{3}H]SCH58261	PD without LID PD with LID	Both groups ON drugs		PD with LID Putamen critical difference=29.78%	a: Increased binding in Putamen in patients with LID vs HC and patients without LID b: Decreased binding in Medial caudate in grouped PD patients vs HC c: Increased binding in Globus pallidus vs HC
(Mishina et al., 2011)	Clinical	6 HC (60.7±8.5), 9 Drug-naïve (64.6±5.7), 7 PD patients with levodopa induced dyskinesia (LID) (65.0±7.5)	[^{11}C]TMSX	Drug naïve PD 2.0±1.2 PD with LID 11.1 ±7.2	OFF=9 ON=7	*DVR* Caudate=1.38 Putamen= 1.47	Drug naïve *(DVR)* Caudate=1.37 Putamen=1.48 PD with LID*(DVR)* Caudate=1.44 Putamen=1.58	a: Inc binding in Putamen in PD with dyskinesia as compared to HC b: Increase in binding in Putamen in 7 drug naïve patients after starting medication 1.46>1.50 (mean scan duration 14.5 months)

STUDY	STUDY TYPE	STUDY POPULATION	TRACER	DISEASE STAGE	ON OR OFF MEDICATION	BINDING (CONTROL)	BINDING (DISEASE GROUP)	MAIN FINDINGS
(Ramlackhansingh et al., 2011)	Clinical	6 HC (65±6.2), 6 PD patients without levodopa induced dyskinesia (LID) (67.7±4.4), 6 PD with LID (65.3±11.4)	[^{11}C]SCH442416	PD without LID 6.2±3.4 PD with LID 13.2±5.6	Both disease groups ON medication	BP_{ND} Caudate=0.53 Putamen=0.99	PD without LID(BP_{ND}) Caudate=0.4 Putamen=0.97 PD with LID (BP_{ND}) Caudate=0.96 Putamen=1.67	Patients with LID show increased A_{2A} receptor availability in the striatum.
(Bonaventura et al., 2014)	Pre-clinical	11 control monkeys (Macaca fasicularis) 10 MPTP treated monkeys (Macaca fasicularis)	[^{3}H]ZM 241385	PD without LID	MPTP lesioned OFF and then ON chronic levodopa treatment			A_{2A}-D_2 heteromer expression in the caudate nucleus significantly diminished in L-Dopa-treated PD monkeys vs Non-treated and Controls
(Zhou et al., 2017)	Pre-clinical	28 Female Wistar rats. Group1/2> Saline (sham) or 6OHDA injection followed by PET scan	[^{11}C]Pre-ladenant	Two groups: PD without LID 2: PD with LID after treatment with Levodopa	6-OHDA lesioned OFF and then ON chronic levodopa treatment	Untreated: BP_{ND}1.00 ± 0.02 After saline injection in 6OHDA rats: 4.90 ± 0.76	Untreated: BP_{ND}: 4.32 ± 0.41 6-OHDA vs. 4.58 ± 0.89 sham; NS, ratio: 0.94 ± 0.03 6-OHDA vs. 1.00 ± 0.02 sham; − 6.1%; p = 0.01	a: Intranigral 6-OHDA injection tended to decrease the A_{2A}R availability in the lesioned striatum. The decrease became significant when data were normalized to the non-affected side. L-DOPA treatment

STUDY	STUDY TYPE	STUDY POPULATION	TRACER	DISEASE STAGE	ON OR OFF MEDICATION	BINDING (CONTROL)	BINDING (DISEASE GROUP)	MAIN FINDINGS
		Group 3/4> 6OHDA lesion followed by saline (sham) or Levodopa treatment and PET scan					After Levodopa treatment: BP_{ND}: 6.02 ± 0.91 L-DOPA vs. 4.90 ± 0.76 saline; + 23.4%; p = 0.02	significantly increased $A_{2A}R$ binding in the affected striatum (BP_{ND}: 6.02 ± 0.91 L-DOPA vs. 4.90 ± 0.76 saline; + 23.4%; p = 0.02). b: Increased $A_{2A}R$ binding in 6-OHDA-lesioned rats with L-DOPA treatment as compared to rats with saline treatment.
(Schröder et al., 2020)	Pre-clinical	Wild–type C57BL/6JRj 5 control mice 7 rotenone treated mice	[^{18}F]FeSch	PD without LID Early to moderate PD	OFF medication			Slightly higher (11-27 %) uptake of [^{18}F]FeSch in the striatum of rotenone treated mice as compared to controls.
(Gündel et al., 2022)	Pre-clinical	Wild–type C57BL/6JRj 7 control mice 6 rotenone treated mice	[^{18}F]FLUDA	PD without LID Early to moderate PD	OFF medication	Striatum: BP_{ND}= 2.5 ± 0.4	Striatum: BP_{ND}= 2.0 ± 0.4	Decreased $A_{2A}R$ availability in rotenone treated mice.

Abbreviations: PD: Parkinson's Disease, HC: Healthy Control, LID: Levodopa-Induced Dyskinesia; $A_{2A}R$: Adenosine A_{2A} Receptor, PET: Positron Emission Tomography, BP_{ND}: Non-Displaceable Binding Potential, DVR: Distribution Volume Ratio.

2.2.3 Adenosine A_{2A} receptor PET tracers

Several PET radiotracers have been developed to study the *in vivo* availability of adenosine A_{2A} receptors. These tracers can be broadly categorized into xanthine and non-xanthine (triazolopyridine) based compounds. Xanthine based radiotracers share the chemical structure with the endogenous purine ligand of A_{2A} receptor.

Although, several xanthine-based tracers were developed over the years, only two, [^{11}C]TMSX (formerly [^{11}C]KF18446) and [^{11}C]KW6002, were evaluated in humans. [^{11}C]KW6002 was later developed into an oral therapeutic (Istradefylline) for patients with PD (LeWitt et al., 2008). However, its radiolabeled form was not pursued further because of its high non-specific binding.

[7-methyl-11C]-(E)-8-(3,4,5-trimethoxystyryl)-1,3,7-trimethylxanthine ([^{11}C]TMSX), a selective A_{2A} receptor antagonist, on the other hand, showed promise demonstrating reproducible binding in the striatum and low non-specific binding in the cortical and cerebellar regions. Within the striatum, it showed greater affinity for A_{2A} receptors in the putamen followed by the caudate and thalamus (Ishiwata et al., 2005). Notably, it showed stronger binding in the human thalamus compared to that observed in non-human primates. [^{11}C]TMSX has been employed in studying various central nervous system (CNS) disorders such as multiple sclerosis and PD as it shows good test-retest variability in human brain (Mishina et al., 2011; Naganawa et al., 2014a; Rissanen et al., 2013; Vuorimaa et al., 2017). Beyond the CNS, it has also been utilized in myocardial and brown adipose tissue imaging (Ishiwata, Kawamura, et al., 2003; Lahesmaa et al., 2019). One potential drawback of xanthine based radioligands is that they are prone to photoisomerization, which requires that radiochemical synthesis and handling be performed under low light to preserve chemical stability (Ishiwata, Wang, et al., 2003).

[^{11}C]SCH442416 was one of the earliest non-xanthine A_{2A} receptor radiotracer developed for use in human PET studies (Todde et al., 2000). It showed strong affinity for A_{2A} receptors and has been used in the investigation of CNS disorders (Marques et al., 2022). However, it was also demonstrated that [^{11}C]SCH442416 had a higher affinity for A_{2A}-A_1 heteromer as compared to A_{2A}-D_2 heteromer which makes it less suitable for studying basal ganglia disorders such as PD, where A_{2A}-D_2 receptor interactions are of primary interest (Orru et al., 2011a). To address these limitations, several newer generation A_{2A} radiotracers have been developed, among them [^{11}C]Preladenant and [^{18}F]MNI-444 have emerged as effective alternatives (Sakata et al., 2017a). These non-xanthine radiotracers are not prone to photoisomerization, unlike xanthine based radioligands, and demonstrate high striatal uptake and good target to background ratio. [^{11}C]Preladenant has demonstrated excellent pharmacokinetic properties but a moderate test-retest reproducibility (Toyohara et al., 2022).

In the present study, [^{11}C]TMSX was used to assess A_{2A} receptor availability in cerebral and striatal regions in patients with PD. Unlike [^{11}C]SCH442416, used in a previous study to assess A_{2A} receptor availability in caudate, putamen and thalamus, [^{11}C]TMSX offers more uniform affinity for striatal A_{2A}-D_2 (Ramlackhansingh et al., 2011). Furthermore, with [^{11}C]TMSX low signal-to-noise ratio is observed in cerebral gray and white matter regions, however, previous test-retest studies have shown that reliable estimates can nonetheless be obtained from these regions (Naganawa et al., 2014).

2.3 Imaging Methodology

2.3.1 Positron Emission Tomography (PET)

PET imaging uses radiopharmaceuticals to image the function of different organs. The radiopharmaceuticals are usually referred to as radiotracers, as they are used in trace amounts that do not perturb the underlying physiology. A radiotracer is tagged with positron-emitting radionuclides and, when administered at trace doses, follows specific biochemical pathways to quantify the distribution of biologically important molecules in vivo (Chandra & Rahmim, 2017). [^{11}C]TMSX is produced using automated radiochemistry techniques that incorporate the short-lived radionuclide carbon-11, generated in a cyclotron via the $^{14}N(p,\alpha)^{11}C$ reaction, typically yielding [^{11}C]CO_2 or [^{11}C]CH_4 (Kawamura & Ishiwata, 2004a). These are converted into reactive intermediates, most commonly [^{11}C]methyl iodide or [^{11}C]methyl triflate, which are used to methylate a desmethyl precursor in a late-stage labeling step to minimize decay losses (Singleton et al., 2019). The radiosynthesis is automated for reproducibility and safety, followed by purification via HPLC and reformulation in a sterile saline solution suitable for human injection. Quality control ensures radiochemical purity, specific activity, sterility, and other safety parameters, all completed within carbon-11's 20.4-minute half-life to maintain adequate activity for PET imaging (Allard et al., 2008; Shegani et al., 2023).

2.3.1.1 Positron Emission, Annihilation and Detection

Radionuclides that emit positrons lose their energy by interacting with the surrounding medium. After traveling a short distance from the site of emission (in case of ^{11}C, 1.2 mm in water), the positron undergoes mutual annihilation by colliding with a negative electron (Conti & Eriksson, 2016). A pair of γ rays are emitted, travelling $180^{o} \pm 0.5°$ apart, with an energy of 511 keV each. These rays are detected by a pair of detectors (scintillator + photomultiplier tube). Octagonal double layered ring of Lutetium Oxyorthosilicate (LSO) and Lutetium-Yttrium

Oxyorthosilicate (LYSO) scintillators are employed in the Siemens High Resolution Research Tomograph (HRRT) PET scanner used in this research (**Fig 4**).

Since the energy of incoming gamma rays is very high i.e. 511 keV, the scintillator decreases its energy via photoelectric or Compton mechanisms. In return the molecules within the LSO and LYSO crystals 'glow' emitting photons (de Jong et al., 2007). Both LSO and LYSO crystals have high density, which helps in trapping the incoming gamma rays and higher conversion efficiency (light output) as compared to other scintillator crystals. Photons from the scintillators are fed into the photomultiplier tube (PMT) which converts the incoming photons from the scintillators into electrical pulses and multiplies (amplifies) the signal. The output of the detector enters a coincidence circuit. The task of the coincidence circuit (coincidence processor) is to analyze the digital 'time stamps' of the outputs of both detectors (placed at 180^{o} of each other). If they were recorded simultaneously or within a short time of each other (10^{-9} seconds), the event is determined to be a 'true coincidence' and is associated with both detectors. This process is known as 'annihilation coincidence detection'(Cherry et al., 2012).

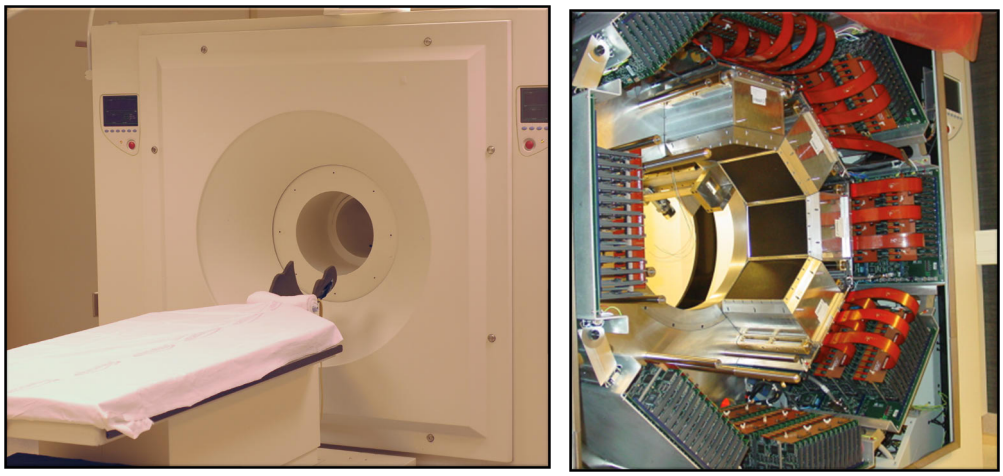

Figure 4. **LEFT:** Siemens High Resolution Research Tomograph (HRRT) PET scanner (*Modified from an image by **Emorycsi**, licensed under CC BY-SA 4.0, via Wikimedia Commons*) **RIGHT:** Octagonal ring of detectors in the Siemens HRRT PET scanner. Picture was taken while the HRRT PET scanner was being installed at the Turku PET Center in 2006. Notice that four of the total eight detectors (silver casing) are yet to be installed *(Courtesy: **Dr. Jarkko Johansson**, Umeå University, Sweden)*

2.3.1.2 Pre-processing and physical corrections

Raw PET data is corrected for different sources of error in order to produce reliable quantitative images to accurately distinguish between normal and diseased states.

Detectors in PET scanners typically have variations in their sensitivity. These require corrections for the uniformity of the response. In addition, photons could enter the detector from different angles with respect to the fronts of the crystals. This means that the cross section of the detector pair for each of the photon is different as compared to if the photon entered the crystal perpendicular to their surface. The process to correct for these phenomena is referred to as normalization. Briefly, normalization is performed in sinogram space, the two-dimensional histogram of coincident events that is directly acquired from the PET scanner and represents the projection of activity along all detector pairs. A uniform rod source is rotated around the axial field of view to expose all detector pairs to the same radioactivity. The 'normalization factors' acquired are compared to the overall average and are either incorporated within the system matrix for image reconstruction algorithm or the overall counts are divided by the normalization factor before reconstruction (Theodorakis et al., 2013).

