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Exploring Dopamine Lateralization with SPECT imaging in Parkinson's Disease

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*To my parents
and friends*

Abstract

Objective: This study investigated the lateralization of dopamine in individuals with Parkinson's disease, starting with a "normal" dopamine lateralization model developed from a sample of healthy controls. **Methods:** A total of 1,029 participants were included in the analysis: 191 healthy controls and 847 Parkinson's disease patients. All data were collected from the Parkinson's Progression Markers Initiative (PPMI) database. Dopamine levels and the Laterality Index were calculated using [^{123}I]FP-CIT SPECT (DaTSCAN) imaging from screening visit data. For each patients a full set of motor, non-motor, and cognitive tests were also available. **Results:** Approximately 26% of the PD patients were classified as Extreme Lateralized (EL), with the remainder categorized as Normal Lateralized (NL). Initial analysis revealed that greater asymmetry in dopamine function within the Putamen was associated with higher SBR values, alongside better cognitive, motor, and autonomic performance. Univariate analysis supported this hypothesis, showing that EL patients scored better on MDS-UPDRS part I, the SDMT, as well as gastrointestinal and urinary function assessments. Furthermore, longitudinal analysis highlighted a growing disparity between the groups over time, with EL patients experiencing a less pronounced progression of motor, cognitive and autonomic symptoms. Although differences between Right and Left Lateralization (EL_{Right} , EL_{Left}) were unexpected, patients with EL_{Left} symptoms exhibited more severe motor impairments in MDS-UPDRS part III, which was the only significant finding in this context. **Conclusion:** The results suggest the presence of a compensatory mechanism in the EL group, where the less affected striatal hemisphere seems to increase dopamine production to compensate for the loss on the opposite side. This finding opens the possibility of using lateralization as a potential prognostic marker, providing the foundation for more personalized rehabilitation or therapeutic strategies. With further research, this understanding could help develop treatments

that focus on each patient's unique dopamine distribution, improving the precision of Parkinson's disease therapies.

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Chapter 1

Introduction

1.1 Parkinson's Disease

Parkinson's disease (PD) is one of the most common neurodegenerative disorders, second only to Alzheimer's disease in prevalence [1]. It is characterized by the progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc), a crucial region of the brain that controls movement through the release of dopamine into the striatum. Over recent years, PD has shown the fastest growth in prevalence among neurological diseases, raising concerns over its rising socioeconomic impact [2]. The hallmark of PD is the depletion of dopamine in the striatum, leading to a wide array of both motor and non-motor symptoms. While virtually anyone could be at risk for developing Parkinson's, some research studies suggest this disease affects more men than women. It is unclear why, but studies are underway to understand factors that may increase a person's risk. One clear risk is age: although most people with Parkinson's first develop the disease after age 60, about 5% to 10% experience onset before the age of 50. Early-onset forms of Parkinson's are often, but not always, inherited, and some forms have been linked to specific alterations in genes [3]. However, the most common view is that PD is dependent on a combination of genetic and environmental factors, such as exposure to toxins. Clinically, PD primarily affects the motor system, manifesting as tremors, bradykinesia (slowness of movement), rigidity, and postural instability.

These motor impairments are often the most noticeable symptoms; however, non-motor symptoms such as sleep disturbances, mood changes, cognitive decline, difficulty swallowing, chewing, speaking, urinary problems, constipation, sexual dysfunction, pain and fatigue frequently precede motor signs and severely impair the quality of life for patients [4] [5]. This combination of motor and non-motor dysfunctions highlights the widespread effects of dopamine depletion in the brain, particularly on both movement and cognitive systems shaping the pathophysiology of PD. The dopaminergic neurons, which are primarily located in the substantia nigra, ventral tegmental area (VTA), and hypothalamus, are responsible for producing dopamine, a neurotransmitter critical for regulating movement, motivation, reward, and cognitive functions such as attention and decision-making. The nigrostriatal pathway, which connects the substantia nigra to the dorsal striatum (including the putamen and caudate nucleus, which are the regions this study will focus on), plays a key role in motor control by releasing dopamine in the striatum. Within this pathway, the dopamine transporter (DAT) regulates dopamine levels in the synaptic cleft by facilitating its reuptake [6] [7]. The main therapy for PD is levodopa. Nerve cells use levodopa to make dopamine to replenish the brain's dwindling supply. Usually, people take levodopa along with another medication called carbidopa. Carbidopa prevents or reduces some of the side effects of levodopa therapy — such as nausea, vomiting, low blood pressure, and restlessness — and reduces the amount of levodopa needed to improve symptoms [8].