Following normalization, another major physical effect that must be addressed is attenuation. Attenuation is the main factor contributing to the deterioration of a PET image and mainly refers to the loss of one of the two annihilation photons. They are either absorbed by the tissue or lost because of Compton scatter. It can be corrected by acquiring an attenuation map using transmission rods (positron emitter). This data is used to correct each line of response (LOR) for attenuation (Bailey, 1998).

In addition to attenuation, scatter coincidences must also be corrected. Scatter coincidence refers to a false event registered when a gamma photon collides with an electron, changes direction and energy, a process known as Compton scattering. It deviates from its intended path and wavelength, resulting in detection by a different detector. Scatter coincidences increase background noise, decrease contrast contributing to an overall 'hazy' scan and contributes to the overestimation of isotope concentrations. Data from the attenuation map, scanner emission and geometry of the detector systems is combined to estimate the scattered events e.g., by using the Klein-Nishina formula (Bowen et al., 1994). In brain studies close attention should be paid to the cerebellum, which is in many cases used as a reference region, as it is at the bottom of the field of view (FOV) and is prone to scatter if there is significant radioactivity close to the FOV (Turkheimer et al., 2014).

Random events are another critical component of data correction and occur when two photons are detected within the coincidence time window that are not arising from the same annihilation event. Random events directly correlate with injected radioactivity. They can be reduced by decreasing the coincidence time window. Random rates can be estimated and subtracted from the projection data (Barker et al., 2004). The corrections for scatter and random events are automatically managed by the scanner.

PET images must also account for dead time effects. Different components of the PET measuring system e.g. a photomultiplier tube (PMT) need a certain amount of time to process an event (incoming photon). During this period the components are insensitive to another event which is known as dead time. Empirical deadtime models are employed by PET scanners to correct for dead time either for the whole systems (global dead time correction factors) or on each pair of detectors (Cherry et al., 2012).

Another basic but essential correction applied during preprocessing is radioactive decay. Each positron emitting radionuclide (e.g. ^{11}C, ^{18}F) decays or disintegrates with time following an exponential e.g. ^{11}C has a half-life of approximately 20 minutes. As the half-life (rate of decay) is known, decay can be easily corrected for frame by frame (inter-frame correction), or decay fraction can be calculated and applied to all the frames (intra-frame correction).

After preprocessing and physical corrections are applied, PET images are reconstructed from this data. This can be achieved by either filtered back projection (FBP) method or iterative reconstruction method. In this thesis, we focus on the HRRT because it was the scanner used for data acquisition and its high spatial resolution makes iterative methods preferable, as FBP is prone to blurring. Three-dimensional ordinary poisson ordered-subset expectation maximization (3D-OP-OSEM) and maximum a posteriori (MAP) are the iterative reconstruction methods utilized to reconstruct images from HRRT PET scanner (Varrone et al., 2009).

With the increased spatial resolution of HRRT PET scanner, ~2.5mm full width at half maximum (FWHM), a measure of scanner's spatial resolution, movements of the patient during the scan become a significant source of image degradation. A motion detection device is typically used in brain PET studies to correct for these movements. Finally, the resolution of a PET image is degraded because of positron range, photon non-collinearity, inter-crystal penetration and inter-crystal scattering. They can be corrected for during reconstruction using PSF modeling (Rahmim et al., 2013; Rousset et al., 1998).

2.3.1.3 PET parameter estimation

The processing of PET images results in the accurate quantification of radioactivity in the brain, but these images do not accurately represent receptor quantity or availability in the region of interest (Cobelli et al., 2002). In addition to specific binding, the primary parameter of interest, PET images also include non-specific binding (e.g. binding to plasma proteins) and free unbound tracer. To accurately assess receptor availability, non-specific binding and the free fraction must be separated, which is achieved through kinetic modeling. This mathematical approach enables the derivation of parameters of interest, such as *distribution volume ratio*

(DVR), which more accurately represents receptor availability in the target region. Kinetic modeling for reversible receptor-ligand binding studies can be performed using two-tissue compartmental modeling (2-TCM), graphical methods such as the Logan plot, or reference tissue models such as simplified reference tissue model (SRTM) and reference Logan (Herholz et al., 2004). Compartmental and graphical methods require blood sampling as they depend on the free, unmetabolized tracer fraction provided by the arterial input function for parameter estimation. Reference tissue models, on the other hand, utilize time-activity curves from a tissue with no specific binding as the input function, thereby eliminating the need for invasive blood sampling (Carson et al., 1998; Turkheimer et al., 2014).

2.3.1.3.1 Blood-based kinetic modeling

Blood-based kinetic modeling for receptor-ligand studies either uses 2-TCM or the Logan graphical method which linearizes the integral form of the compartmental model to improve computational efficiency in parameter estimation. The basic assumption of 2-TCM is that the tracer is transported from plasma ($C_p(t)$) to tissue where it is either in the non-displaceable form (free + non-specific, $C_1(t)$) or bound to target receptors (concentration of specifically bound tracer, $C_2(t)$). The 2-TCM is described by the equation (1) and (2):

$$\frac{dC_1(t)}{dt} = K_1 C_p(t) - (k_2 + k_3) C_1(t) + k_4 C_2(t) \quad (1)$$

$$\frac{dC_2(t)}{dt} = k_3 C_1(t) - k_4 C_2(t) \quad (2)$$

The rate constants (K_1, k_2, k_3 and k_4) are estimated using nonlinear least squares method by minimizing the difference between whole brain TAC measured with PET and the concentration of radiotracer predicted by the kinetic model. The estimated rate constants are then used to calculate macroparameters such as non-displaceable binding potential (BP_{ND}) and total volume of distribution (V_T) as defined by the equation (3) and (4) respectively.

$$BP_{ND} = \frac{k_3}{k_4} \quad (3)$$

$$V_T = \frac{K_1}{k_2}\left(1 + \frac{k_3}{k_4}\right) \quad (4)$$

BP_{ND} denotes the concentration of specifically bound radioligand over the concentration of non-displaceable radioligand in the tissue. V_T, on the other hand, represents ratio of ligand in a given compartment relative to the total plasma ligand concentration (Innis et al., 2007).

2.3.1.3.2 Reference tissue kinetic modeling

Reference tissue models estimate macroparameters without requiring arterial blood sampling. Instead, a reference region devoid of specific binding, containing only free and nonspecifically bound tracer, is used to approximate the non-displaceable tracer kinetics that would otherwise be derived from a measured arterial input function. These models also assume that there is no difference in the non-displaceable (free + nonspecific binding) component between the reference and the target tissue.

Simplified reference tissue model (SRTM), a reduced form of the full reference tissue model, is commonly employed in PET studies for parameter estimation (**Fig 5)**. SRTM fits three parameters instead of four in the full tissue model and can be defined by the following equation:

$$C_T(t) = R_1 C_R(t) + \left[k_2 - \frac{R_1 k_2}{1+BP_{ND}}\right] C_R(t) \otimes e^{-\left(\frac{k_2}{1+BP_{ND}}\right)t} \quad (5)$$

In this equation $C_T(t)$ is the tissue activity measured in the target region, $C_R(t)$ is the tissue activity measured in the reference region, R_1 is the ratio of tracer delivery in the tissue to reference region, k_2 is the efflux rate constant of the target tissue and BP_{ND} is the binding potential of the target tissue (Turkheimer et al., 2014). The model can be applied to reversible tracers with low or medium affinity for target tissue receptors. In addition, the tracer must have rapid clearing kinetics in the target region as well (Lammertsma & Hume, 1996; Turkheimer et al., 2014). To implement SRTM at the voxel level, Basis Function Methods have been devised which improve

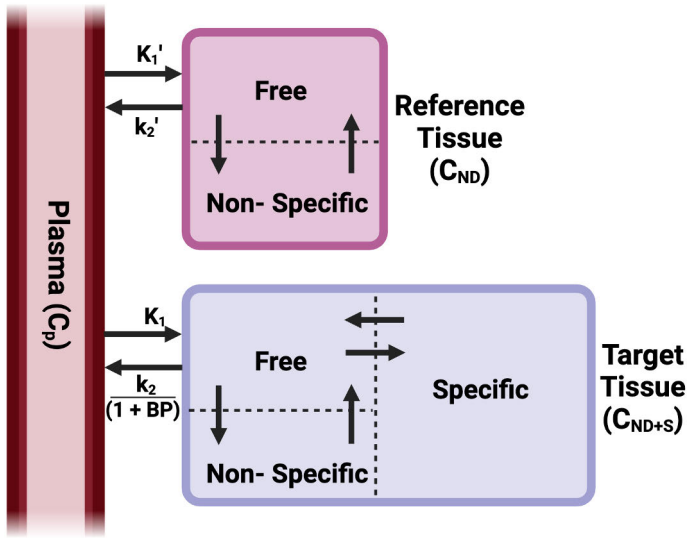

Figure 5. Simplified reference tissue model (SRTM) used in PET imaging to estimate receptor binding without requiring arterial blood sampling. (Modified from Carson et al., 1998) (Created with BioRender.com)

computational efficiency and robustness of parameter estimation (Gunn et al., 1997; Turkheimer et al., 2014).

Graphical approach could also be implemented without arterial input data. For reversible tracers, Logan Reference Plot method can be used which allows the estimation of the macroparameter *DVR* and can be defined by the following equation:

$$\frac{\int_0^t C_T(s)d\tau}{C_T(t)} = DVR \cdot \frac{\int_0^t C_R(s)d\tau}{C_T(t)} + \frac{C_R(t)}{k_2'} + b. \quad (6)$$

The slope of equation (6) represents *DVR* which can be defined as:

$$DVR = \frac{V_T}{V_{ND}} \quad (7)$$

Here V_T is the total volume of distribution in the target tissue and V_{ND} is the volume of non-displaceable tracer distribution in the reference region. Therefore, *DVR* is a measure of receptor availability in the target tissue relative to the reference tissue (Logan et al., 1996; Tuisku, 2021).

Graphical methods are computationally efficient as they rely on linear regression instead of non-linear least squares fitting (Logan et al., 1996). They also do not require a priori selection of the number of compartments and are dependent on whether the tracer kinetics are reversible or irreversible. However, since graphical approach assumes that PET signal originated solely from the free and bound tracer compartments and does not take the vascular component into consideration, the method is less transparent and may lead to biased findings (Turkheimer et al.,2014).

2.3.2 Magnetic Resonance Imaging (MRI)

Magnetic Resonance Imaging (MRI) complements PET data by providing high-resolution anatomical information essential for accurate region of interest (ROI) delineation (Catana et al., 2013). These ROIs are used for defining reference regions, quantifying tracer binding in relevant anatomical structures and normalization of PET data for further analyses (Fig 6).

2.3.2.1 MRI system components

An MRI machine is comprised of a main magnet coil, three gradient coils, shim coils and radiofrequency (RF) transmitter coil. The main magnet coils are superconducting magnets which generate the static magnetic field (B_0), the strength of which is measured in Tesla (T). The gradient coils, placed concentrically inside the main magnet, create a magnetic field along x, y or z axis. These fields gradually alter B_0 along the selected direction, enabling the MRI system to retrieve spatial

information from the signal. The RF transmitter coils are placed within the gradient coils and are used to transmit RF signal to the tissue of interest and receive the signals emitted from the tissue. Shim coils are used to correct inhomogeneities in the main magnetic field (Serai et al., 2021).

2.3.2.2 MR signal acquisition

MR signal in radiologic images typically comes from the hydrogen nuclei. The protons within these nuclei are constantly spinning which generates magnetic fields. When placed within the external magnetic field of an MRI scanner (B_0) they behave like tiny bar magnets. A majority aligns parallel to B_0 (lower energy state) while a smaller number align antiparallel (higher energy state). This difference between the lower and higher energy states creates a small net magnetization along the longitudinal (z) axis, known as longitudinal magnetization (M_0) (Currie et al., 2013).

The protons also undergo a wobbling motion, like a spinning top, when placed along B_0 referred to as precession. The frequency of precession is called the Larmor frequency and is directly proportional to magnetic field strength. As the protons are in the longitudinal magnetization state, the RF pulses, set at Larmor frequency, are switched on and off. These pulses excite some protons, causing them to switch from the lower energy state (parallel) to the higher energy state (antiparallel). Simultaneously, the protons begin to move in phase with other protons generating transverse magnetization in the x-y plane (McRobbie et al., 2006).

As the RF pulse is turned off, the protons begin to revert to their initial condition releasing excess energy to the surrounding tissue. This energy exchange leads to a restoration of longitudinal magnetization, a process known as the T1 relaxation (Pooley, 2005). The pace of relaxation is dependent on the tumbling rate of the molecule within which the proton resides. Hydrogen protons in lipids have a very slow tumbling rate while the ones bound to proteins have a slightly higher tumbling rate. These differences in tumbling behavior underlie the contrast observed between different tissues in T1-weighted MR images (Plewes & Kucharczyk, 2012). T1 and T2 weighted MR images provide complementary information about brain tissue. T1 weighted images offer higher contrast between gray and white matter. This higher contrast offers better anatomical localization and ROI delineation. In contrast, T2 weighted scans are more sensitive to tissue pathology, such as edema or lesions but provide less precise anatomical demarcation between gray and white matter. Hence, T1 weighted images are preferred as anatomical references for co-registration of PET images and ROI delineation (Fig 6).

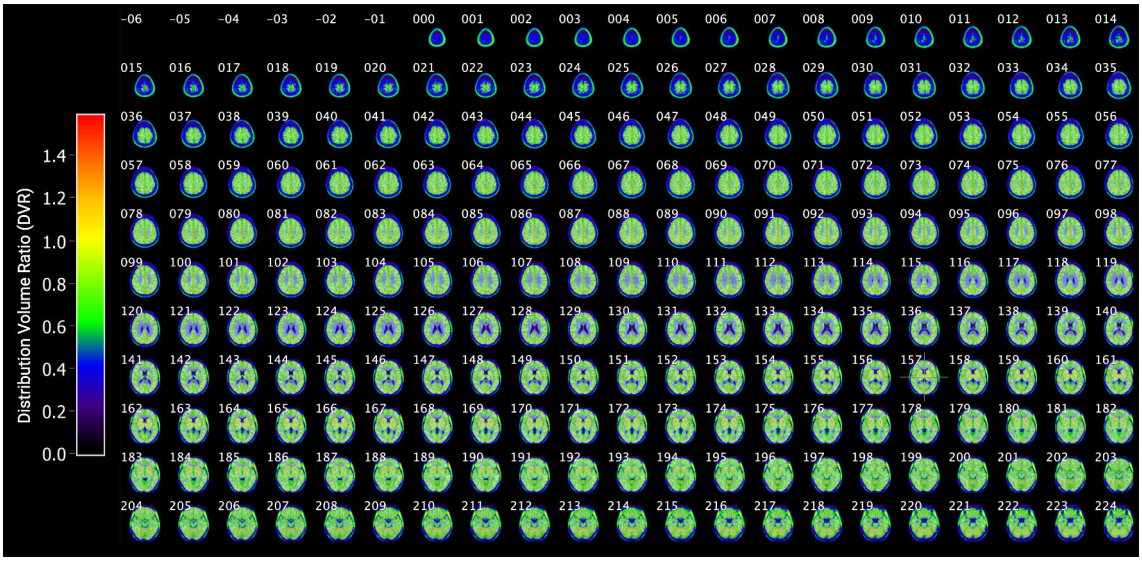

Figure 6. Average PET image from healthy participants, overlaid on CHBET T1 MRI anatomical template, acquired with the A_{2A} receptor specific radiotracer [^{11}C]TMSX. The axial parametric image shows the expected distribution of A_{2A} receptors, with highest binding in the striatum, particularly the putamen and caudate, while cortical regions exhibit lower uptake.

2.3.2.3 Region of interest (ROI) delineation and volumetric analyses

T1-weighted MR images are used for anatomical localization and ROI delineation to analyze the PET data. To enable accurate comparison across subjects and modalities, PET and MRI data are often normalized and co-registered. MRI scans are typically normalized to a standard anatomical template, providing a consistent reference for brain structures, while PET images are co-registered to the corresponding MRI to align molecular signals with anatomical landmarks. This process allows precise localization of PET findings within the brain's structural context in a group level and facilitates both voxel-wise and region-based analyses.

The delineation can be performed manually or via automated methods that segment the brain into different anatomical or functional regions using standardized templates or atlases. Commonly used anatomical parcellations include the Desikan-Killiany atlas in the FreeSurfer and the Automated Anatomical Labeling (AAL) atlas used in SPM (Fischl et al., 2002; Kiebel et al., 1997). The delineated ROIs are used to extract TACs from both the reference and the target regions from the PET images. These TACs serve as input for PET parameter estimation, and these parameters are subsequently used for statistical analyses (Fig 7). An alternative to anatomically defined reference regions is the use of supervised clustering algorithm, such as that implemented in SuperPK software, which groups voxels with kinetically similar

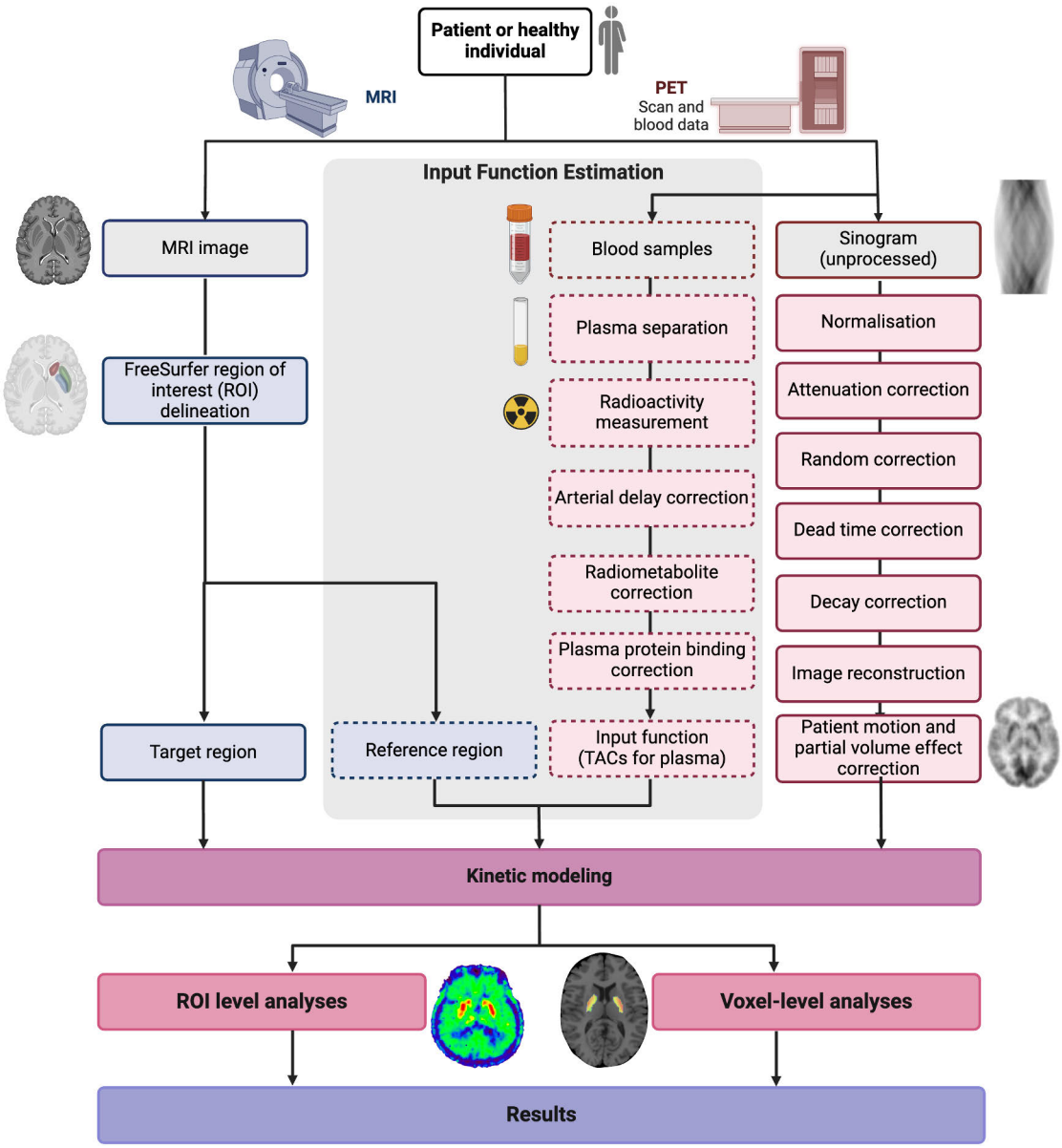

Figure 7. Overview of the PET and MRI data processing pipeline, illustrating input function estimation, image corrections, and kinetic modeling. The flowchart depicts two possible input functions: the **arterial input function (AIF)** derived from blood samples and the **reference region approach** obtained from MRI-based FreeSurfer segmentation. PET image corrections, including normalization, attenuation, and motion correction, are applied before kinetic modeling. The final kinetic modeling step enables **Region of Interest (ROI) level and voxel-level analyses**, leading to quantitative PET imaging results. (Created with BioRender.com)

behaviour to derive a clustered gray matter reference region directly from the PET data, avoiding the need for arterial blood sampling (Turkheimer et al., 2007). This

approach has been validated for use with ^{11}C TMSX in our earlier work (Rissanen et al., 2014).

Volumetric analyses can also be performed to assess structural brain changes in various neurological diseases and to explore their potential associations with PET-derived measures. Regional volumes, typically derived from delineated ROIs, are often corrected for intracranial volume (ICV) to account for inter-individual variability in head size, yielding brain parenchymal fractions (BPF). These fractions can then be included in statistical models to investigate relationships between structural atrophy and molecular imaging markers (Nerland et al., 2022).

2.3.2.4 Voxel-wise analysis

PET voxel-level analyses refer to quantitative approaches that evaluate radiotracer signal at the level of individual voxels rather than averaging uptake in predefined ROIs. For voxel level analysis parametric images are first generated by performing kinetic modeling at each voxel to generate whole-brain maps of binding estimates (Astrakas & Argyropoulou, 2010). Voxel based analyses typically include spatial normalization, partial volume correction and voxel wise statistical modeling such as principal component analysis or non-linear least squares fitting to analyze differences in tracer uptake across different brain regions (Klyuzhin et al., 2018). Another widely used framework for voxel-level PET analysis is Statistical Parametric Mapping, which applies the general linear model (GLM) at each voxel. For group comparisons, this produces a voxel wise t-statistic and corresponding t-maps of differences in PET signal or derived parameters such as binding potential (Friston et al., 1991). The t-test is used to assess whether the mean value at each voxel differs significantly between groups or conditions, with statistical inference based on parametric assumptions and corrections for multiple comparisons using Gaussian random field theory (Markus et al., 2002).Parametric imaging enables quick exploratory whole brain comparisons but at the cost of higher noise sensitivity. Together both ROI and voxel level analyses offer complementary perspectives increasing the overall robustness and interpretability of the study.

3 Aims

The overall aim of this study was to investigate Adenosine A_{2A} receptor availability in patients with PD, examining changes across different disease stages and brain regions, and exploring how these alterations relate to clinical measures of disease severity and progression. The specific objectives of this work, presented as Studies I–III, were as follows:

I. To evaluate the effect of short-term cessation of dopaminergic medication on striatal A_{2A} receptor availability in patients with PD.

II. To compare striatal A_{2A} receptor availability between early- and moderate-stage PD patients and healthy controls.

III. To investigate changes in cerebral white matter A_{2A} receptor availability and their relationship with gray matter volumes in PD.

4 Materials and Methods

4.1 Study population

The protocol for this cross-sectional study was approved by the Ethics Committee of the hospital district of Southwest Finland. This study was conducted according to the ethical principles of medical research defined in the World Medical Association's Declaration of Helsinki. Signed informed consent was acquired from all study participants. Patients were enrolled from the forums of Finnish Parkinson's Foundation as well as from the neurology outpatient clinics of Turku University Hospital (TYKS). All patients enrolled in the study fulfilled the clinical diagnostic criteria of idiopathic PD as outlined in the Finnish Current Care Guidelines of PD and without any accompanying dyskinesia. Inclusion and exclusion criteria for the study are summarized in Table 4.

Table 4. Inclusion and exclusion criteria for PD patients and healthy controls. Modified from (Rissanen, 2015).

GROUP	INCLUSION CRITERIA	EXCLUSION CRITERIA
Healthy Controls	• Age 18–75 years • No previous history of neurological symptoms or diagnoses	• Notable claustrophobia and/or anxiety • Ferromagnetic metallic implants or prostheses (other than titanium) • Pacemakers, stimulators or other MRI-incompatible objects • Active neurological or autoimmune disease or another significant comorbidity
Patients with Parkinson's Disease	• Age 18–75 years • Clinical diagnosis of Parkinson's disease • Eligible for PET/MRI imaging	• Notable claustrophobia and/or anxiety • Ferromagnetic metallic implants or prostheses (other than titanium) • Pacemakers, stimulators or other MRI-incompatible objects • Immunomodulatory treatment within 3 months prior to enrolment • Active neurological or autoimmune disease other than PD or another significant comorbidity

4.1.1 Study I

For Study I, eight of the twenty patients with PD enrolled in Studies II and III were included to be scanned twice: once in the 'ON' state and once after short-term (12–24 hours) cessation of dopaminergic medication. Given caffeine's A_{2A} receptor affinity and half-life, participants were restricted from caffeinated beverages for at least 24 hours prior to each scan. The UPDRS, Levodopa Equivalent Dose (LED), and Mini-Mental State Examination (MMSE) were recorded as part of the clinical assessment performed before and after the short-term withdrawal of dopaminergic medication, prior to each PET scan. Of the eight patients included in the study, seven were treated with a combination of dopamine agonists and a monoamine oxidase-B (MAO-B) inhibitor, of whom six were also receiving levodopa. The remaining patient was treated with dopamine agonists alone.

4.1.2 Study II & III

For Study II, ten patients with early and ten with moderate stage PD were enrolled along with six healthy controls. To minimize potential short-term effects of dopaminergic medication on A_{2A} receptor availability, PET scans in patients with PD were conducted following a medication withdrawal period of 12 hours for standard levodopa and 24 hours for prolonged release levodopa/carbidopa, MAO-B inhibitors and/or dopamine agonists. In addition, all participants were instructed to abstain from caffeinated beverages for at least 24 hours prior to scanning, given caffeine's antagonistic action on A_{2A} receptors and its reported half-life of 2.3–9.9 hours (Ferré et al., 2016; Ishibashi et al., 2022; Nehlig, 2018). One patient from the early PD group and one from the moderate PD group were excluded from the final analyses, as the [^{11}C]TMSX PET data was not reliably quantifiable due to a relatively low injected dose of the radiotracer and high injected mass, respectively.

For Study III, patients from early and moderate PD groups were combined and an additional healthy control was included. This was done to improve the reliability of the cross-sectional design and to increase the number of healthy controls for group comparisons. Recruitment of further participants was not feasible due to logistic constraints, including the discontinuation of the [^{11}C]TMSX radiotracer production in our facilities.

4.2 Image acquisition and processing and radioligand binding estimation

All studies utilized the adenosine A_{2A} receptor radioligand [7-methyl-11C]-(E)-8-(3,4,5-trimethoxystyryl)-1,3,7-trimethylxanthine ([^{11}C]TMSX), which was synthesized following procedures described previously in earlier publications

(Ishiwata, Wang, et al., 2003; Kawamura & Ishiwata, 2004b). Briefly, [^{11}C]methane generated in situ was first converted to [^{11}C]methyl triflate, which was subsequently reacted with 0.4 mg of the precursor and 10 mg of cesium carbonate in 200 µl of N,N-dimethylformamide. After the reaction, 0.6 ml of the high-performance liquid chromatography (HPLC) mobile phase (acetonitrile/0.01 M phosphoric acid, 41:59) was added, and the product was purified using a C18 column. The collected radioactive fraction was stabilized by adding 150 µl of ascorbic acid (100 mg/ml) and 0.5 ml of propylene glycol/ethanol (7:3), followed by evaporation of the mobile phase. The final formulation was prepared in 0.1 M phosphoric acid buffer containing propylene glycol/ethanol/ascorbic acid (83:15:2) and sterilized by filtration through a 0.2 µm Tuffryn membrane filter (Acrodisc, Pall Corp.) (Rissanen, 2015). The radiochemical purity of the tracer exceeded 97%. For each PET scan, a smooth single bolus of [^{11}C]TMSX was injected into the antecubital vein, followed by saline flush. The injected doses were comparable between controls and PD subgroups.

PET imaging was performed using the ECAT high-resolution research tomograph (HRRT, CTI PET Systems, Knoxville, TN, USA), providing a spatial resolution of approximately 2.5 mm in both axial and radial directions. Before the emission scans, a 6-minute transmission scan using a ^{137}Cs point source was acquired for attenuation correction. Dynamic PET data were collected over a 60-minute period consisting of 27 sequential frames (6 × 10 s, 3 × 30 s, 5 × 60 s, 5 × 150 s, and 8 × 300 s; total 3600 s).