1.2 Lateralization in Parkinson's Disease

1.2.1 Lateralization of symptoms

A striking feature of PD is the lateralization of symptoms. PD typically presents with asymmetric motor symptoms, where more than 95% of patients show unilateral motor impairment at disease onset [9]. The onset side, also known as the dominant symptomatic side, usually presents more severe motor symptoms earlier and more intensely than the opposite side, even after the disease progresses to affect both sides of the body.[10]. This asymmetry is due to a greater loss of dopaminergic neurons in one hemisphere, with the contralateral side of the body showing more pronounced motor dysfunction [11]. While the disease eventually progresses to involve both sides of the body, the motor asymmetry remains a key clinical feature even in later stages [12]. This asymmetry distinguishes PD from some atypical Parkinsonian syndromes and neurodegenerative disorders with intracellular deposition of amyloidogenic proteins (such as multiple system atrophy, progressive supranuclear palsy and Lewy body dementia), reflecting the pathophysiology of PD [10].

1.2.2 Dopamine Lateralization

The asymmetry of symptoms is biologically explained by the lateralized loss of dopamine. However, this hemispheric difference seems to affect not only motor symptoms but also appears to play a role in non-motor aspects of PD, including cognitive impairments, pain, and fatigue. [13]. Dopamine lateralization in the brain may provide insights into the potential role of asymmetry as a prognostic marker for disease severity and the likelihood of cognitive decline [14]. In contrast, studies examining dopaminergic function in healthy individuals (HC) indicate that dopamine lateralization is not as pronounced as in PD. Although some studies show a slight preference for dopaminergic activity in one hemisphere, this does not seem to have a significant or clinically relevant

impact on motor or cognitive function in healthy populations [15] [16]. This difference highlights the importance of lateralized dopamine loss in PD and its role in driving the disease's motor and cognitive symptoms. Even though dopamine loss is always bilateral, and asymmetries are thought to become less noticeable over the course of the illness, the lateralization of dopamine loss in Parkinson's disease is informative as it indicates the degree of dysfunction in the basal ganglia and related cortical areas, creating a direct link between the biology of PD to its clinical manifestations [10]. A deeper understanding of dopamine lateralization in PD holds significant potential for advancing the knowledge on this disorder. By gaining insights into how dopaminergic asymmetry contributes to the onset and progression of PD symptoms, it could be possible to better refine diagnostic criteria and develop targeted treatment approaches. Improved knowledge in this area may also help to differentiate between subtypes of PD, allowing for more personalized therapeutic interventions. Ultimately, unraveling the complexities of dopamine lateralization could lead to enhanced prognostic tools and improved clinical outcomes for patients, contributing to a broader understanding of neurodegenerative processes.

1.3 DATSCAN an imaging biomarker

The striatum, a critical component of the basal ganglia, serves as the primary output region of the substantia nigra, with dopaminergic neurons from the SNpc projecting into its two key areas: the caudate nucleus and the putamen. While the caudate nucleus is involved not only in planning and executing movements but also in higher-order functions such as learning, memory, reward, motivation, and emotional responses [17], the putamen predominantly regulates motor control, speech articulation, and cognitive functions [18]. These regions are intimately connected with the dopaminergic system, which becomes dysregulated in Parkinson's disease (PD).

In clinical practice, traditional assessments of PD severity have relied heavily on examinations and standard rating scales. However, such assessments are complicated by variability in symptoms, patient-specific factors, and the influence of medications. This variability highlights the need for more objective markers to understand and monitor PD onset, severity, and progression. Dopamine transporters, which are proteins located in the membrane of dopaminergic neuron terminals, are responsible for regulating dopamine levels through active reuptake from the synaptic cleft. These transporters thus serve as a reliable marker for the integrity of nigrostriatal neurons and are crucial for assessing disease severity [19]. The relationship between the dopaminergic system and the striatum's key regions, especially in the context of motor and cognitive dysfunctions, underscores the importance of these objective biomarkers in the management of PD.