All participants also underwent brain MRI scanning using a Philips Gyroscan Intera 1.5 T Nova Dual scanner (Philips, Best, Netherlands). High-resolution 3D axial T1-weighted images were acquired for individual neuroradiological assessment, to provide anatomical reference for PET image analysis and, in Study 3, also for volumetric analysis. Co-registration of motion-corrected dynamic PET and T1-weighted MR images was performed using Statistical Parametric Mapping software (SPM12, The Wellcome Centre for Human Neuroimaging, UCL, London) as mentioned in our earlier work (Rissanen et al., 2014).

Distribution volume ratios (DVR) were estimated with the Logan reference tissue-input model (20–60 min interval), applied to ROI-based time activity curves (TACs) using clustered gray matter derived from a supervised clustering algorithm (SVCA). The algorithm, modified from the Super-PK software, modeled each voxel TAC as a linear combination of four kinetic classes (gray matter, white matter, blood, and high-specific-binding gray matter), using predefined kinetic class TACs from healthy volunteers and patients (Rissanen et al., 2014; Turkheimer et al., 2007b).

4.2.1 Study I

Antiparkinsonian medication was withheld for 12 hours (standard levodopa) or 24 hours (dopamine agonists and/or MAO-B inhibitors) before the first scan, after which medication was resumed. A second PET scan was performed under identical conditions but without medication withdrawal within a median of 13 days (IQR 7.8–14.0. ROIs for the caudate, putamen, and pallidum were automatically segmented from MR images using FreeSurfer (Fischl et al., 2002). PET images were subsequently co-registered to the MRI using SPM8. Additional manual ROIs were drawn on the caudate (anterior and posterior subdivisions) using Carimas software (v2.10), with the anterior commissure serving as the landmark for regional anterior/posterior demarcation.

4.2.2 Study II

For Study II, ROIs were defined using Freesurfer software (v6.0, http://surfer. nmr. mgh. harvard. edu/) for anatomical parcellation of the 3D T1 MR images for the caudate, putamen, and pallidum (Fischl et al., 2002). These parcellations were used to extract DVR values for the aforementioned regions. Furthermore, mean DVR values for the entire dorsal striatum were calculated as the volume-weighted average of the caudate and putamen binding potentials to evaluate associations with clinical measures. To examine lateralization effects both within and between groups, contralateral and ipsilateral ROIs were manually delineated for the caudate and putamen using an in-house software (Carimas v2.9). These ROIs were classified as contralateral or ipsilateral relative to each patient's clinically more affected side, based on unilateral sums of UPDRS III scores. DVR values in the ipsilateral and contralateral ROIs of PD patients were then compared with the mean DVR of the left and right striatal ROIs in healthy controls. Voxel-level parametric maps of non-displaceable binding potential (BP_{ND}) were generated using a basis function implementation of the simplified reference tissue model (SRTM) with 250 basis functions and θ3 limits of 0.06–0.8 (Waggan et al., 2022).

4.2.3 Study III

T1-weighted MR images were segmented with FreeSurfer to obtain frontal, parietal, occipital, and temporal gray and white matter ROIs. These volumes were corrected for individual total intracranial volume, and brain parenchymal fractions were calculated for volumetric analyses. To minimize potential spill-in from adjacent high-binding areas, cerebral gray and white matter masks were eroded by one voxel layer (1.22 mm) along the outer rim before analysis.

4.3 Statistical analysis

All statistical analyses were carried out using GraphPad Prism (versions 9.1–9.4.) and RStudio (RStudio 2021.09.0 + 351). The normality of data distribution was assessed graphically and verified with the Shapiro–Wilk test.

4.3.1 Study I

Paired comparisons of DVR and reference region AUC values between the 'OFF' and 'ON' medication conditions were performed using paired t-tests. The equivalence of DVR and AUC values between medication states was further tested using the two one-sided test (TOST) approach for paired data, with the threshold for negligible difference (ε) set at 0.04, based on prior work assessing dopaminergic effects on $A_{2A}R$ availability (Mishina et al., 2011). Pearson's correlation was applied to evaluate pairing efficiency, and p-values <0.05 (two-tailed) were considered significant.

4.3.2 Study II

Between-group comparisons of demographic and imaging parameters were performed using one-way ANOVA (for continuous variables such as age, injected dose, molar activity, injected mass, and radiochemical purity) and Fisher's exact test (for categorical variables). The Mann–Whitney U test was applied to assess differences in disease duration between early- and moderate-stage PD. ROI-level DVR differences were analyzed using independent t-tests with Bonferroni correction for multiple comparisons, and within-group ipsilateral vs. contralateral differences were assessed using paired t-tests. Cohen's d was calculated as the measure of effect size. Spearman's rank correlation coefficient was used to evaluate relationships between clinical parameters and striatal or pallidal DVR values. For voxel-wise analyses, two-sample t-tests were performed in SPM12 using smoothed BP_{ND} maps (Gaussian 4 mm FWHM) with a cluster-defining threshold of $p = 0.001$ ($T = 3.85$) and cluster-level family-wise error correction at $p < 0.05$ (critical cluster size = 115 voxels).

4.3.3 Study III

Differences between PD patients and controls in age, injected dose, injected mass, and radiochemical purity were evaluated with independent t-tests, while sex differences were assessed using Fisher's exact test. Group-level differences in DVRs and parenchymal volume ratios were examined using unpaired t-tests with Bonferroni correction applied post hoc. Pearson correlation was used to assess the

relationship between DVRs and volumetric parameters. To adjust for potential confounding by age and sex, analysis of covariance (ANCOVA) was performed. Two-tailed p-values <0.05 were considered statistically significant.

5 Results

5.1 Demographic data (Studies I-III)

For study I, the mean administered [^{11}C]TMSX dose was 473.6 MBq (± 51.9) for the first scan and 500.4 MBq (± 20.7) for the second, showing no significant difference between them (P = 0.19). All participants tolerated the temporary withdrawal of their PD medication well. Clinical characteristics, dopaminergic medications, and levodopa equivalent doses (LED) of patients with PD in **Study I** are summarized below (Table 5).

Table 5. Description of clinical parameters, dopaminergic medications and their levodopa equivalent doses (LED) of the patients with Parkinson's disease for **Study I**.

PATIENT	MEDICATION	LED (MG)	UPDRS III	DISEASE DURATION (YEARS)	DURATION BETWEEN SCAN 1 AND 2 (DAYS)
1	Rasagiline, Ropinirole, Levodopa	700	28	2.2	14
2	Pramipexole	105	14	1.1	7
3	Selegiline, Pramipexole	260	32	5.3	119
4	Selegiline, Pramipexole, Levodopa	1027	28	10.9	14
5	Selegiline, Pramipexole, Levodopa	312	32	5.3	7
6	Rasagiline, Ropinirole, Levodopa	1115	29	7.8	14
7	Rasagiline, Ropinirole, Levodopa	890	33	8.4	12
8	Selegiline, Pramipexole, Levodopa	356	34	9.7	8

Abbreviations: LED = Levodopa equivalent dose; UPDRS = Unified Parkinson's Disease Rating Scale.

For study II, no significant differences were found in age (P = 0.336) or sex distribution (P = 0.318) between healthy controls and patients with early- or moderate-stage PD. Compared with early-stage PD patients, those with moderate-stage PD exhibited longer disease duration (P < 0.001), higher UPDRS III scores (P < 0.001), and greater LED (P < 0.001). (Table 6)

Table 6. Demographic, clinical, and imaging characteristics of healthy controls, early PD, and moderate PD patients for **Study II**.

	HEALTHY CONTROLS (N = 6)	PD EARLY STAGE (N = 9)	PD MODERATE STAGE (N = 9)	P-VALUE
SEX (F/M)	5/1	4/5	5/4	0.318
AGE (YEARS)	60.6 (± 8.8)	65.1 (± 8.2)	67.1 (± 7.5)	0.336
DISEASE DURATION (years), MEDIAN (range)	NA	1.8 (1.5–2.2)	8.4 (5.6–10.8)	**< 0.001**
HANDEDNESS (R/L)	Not available	9/0	9/1	1.000
UPDRS I	NA	1.1 (± 1.7)	1.8 (± 1.3)	0.362
UPDRS II	NA	5.4 (± 2.3)	9.3 (± 3.9)	**0.020**
UPDRS III	NA	17.9 (± 5.9)	31.8 (± 2.7)	**< 0.001**
UPDRS IV	NA	1.7 (± 2.1)	1.4 (± 1.2)	0.785
UPDRS V	NA	2.0 (± 0.4)	2.5 (± 0.4)	**0.001**
LED (mg)	NA	196.8 (± 202.8)	727.3 (± 353.7)	**< 0.001**
$LEDD_{DA}$ (mg)	NA	210.5 (± 234.3)	177.9 (± 59.0)	0.708
MMSE	Not available	28.9 (± 0.6)	28.6 (± 1.0)	0.408
INJECTION DOSE (MBq)	490.7(± 25.1)	483.2 (± 26.6)	492.4 (± 21.0)	0.705
RADIOCHEMICAL PURITY (%)	97.8 (± 0.4)	97.7 (± 0.5)	97.3 (± 0.5)	0.054
INJECTED MASS (µg)	0.64 (± 0.3)	0.60 (± 0.3)	0.38 (± 0.2)	0.188
MOLAR ACTIVITY (MBq/nmol)	350 (± 120)	410 (± 200)	570 (± 180)	0.277

Notes: Sex and handedness: Fisher's exact test. Age, injection dose, radiochemical purity, injected mass: one-way ANOVA. Other parameters: Mann–Whitney U test. Bold values indicate significance. **Abbreviations:** UPDRS = Unified Parkinson's Disease Rating Scale; LED = Levodopa equivalent dose; $LEDD_{DA}$ = Levodopa equivalent daily dose of dopamine agonists; MMSE = Mini-Mental State Examination.

Similarly for study III, there were no significant differences between healthy controls and PD patients in injected dose (P = 0.52), injected mass (P = 0.34), radiochemical purity (P = 0.50), age (P = 0.06), or sex (P = 0.41).

Table 7. Demographics, clinical and imaging parameters of healthy controls and PD patients for **Study III**.

	HEALTHY CONTROLS (N = 7)	PD PATIENTS (N = 18)	P-VALUE
SEX (F/M)	5/2	9/9	0.41
AGE (YEARS)	58.6 (± 9.9)	66.1 (± 7.6)	0.06
DISEASE DURATION (YEARS)	NA	8.4 (5.6–10.8)	–
UPDRS I	NA	1.4 (± 1.5)	–
UPDRS II	NA	7.3 (± 3.6)	–
UPDRS III	NA	24.8 (± 8.5)	–
UPDRS IV	NA	1.5 (± 1.6)	–
UPDRS V	NA	2.3 (± 0.5)	–
LED (mg)	NA	462.1 (± 390.9)	–
MMSE	Not available	28.7 (± 0.8)	–
INJECTED DOSE (MBq)	494.9 (± 25.4)	492.4 (± 21.0)	0.52
RADIOCHEMICAL PURITY (%)	97.7 (± 0.5)	97.5 (± 0.5)	0.50
INJECTED MASS (µg)	0.62 (± 0.3)	0.49 (± 0.3)	0.34

Notes: Sex: Fisher's exact test. Other parameters: Student's t-test. Bold values indicate significance. **Abbreviations:** UPDRS = Unified Parkinson's Disease Rating Scale; LED = Levodopa equivalent dose, MMSE = Mini-Mental State Examination, NA = Not applicable

5.2 Study I: Short-term cessation of dopaminergic medication shows no effect on A_{2A} receptor availability in putamen and pallidum, but low repeatability in caudate

There were no significant changes in the global mean DVRs between the two imaging sessions (median [IQR] % difference = 0.12 [−0.93 to 0.28], P = 0.76). Global DVRs demonstrated a strong pairing between scans (R = 0.96, P < 0.001), and statistical equivalence was confirmed between the two medication states (P < 0.001).

No significant differences were found in the mean striatal DVR values between the 'ON' and 'OFF' medication states (P = 0.43) (Fig. 8A). The mean striatal DVRs were correlated (R = 0.71, P = 0.048) and demonstrated statistical equivalence (P = 0.047) (Fig. 8B).

ROI-specific analyses revealed no significant differences in [^{11}C]TMSX binding between 'ON' and 'OFF' dopaminergic medication in the caudate (median [IQR] % difference = 1.40 [−1.88 to 6.21], P = 0.25), pallidum (0.00 [−1.37 to 2.95], P = 0.59), or putamen (0.00 [−1.74 to 1.34], P = 0.83) (Fig. 8C). Strong correlations between the two medication states were observed in the caudate (R = 0.83, P = 0.011), pallidum (R = 0.85, P = 0.007), and putamen (R = 0.89, P = 0.003). Statistical equivalence was reached in the pallidum (P = 0.045) and putamen (P = 0.022), though not in the caudate (P = 0.201).

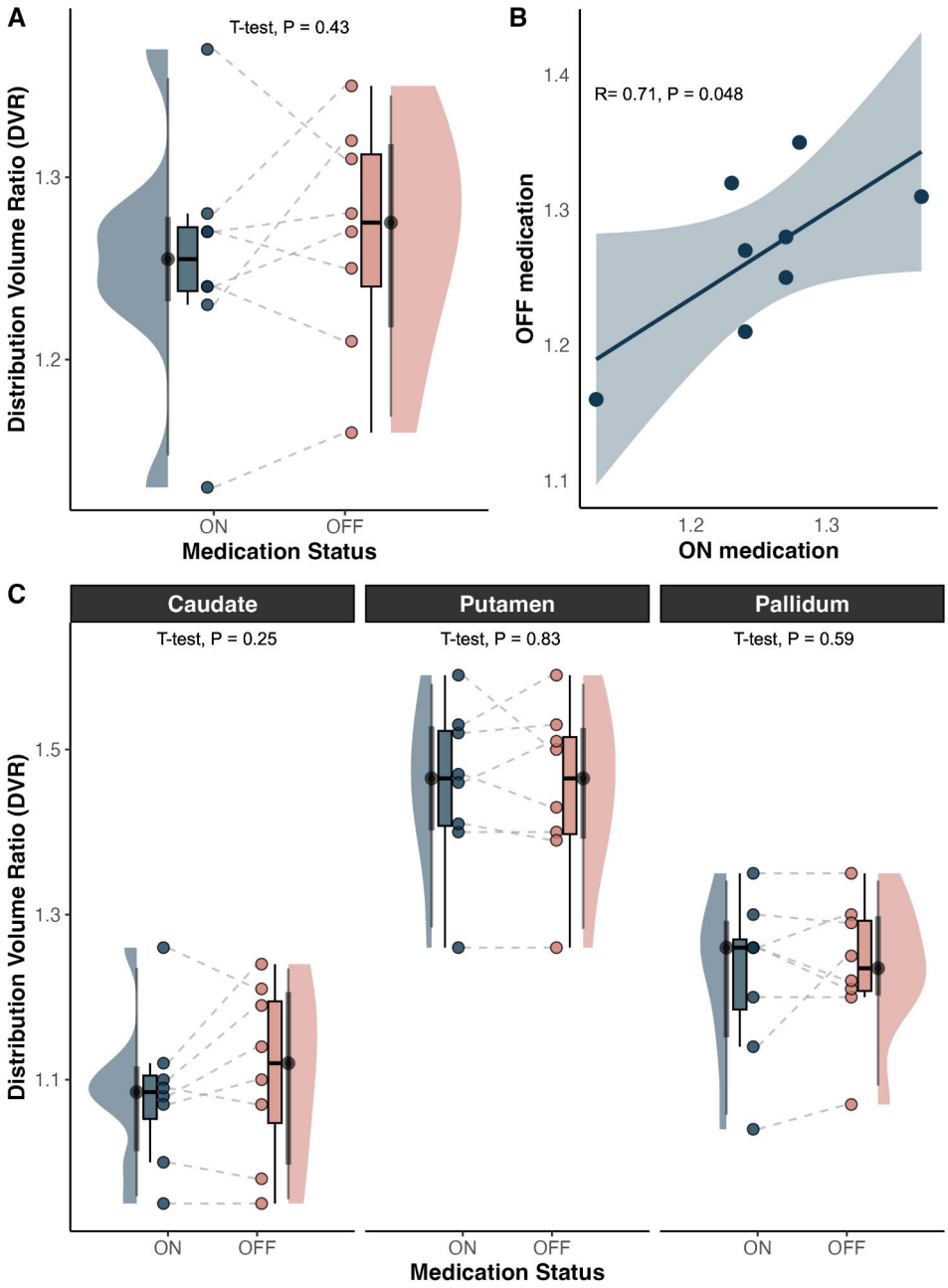

Figure 8. Paired raincloud and scatter plots comparing [^{11}C]TMSX PET parameters in PD patients during ON and OFF dopaminergic medication states. (A) Paired raincloud plot showing mean striatal DVR values in ON and OFF conditions. (B) Scatter plot illustrating Pearson's correlation of mean striatal DVR values between ON and OFF states. (C) Paired raincloud plot presenting DVR values in the caudate, pallidum, and putamen during ON and OFF dopaminergic medication.

Given the lack of equivalence in caudate DVR values and the typically asymmetric clinical manifestation in early PD, further analysis was performed on caudate subdivisions relative to the clinically affected side. No significant differences or equivalence in $A_{2A}R$ availability were detected between the medicated and non-medicated states in any caudate subdivision. Effective pairing was observed only in the ipsilateral posterior caudate (Table 8).

Table 8. Summary of correlations, differences, and equivalence in [^{11}C]TMSX binding across caudate subdivisions under ON and OFF dopaminergic medication. Results are reported as Pearson correlation coefficients, paired t-test outcomes, median (interquartile range) percent differences, and paired two one-sided t-tests (TOST) for DVR equivalence. Caudate subdivisions are designated as ipsilateral or contralateral relative to the side most affected by motor symptoms. Statistical significance was defined as $P < 0.05$. Modified from (Waggan et al., 2021).

CAUDATE AND ITS SUBDIVISIONS	PEARSON R (P)	PAIRED T-TEST (P)	MEDIAN (IQR) % DIFFERENCE	PAIRED TOST (P)
CAUDATE	**0.827 (0.011)**	0.252	1.40 (-1.88–6.21)	0.201
ANTERIOR CAUDATE	0.538 (0.169)	0.677	1.51 (-3.41–4.16)	0.295
POSTERIOR CAUDATE	0.650 (0.080)	0.529	0.51 (-6.58–3.91)	0.154
CAUDATE (CONTRALATERAL)	0.377 (0.356)	0.494	-1.05 (-4.14–2.11)	0.353
ANTERIOR CAUDATE (CONTRALATERAL)	0.445 (0.269)	0.471	-1.62 (-4.61–1.81)	0.404
POSTERIOR CAUDATE (CONTRALATERAL)	0.459 (0.252)	0.592	-0.14 (-6.49–5.87)	0.195
CAUDATE (IPSILATERAL)	0.648 (0.081)	0.857	-1.02 (-3.11–5.44)	0.200
ANTERIOR CAUDATE (IPSILATERAL)	0.621 (0.100)	0.955	-0.09 (-2.53–6.13)	0.202
POSTERIOR CAUDATE (IPSILATERAL)	**0.810 (0.015)**	0.495	-2.20 (-6.18–2.49)	0.127

5.3 Study II: A_{2A} receptor availability reduced in the caudate in early-stage PD and elevated in the pallidum in moderate-stage PD.

ROI-level analyses showed that patients with early-stage PD exhibited lower mean [^{11}C]TMSX DVR in the bilateral caudate compared to healthy controls (effect size [ES] = 1.64, $P = 0.02$) (Fig. 9A, B). No significant differences were observed in bilateral caudate DVRs between early- and moderate-stage PD patients ($P = 0.14$), or between moderate-stage PD patients and healthy controls ($P > 0.99$). In contrast, mean [^{11}C]TMSX DVR in the bilateral pallidum was higher in moderate-stage PD

compared to controls (ES = 1.64, P = 0.03), while no differences were found when comparing early-stage PD with moderate-stage PD (P > 0.99) or with healthy controls (P = 0.64) (Fig. 9A). Bilateral putamen DVRs did not differ significantly across any group comparisons: early-stage PD versus controls (P > 0.99), moderate-stage PD versus controls (P = 0.74), and early-stage versus moderate-stage PD (P = 0.42) (Fig. 9A).

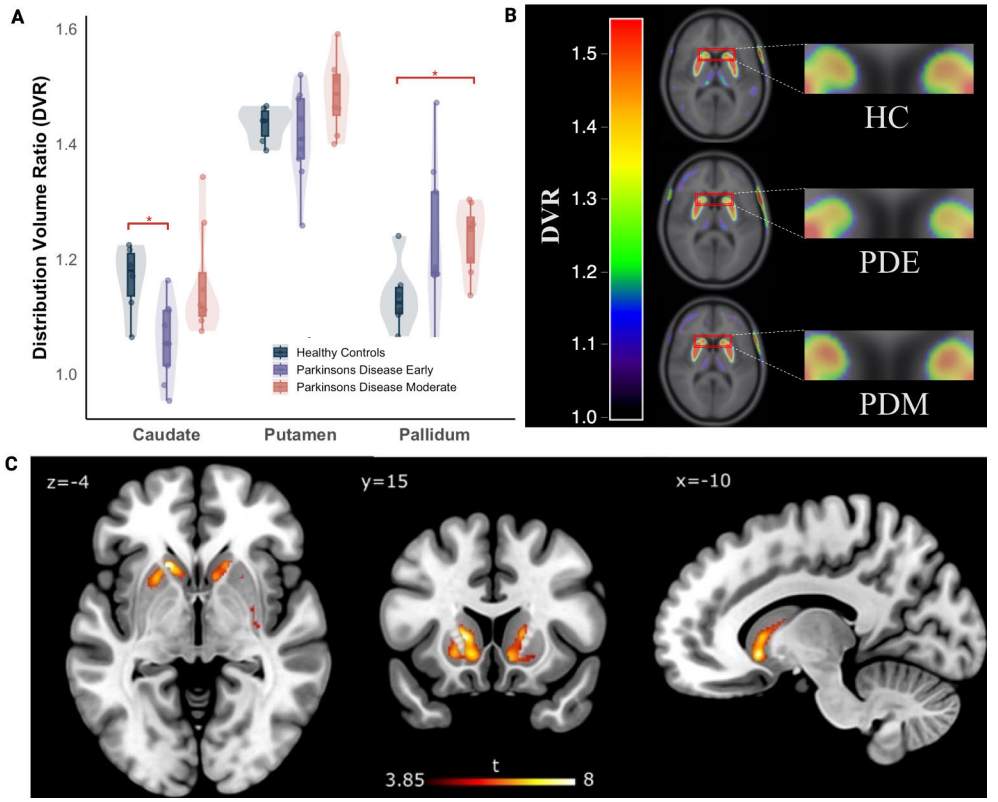

Figure 9. [^{11}C]TMSX binding to adenosine A_{2A} receptors in the striatum. (A) Raincloud plot of DVR values in healthy controls (HC), early-stage PD (PDE), and moderate-stage PD (PDM) groups. A_{2A} receptor availability is decreased in the bilateral caudate of PDE (P = 0.02) and increased in the bilateral pallidum of PDM (P = 0.03); *P < 0.05 after multiple comparison correction. (B) Mean parametric DVR images overlaid on the MNI 152 template, highlighting striatal binding especially in the caudate head. (C) Voxel-level analysis showing reduced BP_{ND} in bilateral caudate (P < 0.001) and left anterior putamen (lesser extent in right) of PDE patients versus HC; cluster-defining threshold P = 0.001, FWE-corrected cluster size P < 0.05. Modified from (Waggan et al 2023).

Voxel-level analyses revealed that early-stage PD patients had reduced BP_{ND} in clusters corresponding to the bilateral caudate (P < 0.001) compared with healthy controls (Fig. 9C). Decreases in BP_{ND} were also noted in the left anterior putamen

and, to a lesser degree, in the right anterior putamen of early-stage PD subjects relative to controls. In contrast, no significant differences were found at voxel level when comparing moderate-stage PD patients with either healthy controls or early-stage PD patients.

Table 9. Average ± SD DVR values reflecting [^{11}C]TMSX binding to adenosine A_{2A} receptors in whole, ipsilateral (ipsi), and contralateral (contra; relative to the clinically more affected side) striatal regions of healthy controls (HC), early-stage PD (PDE), and moderate-stage PD (PDM) groups. **(b)** Within- and between-group comparisons of ipsilateral and contralateral striatal regions, presented with and without Bonferroni correction. $P < 0.05$ was considered statistically significant. Independent *t*-test was used for statistical comparison. Reproduced from (Waggan et al. 2023)

	CAUDATE	**PUTAMEN**	**PALLIDUM**
(A)			
HC (AVG LEFT + RIGHT), MEAN ± SD	1.163 ± 0.063	1.435 ± 0.030	1.135 ± 0.059
PDE (AVG LEFT + RIGHT), MEAN ± SD	1.056 ± 0.056	1.411 ± 0.080	1.217 ± 0.139
PDE IPSI, MEAN ± SD	1.054 ± 0.061	1.421 ± 0.067	1.234 ± 0.169
PDE CONTRA, MEAN ± SD	1.080 ± 0.061	1.400 ± 0.125	1.193 ± 0.122
PDM (AVG LEFT + RIGHT), MEAN ± SD	1.146 ± 0.093	1.472 ± 0.071	1.231 ± 0.058
PDM IPSI, MEAN ± SD	1.151 ± 0.100	1.454 ± 0.075	1.239 ± 0.059
PDM CONTRA, MEAN ± SD	1.147 ± 0.094	1.496 ± 0.091	1.223 ± 0.086
(B)			
HC LEFT VS RIGHT, (*P*)	> 0.99 (0.77)	> 0.99 (0.62)	> 0.99 (0.59)
PDE IPSI VS HC, (*P*)	**0.01 (0.005)**	> 0.99 (0.64)	0.57 (0.18)
PDE CONTRA VS HC, (*P*)	0.06 **(0.02)**	> 0.99 ((0.52)	> 0.87 (0.29)
PDE IPSI VS CONTRA, (P)	> 0.99 (0.39)	> 0.99 (0.66)	> 0.99 (0.56)
PDM IPSI VS HC, (*P*)	> 0.99 (0.50)	> 0.99 (0.59)	**0.02 (0.006)**
PDM CONTRA VS HC, (P)	> 0.99 (0.52)	0.92 (0.31)	0.92 (0.06)
PDM IPSI VS CONTRA, (*P*)	> 0.99 (0.92)	0.93 (0.30)	> 0.99 (0.66)

In the analysis of unilateral striatal ROIs relative to the clinically more affected (contralateral) and less affected (ipsilateral) sides in PD patients, early-stage PD subjects showed a significant reduction in ipsilateral caudate DVR compared to the mean caudate DVR of healthy controls (ES = 1.76, P = 0.01). A similar, though non-significant, trend was observed for the contralateral caudate in early-stage PD versus controls (ES = 1.38, P = 0.06). No significant difference was found between ipsilateral and contralateral caudate within the early-stage PD group (Table 9b). In

moderate-stage PD patients, ipsilateral pallidum DVR was elevated compared to healthy controls (ES = 1.83, P = 0.02), whereas no change was seen in the contralateral pallidum (P = 0.92). Within-group comparison of ipsilateral versus contralateral pallidum in moderate-stage PD revealed no significant differences (Table 9b).

The mean striatal [^{11}C]TMSX DVR showed a significant correlation with total UPDRS III scores (R = 0.47, P = 0.02) across the pooled PD cohort (Fig. 10A). When examining individual regions, no significant correlations were found between mean DVRs in caudate, putamen, or pallidum and UPDRS III scores (Table 10). Notably, [^{11}C]TMSX binding in the striatum contralateral to the side with predominant motor symptoms was moderately associated with the UPDRS III score of the clinically less affected side (R = 0.47, P = 0.04) and showed a similar, though non-significant, trend with the score of the more affected side (R = 0.42, P = 0.08) (Fig. 10B, C). Additionally, striatal DVR ipsilateral to the side with predominant motor symptoms displayed moderate correlations with UPDRS III scores of both the clinically more affected (R = 0.48, P = 0.04) and less affected sides (R = 0.49, P = 0.04) within the pooled PD group (Fig. 10D, E).

Table 10. Spearman correlation analyses between [^{11}C]TMSX DVR values in the whole striatum, caudate, putamen, and pallidum and clinical measures, including disease duration, UPDRS III scores, and levodopa equivalent dose (LED), in all PD patients combined (pooled), as well as in early-stage (PDE) and moderate-stage (PDM) PD subgroups.

REGIONS	DISEASE DURATION R (*P*)	UPDRS III *RHO* (*P*)	LED *R* (*P*)
STRIATUM (POOLED)	0.40 (0.05)	**0.47 (0.02)**	0.38 (0.06)
STRIATUM PDE	-0.43 (0.13)	0.01 (0.49)	**-0.68 (0.02)**
STRIATUM PDM	0.29 (0.24)	-0.03 (0.47)	0.28 (0.23)
CAUDATE (POOLED)	0.46 (0.07)	0.46 (0.06)	**0.55 (0.02)**
CAUDATE PDE	0.25 (0.51)	0.22 (0.57)	0.12 (0.77)
CAUDATE PDM	0.17 (0.69)	0.24 (0.54)	0.47 (0.21)
PUTAMEN (POOLED)	0.17 (0.52)	0.22 (0.78)	0.07 (0.78)
PUTAMEN PDE	**-0.82 (0.01)**	-0.24 (0.53)	**-0.76 (0.02)**
PUTAMEN PDM	0.35 (0.40)	-0.22 (0.57)	0.17 (0.68)
PALLIDUM (POOLED)	-0.13 (0.62)	0.06 (0.79)	-0.10 (0.70)
PALLIUM PDE	-0.66 (0.06)	-0.35 (0.35)	-0.42 (0.26)
PALLIDUM PDM	-0.08 (0.85)	0.36 (0.34)	0.00 (> 0.99)

Abbreviations: UPDRS: United Parkinson's disease rating scale, **LED**: Levodopa equivalent dose. **Bold** values represent statistical significance.

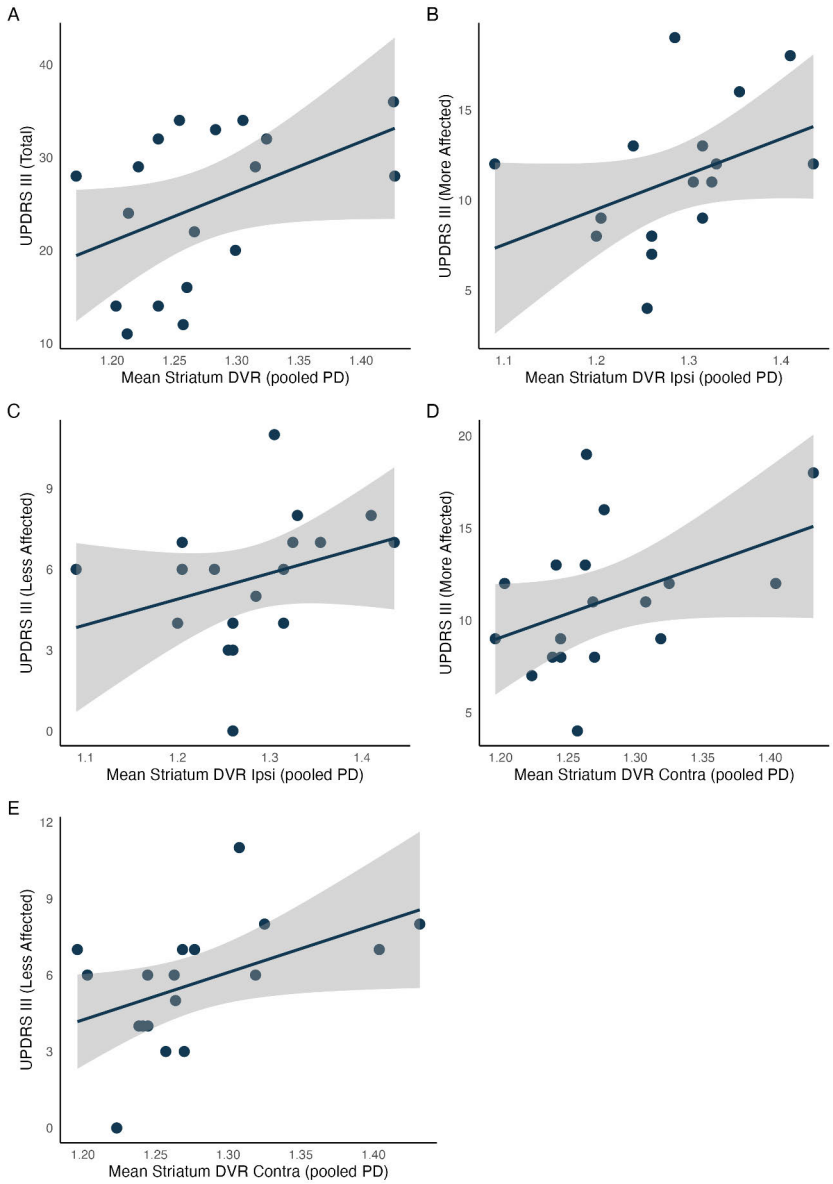

Figure 10. Scatter plots illustrating the relationships between [^{11}C]TMSX distribution volume ratio (DVR), reflecting adenosine A_{2A} receptor availability in the whole striatum, ipsilateral (Ipsi) and contralateral (Contra; relative to the clinically more affected side) striatum, and UPDRS III scores in pooled Parkinson's disease (PD) patients (early + moderate stage). (A) Association between mean bilateral striatum DVR and total UPDRS III score. (B) Association between mean contralateral striatum DVR and UPDRS III score of the clinically more affected side. (C) Association between mean contralateral striatum DVR and UPDRS III score of the clinically less affected side. (D) Association between mean ipsilateral striatum DVR and UPDRS III score of the clinically more affected side. (E) Association between mean ipsilateral striatum DVR and UPDRS III score of the clinically less affected side. UPDRS: Unified Parkinson's Disease Rating Scale. Modified from (Waggan et al. 2023)

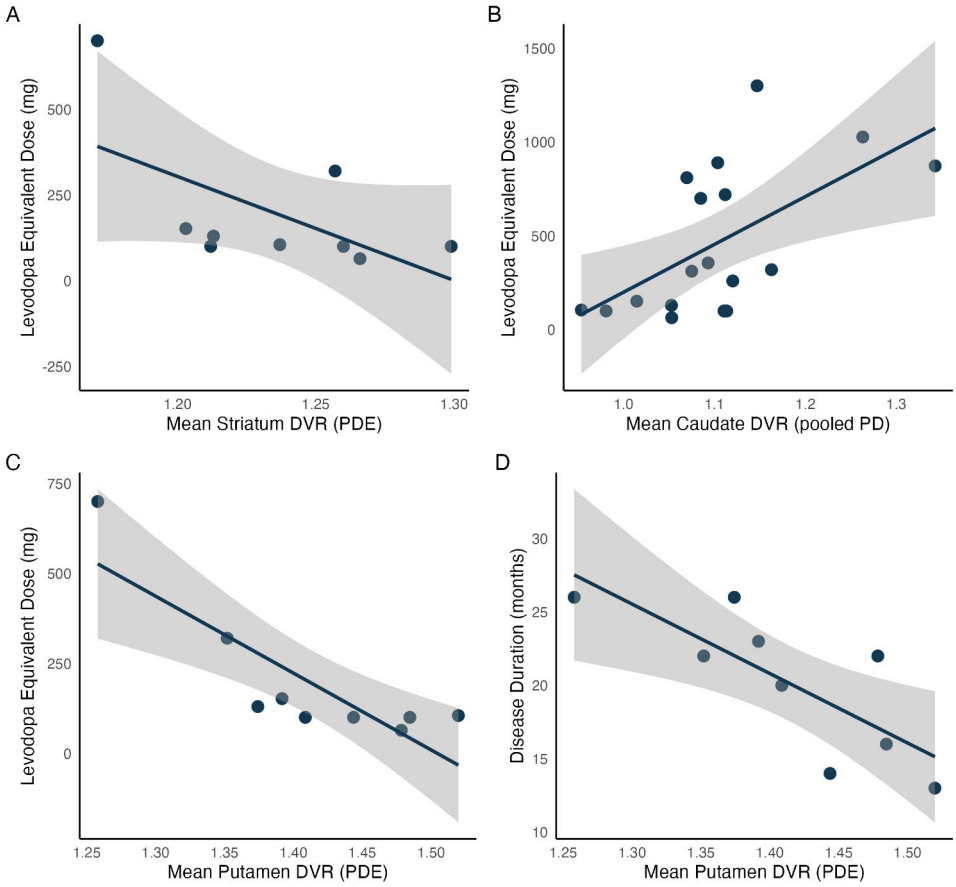

Figure 11. Scatter plots illustrating relationships between [^{11}C]TMSX distribution volume ratio (DVR), reflecting adenosine A_{2A} receptor availability in striatal regions, and clinical measures in Parkinson's disease (PD) patients. (A) Correlation of mean bilateral striatum DVR with Levodopa equivalent dose (LED) in early-stage PD (PDE) patients. (B) Correlation between mean bilateral caudate DVR and LED in the pooled PD group (PDE + moderate-stage PD). (C) Correlation of mean bilateral putamen DVR with LED in PDE patients. (D) Correlation of mean bilateral putamen DVR with disease duration in PDE patients.

We observed a significant relationship between striatal [^{11}C]TMSX binding and levodopa equivalent dose (LED) in early-stage PD patients (R = –0.68, P = 0.02) (Fig. 11A). Additionally, mean bilateral caudate [^{11}C]TMSX DVR showed a positive correlation with LED in the pooled PD group (R = 0.55, P = 0.02) (Fig. 11B). A strong negative correlation was also noted between [^{11}C]TMSX binding in bilateral putamen and both LED (R = –0.76, P = 0.02) and disease duration (R = –0.82, P = 0.01) in early-stage PD patients (Table 10, Fig. 11C, D).

5.4 Study III: Increased A_{2A} receptor availability in the frontal and parietal white matter of PD patients compared to controls

ROI-level analyses revealed that patients with PD exhibited increased A_{2A} receptor availability in the bilateral frontal ($P < 0.001$) and parietal ($P < 0.001$) white matter compared to healthy controls (Fig. 12A). No significant differences were found in temporal ($P = 0.80$) or occipital white matter regions ($P > 0.99$). Conversely, occipital gray matter showed reduced A_{2A} receptor availability in PD patients ($P = 0.02$), while frontal ($P = 0.35$), parietal ($P > 0.99$), and temporal gray matter regions ($P = 0.06$) did not differ (Fig. 12B). Gray matter volume ratios were decreased in frontal ($P < 0.01$), parietal ($P < 0.001$), temporal ($P < 0.01$), and occipital ($P < 0.01$) ROIs in PD patients relative to controls, whereas white matter volume ratios across all regions showed no significant differences ($P > 0.05$, Fig. 13A, B).

Furthermore, we observed a trend suggesting that higher A_{2A} receptor availability in frontal white matter is linked to reduced frontal gray matter volume ($R = -0.52$, $P = 0.03$), although this association did not remain significant after correcting for multiple comparisons (adjusted $P = 0.12$). No significant relationships were found between white matter DVRs and gray matter volumes in the parietal ($R = -0.03$, $P > 0.99$), temporal ($R = -0.14$, $P > 0.99$), or occipital ($R = -0.08$, $P > 0.99$) regions. A positive correlation was detected between temporal gray matter DVR and temporal gray matter volume ($R = 0.63$, $P = 0.005$; adjusted $P = 0.02$). No significant associations were observed between DVRs and gray matter volumes in the frontal, parietal, or occipital regions ($P > 0.05$), nor between white matter DVRs and their corresponding white matter volumes across any region ($P > 0.05$). Additionally, neither white nor gray matter DVRs in frontal, parietal, temporal, or occipital areas were associated with clinical parameters ($P > 0.05$).

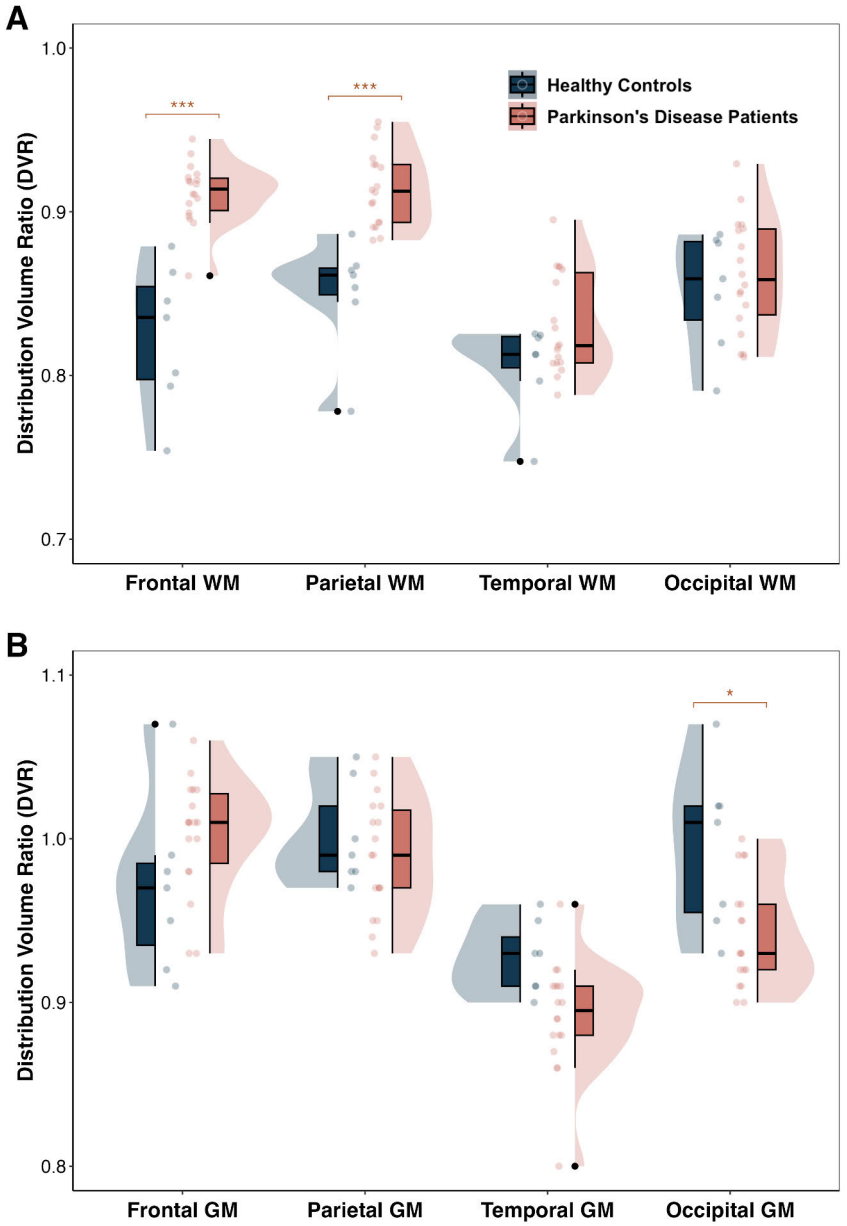

Figure 12. Raincloud plots comparing [^{11}C]TMSX PET parameters between healthy controls and Parkinson's disease (PD) patients. (A) Distribution volume ratios (DVR) of adenosine A_{2A} receptors in cerebral white matter (WM) regions of interest. (B) DVRs in cerebral gray matter (GM) regions of interest. Significance levels: ***P < 0.001, **P < 0.01, *P < 0.05. Modified from (Waggan et al. 2023)

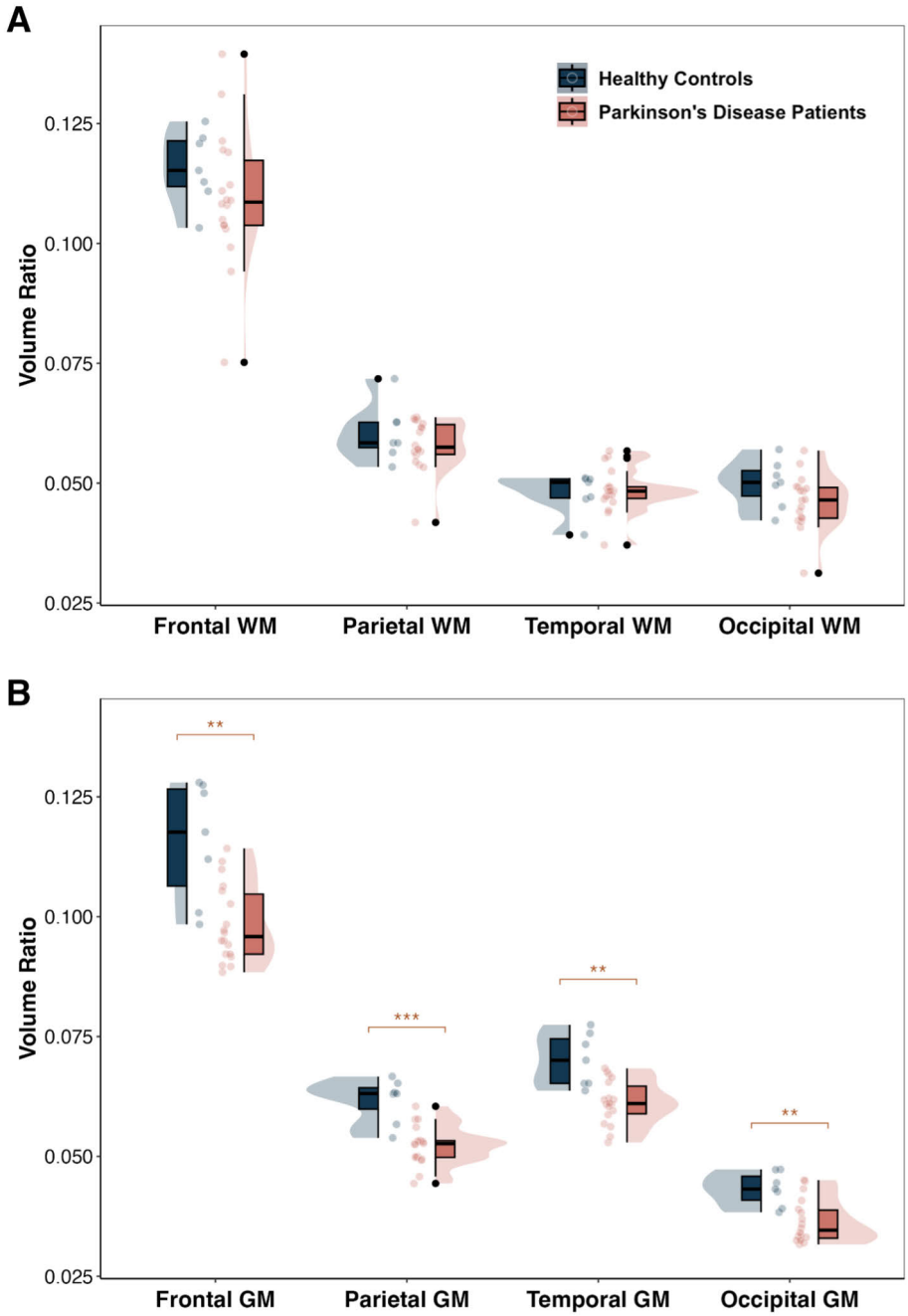

Figure 13. Raincloud plots comparing MRI-derived volume ratios (parenchymal fractions) between healthy controls and Parkinson's disease (PD) patients. (A) Volume ratios of cerebral white matter (WM) regions of interest. (B) Volume ratios of cerebral gray matter (GM) regions of interest. Significance levels: ***P < 0.001, **P < 0.01, *P < 0.05. Modified from (Waggan et al 2023)

6 Discussion

6.1 Effect of short-term cessation of dopaminergic medication on A_{2A} receptor availability

In study I, we showed that there was no significant difference in the striatal A_{2A} receptor availability between 'ON' and 'OFF' dopaminergic medication states. There was high and statistically significant correlation in A_{2A} receptor binding between the two medications states. In addition, the A_{2A} receptor binding was statistically equivalent in pallidum and putamen. However, the binding was neither statistically different nor equivalent in caudate or its subdivisions. The correlation between 'ON' and 'OFF' medication states were also relatively weaker in caudate subdivisions.

The non-equivalence of A_{2A} receptor availability between the 'ON' and 'OFF' medication states in the caudate may stem from its later involvement in the disease process. The relative preservation suggests that a greater number of viable dopaminergic neurons in the caudate allow for allosteric interactions between dopaminergic neurons and A_{2A} receptors. Differences in cortical afferent input between the caudate and putamen along with the relative differences in presynaptic A_1-A_{2A} heteromer in both these structures may also underlie the asymmetry in A_{2A} receptor availability observed in the caudate nucleus (Casadó et al., 2010; Gordon et al., 2022). Pramipexole is one of the principal negative allosteric modulators of A_{2A} receptors and many of our patients were indeed taking this medication (Fernández-Dueñas et al., 2013). However, this effect may have been attenuated or diluted by using other dopaminergic medications.

A previous PET study reported an increase in A_{2A} receptor availability in drug-naïve patients with PD after they started antiparkinsonian therapy. The increase was localized to the putamen and no corresponding increase was observed in the caudate (Mishina et al., 2011). Notably, none of the patients had developed dyskinesia at the time of the second scan. The authors predictably hypothesize that the increase in A_{2A} receptor observed in putamen can be attributed to the initiation of dopaminergic medication (Mishina et al., 2011). In contrast, similar increase in A_{2A} receptor availability was not observed in our cohort as they were already on stable medication and were scanned while both on treatment and after a short-term cessation. Unlike

the study by Mishina et al, which investigated the receptor availability in drug naïve participants, our patients had already undergone chronic dopaminergic exposure.

6.2 Disease stage-specific changes in striatal A_{2A} receptor availability

In study II, we reported a significant decrease in A_{2A} receptor availability in bilateral caudate of early-stage PD patients as compared with healthy controls. We also demonstrated an increase in pallidal A_{2A} receptor availability in moderate-stage PD patients relative to healthy controls.

Unlike the increase in A_{2A} receptor availability in pallidum, the decrease in caudate was observed both at the ROI level and with the voxel level analyses. This decrease in the caudatal A_{2A} receptors has also been previously reported by preclinical and postmortem studies (Calon et al., 2004; Hurley et al., 2000; Trincavelli et al., 2012). What is particularly intriguing is that D_2 receptors, which are co-localized with A_{2A} receptors on MSNs in the indirect pathway, have also been shown to decrease in caudate in patients with PD as compared to those with other neuropsychiatric diseases and healthy controls (Malén et al., 2024). Furthermore, reduced glucose metabolism has been observed in the caudate of patients with PD compared to healthy controls suggesting a functional dampening of caudate neural activity as compared to the rest of basal ganglia structures (Rao et al., 2022). Similarly, studies in early stage PD patients have also reported a decrease in dopamine D_2 receptor availability in caudate compared to healthy volunteers (Antonini et al., 1997; Politis et al., 2017). Studies also demonstrate a negative allosteric interaction between D_2 agonists and A_{2A} receptors (Fernández-Dueñas et al., 2013). We hypothesize that this heteromeric allosteric interaction may change the conformation or internalization dynamics of A_{2A} receptors via chronic D_2 stimulation with dopamine receptor agonists. Another potential mechanism could be the masking of the binding sites by increased endogenous adenosine which competes with [^{11}C]TMSX at the orthosteric site and could lead to the drop in PET signal observed in our study.

Previous studies suggest that the pattern of degeneration in PD follows a postero-anterior gradient, meaning that the putamen is affected early in the course of the disease while caudate is relatively spared during that period (Kish et al., 1988; Nandhagopal et al., 2009; Winogrodzka et al., 2003). In study I, we showed that the binding in the caudate was not statistically equivalent between the ON medication and short-term OFF medication states in patients with PD (Waggan et al., 2021). Furthermore, early-stage PD patients are typically treated with dopamine agonists as was the case in our cohort. Because D_2 receptors in the caudate are relatively spared, they remain highly responsive to dopamine agonist therapy. This abundance of

viable D_2 targets likely facilitates a stronger heteromeric allosteric interaction, thereby causing a more significant drop in A_{2A} receptor availability compared to other regions. (Fernández-Dueñas et al., 2013). As explained before, this could result from either conformational changes or alterations in receptor affinity. Another possibility is that A_{2A} receptors in the caudate are differentially affected compared to other basal ganglia structures possibly because of difference in heteromeric or trimeric receptor complexes in the caudate versus the putamen (Bonaventura et al., 2014). The disparity in A_{2A} receptor availability could also stem from differences in functional circuitry, as the caudate is primarily involved in cognitive pathways and is less affected in the earlier stages of the disease (Grahn et al., 2008).

We also observed an increase in bilateral pallidal A_{2A} receptor availability in patients with moderate stage PD relative to healthy controls. Although the finding could not be replicated at voxel level, possibly because of high level of noise and strict cluster defining threshold, they are consistent with earlier postmortem studies (Calon et al., 2004). A_{2A} receptors are expressed on the nerve terminals of GABAergic MSNs in the external segment of globus pallidus (GPe) (Bogenpohl et al., 2012; Rosin et al., 2003; Svenningsson et al., 1997). The pallidal A_{2A} receptors also contribute to the modulation of the indirect pathway, however, this 'dual excitatory modulation' is less effective than that mediated by striatal A_{2A} receptors (Ochi et al., 2000). Indeed, it has been observed in preclinical models that pallidal microinjection of A_{2A} agonists suppresses pallidal firing whereas A_{2A} antagonists increase firing rates, thereby helping to normalize pallidal output and suggesting that A_{2A} receptors at this level play a significant role in modulating striatal output (Diao et al., 2017).

Increased A_{2A} receptor availability at the pallidal level also suggests higher GPCR mediated GABAergic inhibition of GPe which may contribute to the reduced efficacy of dopaminergic therapy as the disease progresses, potentially explaining the plateau often observed in clinical response despite escalating doses (Fredholm & Svenningsson, 2020; LeWitt et al., 2008). Furthermore, altered GPe output resulting from increased A_{2A} receptor availability may disrupt signaling in both upstream and downstream basal ganglia structures, given the GPe's critical role as an intrinsic nucleus that functions as a conduit between the input (striatum) and output (GPi/SNr) nuclei of the basal ganglia (Plotkin & Goldberg, 2019). This notion is supported by dynamic clamp experiments which show that small changes in GPe output can suppress subthalamic firing and synchronize the autonomous STN activity (Baufreton et al., 2009). Furthermore, changes in receptor availability on indirect MSNs may also modulate intrastriatal lateral inhibition thereby indirectly affecting striatal output (Burke et al., 2017).

In study II, we also observed that the changes in A_{2A} receptor availability in both early and moderate stage patients were marginally greater on the ipsilateral side with

respect to predominant motor symptoms. This may appear inconsistent, given that the contralateral side typically shows more pronounced deficits in dopaminergic function, as observed in PET studies studying dopaminergic function in patients with PD (Rinne et al., 1993; Eidelberg et al., 1990; Morrish et al., 1995). However, this finding can be explained by the greater number of viable dopamine terminals preserved on the ipsilateral side (Djaldetti et al., 2006). This relative preservation may allow for larger compensatory changes in A_{2A} receptor availability, possibly driven by allosteric interactions between D_2 and A_{2A} receptors.

Similarly, an association was found between ipsilateral striatal A_{2A} receptor availability with the UPDRS III score of the clinically more and less affected sides of the body. In contrast, [^{11}C]TMSX binding on the contralateral striatum had an association with the UPDRS III score of the clinically less affected side of the patient only. Overall, there was a significant association between bilateral striatal A_{2A} receptor availability and bilateral UPDRS III scores of pooled patients with PD. Taken together, these findings underscore an essential role played by the purinergic system, particularly the A_{2A} receptors, in modulating the basal ganglia motor circuitry. The observation that the alterations in receptor availability are more pronounced on the ipsilateral side relative to the predominant motor system may also be explained by 'floor effect' on the contralateral side, where receptor availability has already reached a minimal threshold, limiting further detectable changes (Kaasinen et al., 2021; Simuni et al., 2018).

A strong association between lower bilateral putaminal A_{2A} receptor availability and longer disease duration was also observed in our work though this correlation was only limited to early-stage patients with PD. This may be attributed to early dopaminergic degeneration in the putamen which, in some cases, even precedes motor symptom onset (Nandhagopal et al., 2009). A compensatory increase in the putaminal availability of A_{2A} receptors in patients with late stage PD suffering from levodopa induced dyskinesia has already been reported previously (Mishina et al., 2011; Ramlackhansingh et al., 2011).

6.3 Cerebral gray and white matter changes in A_{2A} receptor availability

Our results from study III indicated an increase in A_{2A} receptor availability in frontal and parietal white matter and a decrease in occipital gray matter of patients with PD compared with healthy controls. Furthermore, we showed that increased availability of A_{2A} receptors in frontal white matter was associated with decreased frontal gray matter volume. An association was also observed between temporal gray matter volume and corresponding A_{2A} receptor availability.

Alpha synuclein, a hallmark of PD, has been shown to initiate cerebral white matter changes (Y. Fu et al., 2022). These changes, often reported as decreased fractional anisotropy (FA), precede gray matter and cognitive alteration observed in patients with PD (Park et al., 2022). Indeed, there is evidence to suggest a temporal association between gray and white matter changes (Tang et al., 2021; Zhang et al., 2014). Increased A_{2A} receptor expression has been reported on glial cells in animal models of synucleinopathies (Hu et al., 2016). Activation of A_{2A} receptors results in astrocytic proliferation and a marked decrease in Na^+/K^+-ATPase activity which results in glutamate mediated toxicity leading to neuronal death (Matos et al., 2013). Integrating our findings with the previously discussed preclinical evidence we propose that A_{2A} receptors actively modulate white matter changes which in turn contribute to gray matter degeneration (Waggan et al., 2023).

Studies also indicate that activation of A_{2A} receptors in neurons leads to an increase in NMDA receptor function which results in an impairment of Ca^{2+} entry into the neurons (Rebola et al., 2008). This impairment enhances intraneuronal *a*-synuclein aggregates which results in neuronal degeneration (Rcom-H'cheo-Gauthier et al., 2014). Notably, evidence from preclinical research shows that A_{2A} receptor antagonism prevents neuronal death triggered by synuclein aggregates (Ferreira et al., 2017). In addition, consumption of caffeine, a known non-selective adenosine receptor antagonist, has been shown to be associated with reduced risk for developing PD in numerous epidemiological studies (Ascherio et al., 2001).

Recent evidence suggests that within the white matter, A_{2A} receptors are primarily expressed in axonal initial segments (AIS) as well as on the nodes of Ranvier (Lezmy et al., 2021). A_{2A} receptor activation on AIS alters neuronal excitation while their activation on the nodes of Ranvier decreases signal conduction speed (Lezmy et al., 2021). Impaired fronto-striatal and frontoparietal connectivity has been observed in patients with PD without significant white matter alteration (Tinaz et al., 2016). We therefore speculate that the increased A_{2A} receptor availability in frontal and parietal white matter seen in our cohort could be linked with the aberrant connectivity patterns observed in patients with PD (Waggan et al., 2023).

Our study also demonstrated higher parietal white matter availability but, in contrast to frontal white matter, no association with gray matter volume loss was observed. Gray matter volume decrease was also seen in occipital and temporal lobes, but this was not accompanied with any significant increase in the availability of A_{2A} receptors in their respective white matter regions. An international multicenter study analyzing thousands of MRI scans revealed that cortical thinning initiates from the occipital regions in the early stages of PD, extending to rostral cerebral regions as the disease progresses (Laansma et al., 2021). Upregulation of neuronal A_{2A} has been associated with neurodegenerative changes in several

neurodegenerative diseases. It is possible that, in PD, neuronal A_{2A} receptors are upregulated during active pathology but subsequently get downregulated as degeneration advances to more rostral brain regions and the overall number of viable neurons decline (Carvalho et al., 2019; Ferreira et al., 2017; Gomez-Murcia et al., 2024).

A decrease in occipital A_{2A}R gray matter availability was observed in our patients which could suggest a downregulation or decrease in the number of viable A_{2A} expressing neurons. An association between temporal gray matter volume and corresponding A_{2A} receptor availability was also evident in our cohort. This may suggest a region-specific role of A_{2A} receptors in modulating neurodegenerative processes. It is also possible that this variability arises from distinct cell types expressing A_{2A} receptors in these regions such as neurons vs glia (Gao, 2023; Launay et al., 2025; Xu et al., 2022).

6.4 Clinical implications

The main implication of our findings from study I is that patients with early and moderate stage PD, particularly those unable to tolerate even short-term cessation of their dopaminergic medication, can undergo PET imaging to assess A_{2A} receptor availability without discontinuing their medication and still obtain reliable estimates for pallidum and putamen. However, binding estimates for caudate under these conditions require cautious interpretation.

In study II, we showed a decrease in the availability of A_{2A} receptors in caudate of patients with early stage PD and an increase in pallidum in moderate stage PD (Waggan et al., 2022). It is important to highlight that most trials for Istradefylline, an adenosine A_{2A} receptor antagonist, recruited patients with Hoehn & Yahr (H&Y) stage 2-4 (Jenner et al., 2021). Patients in early or mild stage of the disease are typically classified as H&Y stage 1-2, those with moderate disease as H&Y stage 3 and patients with severe or advanced PD are classified as H&Y stage 4-5 (Martínez-Martín et al., 2015). Based on our results we speculate that Istradefylline would be more efficacious in alleviating motor symptoms in patients with moderate to advanced stage of the disease (H&Y 3-4) by counteracting the ‘bottle neck’ of higher pallidal A_{2A} receptor availability and normalizing pallidal output.

The increased availability of A_{2A} receptors in frontal and parietal white matter observed in study III could potentially underlie the impaired fronto-striatal circuits observed in patients with PD primarily because of their role on the axonal initial segment of the neuron (Lezmy et al., 2021). This impaired connectivity is hypothesized to underlie some of the non-motor symptoms associated with PD such as apathy, executive dysfunction and cognitive impairment (Baggio et al., 2015; Betrouni et al., 2022; T. Hattori et al., 2017). Supporting this notion, recent evidence

indicates that Istradefylline can improve non-motor symptoms such as apathy and mood in patients with PD (Nagayama et al., 2019, 2025).

Astrocytic A_{2A} receptors modulate neuroinflammatory processes through several mechanisms including control of glutamate uptake and release of cytokines, neurotrophins and growth factors (George et al., 2015; Launay et al., 2025; Matos et al., 2012; A. G. Orr et al., 2015). Chronic neuroinflammation, mediated by astrocytes and microglia, is one of the hall marks of PD pathology alongside *a*-synuclein aggregation and degeneration of dopaminergic neurons (Roodveldt et al., 2024). We, therefore, speculate that the increased A_{2A} receptor availability observed in several cerebral regions in our study could represent a target thorough which istradefylline may reduce neuroinflammation, potentially via its action on astrocytes (Zaki et al., 2025).

Adenosine A_{2A} receptors are also expressed on peripheral immune cells including lymphocytes, natural killer cells and neutrophils (Haskó & Pacher, 2008). Th17 cells, a proinflammatory profile of $CD4^+$ T lymphocytes, play a role in activating microglia and promoting neuroinflammation (Roodveldt et al., 2024). Interleukin (IL) 17A, a cytokine of Th17 cells, has been shown to promote neuronal death through activated microglia (J. Fu et al., 2022). Furthermore, the inhibition of microglial IL-17A receptor prevents this cascade of neuronal degeneration (Liu et al., 2019). Interestingly, Istradefylline has been found to suppress IL-17A production in human peripheral blood mononuclear cells (Tokano et al., 2022). These results indicate that Istradefylline may be beneficial in alleviating neuroinflammation triggered by peripheral immune system and may serve as a potential disease modifying therapy. There is also evidence suggesting that A_{2A} antagonism may prevent the formation of *a*-synuclein inclusions in the neurons and hence, the resulting neurotoxicity, however, this needs to be corroborated by clinical evidence (Ferreira et al., 2017).

6.5 Methodological considerations

One of the main limitations of our study was the relatively modest sample size for study I and II and limited number of healthy controls for study III, although not unusual for human brain PET studies. While our cohort sizes were at par or larger than previous PET studies investigating A_{2A} receptor availability in PD and appropriate sample size calculations were performed, the numbers still remain a limitation (Mishina et al., 2011; Ramlackhansingh et al., 2011). To obtain more robust and generalizable estimates future research should aim for larger, multicenter studies that can pool resources and increase statistical power.

For our study we utilized [^{11}C]TMSX radiotracer to study the availability of A_{2A} receptor in cerebral and striatal regions of patients with PD. One previous study used

SCH442416 to investigate A_{2A} receptor availability in caudate, putamen and thalamus. It has been shown that SCH442416 has lower affinity for striatal A_{2A} receptors forming heteromers with D_2 receptors as compared to presynaptic A_{2A}-A_1 heteromers (Orru et al., 2011b). Furthermore, we encountered low signal to noise ratio for cerebral gray and white matter in both patients and healthy controls, however, previous test-retest studies have suggested that reliable estimates can be still be obtained from these regions (Naganawa et al., 2014a).

Previous studies using [^{11}C]TMSX radiotracer in PD used cerebellum or foramen semi-ovale as a reference region for estimation of PET measures (Mishina et al., 2011). Instead, to omit the need for arterial input requiring arterial cannulation, we used supervised clustering algorithm implemented with SuperPK software to derive a clustered gray matter reference region (Turkheimer et al., 2007b). This method was already validated in our earlier work (Rissanen et al., 2014).

Another limitation of our work was that our study was designed cross-sectionally which limits our ability to understand the disease progression and corresponding A_{2A} receptor dynamics over time (Caruana et al., 2015). It would be interesting to study A_{2A} receptor availability in patients with idiopathic PD, from the prodromal to advanced disease stages, in a longitudinal setting.

6.6 Future directions

Future studies would benefit from utilizing more recently developed A_{2A} receptor radioligands having better signal to noise ratio and greater target specificity, particularly in a longitudinal setting, to more accurately understand A_{2A} receptor availability during disease progression (Barret et al., 2015; Sakata et al., 2017b). Utilizing radioligands with better signal to noise ratio would also make it more feasible to analyze smaller regions in the mid brain relevant to PD pathology.

Use of A_{2A} antagonists in patients with PD have shown a beneficial effect in alleviating some of the non-motor symptoms (Nagayama et al., 2019, 2025). Therefore, examining extra-striatal regions associated with non-motor symptoms may help to further elucidate the role A_{2A} receptors play in non-motor symptoms. This added understanding of the role played by A_{2A} receptors in the pathophysiology of non-motor symptoms would not only strengthen the rationale of using A_{2A} antagonists as an adjunct to levodopa but also provide evidence that distinguish them from other adjunct medications by highlighting their potential added benefit for non-motor symptoms. Furthermore, A_{2A} receptors are also expressed in the human retinal pigment epithelial cells which is involved in maintenance of the photoreceptor (Boulton & Dayhaw-Barker, 2001; Friedman et al., 1989; Taomoto et al., 2000). *A*-synuclein aggregates in the retinal pigment epithelium may underlie the retinal degeneration observed in patients with PD (Baksi & Singh, 2017). A_{2A} antagonism

has been shown to attenuate age related macular degeneration by their effect on retinal pigment epithelium (Madeira et al., 2018). Since retinal pigment epithelium is also involved in PD related retinopathy, the role of A_{2A} receptors and A_{2A} antagonists could be further investigated in alleviating ocular complications in patients with PD (Xiao et al., 2025).

There is evidence to suggest that peripheral immune cells could be involved in initiating or worsening neuroinflammatory processes contributing to neurodegeneration in patients with PD (Tansey et al., 2022). A_{2A} receptors also have an increased expression on peripheral immune cells such as leukocytes and neutrophils with critical importance in the modulation of peripheral immune response (Preti et al., 2015; Varani et al., 2010). Notably, it has been suggested that on peripheral immune cells A_{2A} agonists rather than A_{2A} antagonists may have an anti-inflammatory action (Lappas et al., 2005; Welihinda & Amento, 2014). It would be interesting to study whether the anti-neuroinflammatory effect of A_{2A} antagonists in comparison with the anti-inflammatory effect of A_{2A} agonists is more profound and robust in reducing the overall pathological burden in patients with PD.

Although idiopathic PD is the most common cause of parkinsonism, the syndrome can also manifest in conditions with lesions outside of the nigrostriatal tract (Handley et al., 2009). Parkinsonism can also manifest in other neurological disorders such as progressive supranuclear palsy and multiple system atrophy, the so called Parkinson-plus syndrome or atypical parkinsonism (Keir et al., 2024). It would be interesting to explore whether, and how, availability of A_{2A} receptors changes particularly in cases where nigrostriatal tract, which is the primary site of A_{2A} receptor expression, is not directly affected.

7 Conclusions

The purpose of this thesis was to investigate the role of adenosine A_{2A} receptors in PD using in vivo [^{11}C]TMSX PET imaging. The studies aimed to evaluate the effects of short-term cessation of dopaminergic medication on A_{2A} receptor availability, to characterize receptor availability across different stages of PD and to examine A_{2A} receptor availability in extra-striatal brain regions. Based on the findings presented in this thesis, the following conclusions can be drawn:

I [^{11}C]TMSX PET imaging provides a reliable and reproducible method for quantifying adenosine A_{2A} receptor availability in the human brain. In patients with PD, striatal A_{2A} receptor binding was statistically equivalent between the ON and OFF medication state in the putamen and pallidum. Although the binding in caudate did not meet the strict statistical equivalence criteria, no meaningful difference in binding was observed, suggesting that this finding should be examined further in larger cohorts. Based on these results, we conclude that patients with early and moderate stage PD do not need to discontinue their regular dopaminergic medication when undergoing A_{2A} receptor PET imaging in future studies, as reliable estimates of A_{2A} receptor binding in the putamen and pallidum can be obtained without medication withdrawal.

II Adenosine A_{2A} receptor availability differs from healthy controls in early and moderate stages of PD. We showed a decrease in A_{2A} receptor availability in caudate in early stage, and increased A_{2A} receptor binding in the pallidum in moderate-stage patients with PD compared to healthy controls. This upregulation in pallidum appears to progress with disease severity and may reflect adaptive changes within the indirect basal ganglia pathway contributing to motor dysfunction.

III Adenosine A_{2A} receptor expression extends beyond the striatum to cerebral gray matter and white matter regions. The increased A_{2A} receptor availability observed in frontal and parietal white matter represents a novel finding that extends the focus of A_{2A} receptor research beyond the basal ganglia. These

results underscore the importance of investigating extra-striatal regions to fully understand the receptor's broader role in PD pathology.

The findings from our PET imaging studies lead us to hypothesize that A_{2A} antagonists may exert greater therapeutic benefit in patients with moderate-stage PD, where A_{2A} receptor availability is increased in the pallidum. By targeting this heightened adenosinergic signaling within the indirect pathway, A_{2A} blockade may more effectively improve motor performance and reduce “OFF” periods. In contrast, early-stage PD patients show reduced A_{2A} receptor availability in the caudate, suggesting that the therapeutic response to A_{2A} antagonists may differ according to disease stage.

Future studies should focus on longitudinal A_{2A} PET imaging to determine the temporal evolution of receptor changes across disease progression and in prodromal PD cohorts, such as individuals with REM sleep behavior disorder. The integration of A_{2A} receptor PET with complementary imaging modalities, such as dopaminergic, cholinergic, microglial, or synaptic density tracers, could offer a more comprehensive understanding of neurochemical interactions underlying PD. Taking into account our findings of increased A_{2A} receptor availability in white matter, future research should expand on these observations and investigate the potential role of white matter A_{2A} receptors in contributing to or alleviating also the non-motor symptoms commonly observed in patients with PD.

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