Initially Positron emission tomography (PET) has shown potential in imaging dopamine transporters in PD. In particular, cocaine-like ligands ^{11}C -nomifensine and ^{11}C -WIN 35,428 or β -CFT, ((-)-2- β -Carbomethoxy-3- β -(4-fluorophenyl)tropane) showed a dramatic loss of striatal dopamine transporters in patients with Parkinson's disease with high signal to noise ratios but ^{11}C CIT (carbomethoxy-3 β -(4-iodophenyl)nortropane) in PET imaging failed to significantly discrimi-

nate between small groups of patients with early PD and healthy controls [18]. Single photon emission computerized tomography (SPECT) is a less expensive and more available alternative. However, in SPECT, the gamma rays are emitted in all directions, unlike PET, where they are emitted in opposite directions. This difference results in slightly lower spatial resolution compared to PET. Prior SPECT studies of dopamine transporters with ^{123}I - β -CIT (Ioflupane) cocaine analogue, have reported a correlation with PD severity. But ^{123}I - β -CIT in the human striatum is characterized by a very slow kinetics, which is a serious drawback. Radioactivity in the striatum increases for 20 hours after injection of this radioligand, and stabilises thereafter up to 30 hours [20]. The stable level of radioactivity between 20 and 30 hours satisfies conditions of prolonged equilibrium. However, this indicates that an image acquisition should be performed on the day after the injection, which is not convenient for outpatient evaluation. Moreover, it is not optimal for counting statistics as the half life of [^{123}I] is about 13 hours. ^{123}I -FP-CIT is a more convenient alternative as a result of its faster kinetics which allow for scanning 3 to 6 hours after administration, and it has high specific affinity in binding to dopamine transporters in preclinical, volunteer, PD studies, matching observations with ^{123}I - β -CIT. ^{123}I -FP-CIT also has a better dopamine to 5-HT transporter selectivity than ^{123}I - β -CIT [18]. ^{123}I -FP-CIT SPECT is commonly called DaTSCAN (dopamine transporter single-photon emission computed tomography) because it selectively binds to dopamine transporters in the brain.

The radiotracer is injected into the bloodstream, and a special camera called a gamma camera is used to detect the radioactive emissions produced by the tracer. By measuring the uptake of the radiotracer in specific regions of the brain, particularly the striatum, DATSCAN can provide valuable information about the density and functioning of dopamine transporters as shown in the [Fig. 1.1] [21].

The quantitative measure used to assess the density of dopamine transporters in the striatum of the brain is the specific binding ratio (SBR). The SBR is calculated by comparing the activity in the region of

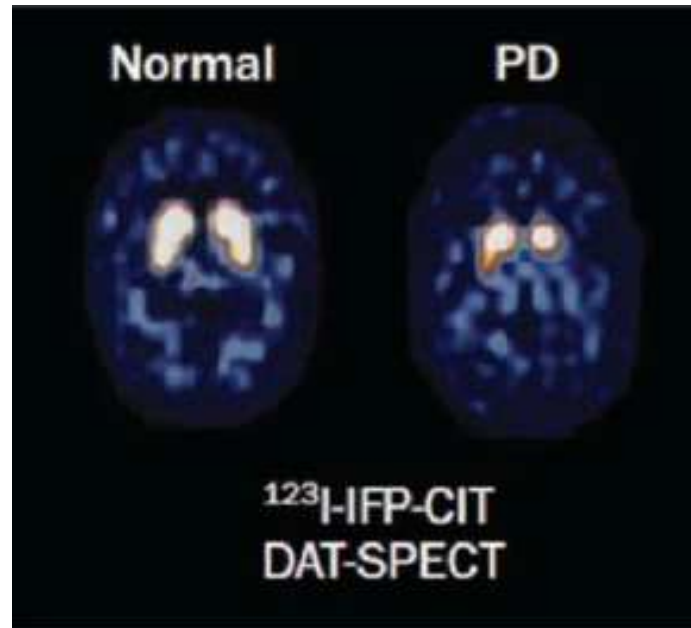


Figure 1.1: In PD patients, SPECT studies reveal a reduction DAT availability in the Striatal region when compared to healthy controls. SPECT imaging provides valuable insights into the molecular changes associated with PD, showcasing lower levels of DAT, which is indicative of dopaminergic dysfunction in the disease [21]

interest (usually the striatum: Putamen or Caudate) to a reference region (typically the occipital cortex), where there are few or no dopamine transporters. The SBR provides an index of the availability of dopamine transporters in the striatum and is calculated using the following formula:

$$\text{SBR} = \frac{\text{Striatal binding} - \text{Non specific binding}}{\text{Non specific binding}}$$

The result is a dimensionless ratio. In DatTSCAN imaging studies, the average activity is typically measured in standardized uptake value (SUV) or counts per voxel.

A higher SBR indicates greater binding of the radiotracer to dopamine transporters, suggesting higher DAT density. Conversely, a lower SBR indicates lower DAT density. It is now established that the dopamine transporter imaging provides an objective tool for the assessment of dopaminergic function of presynaptic terminals which is valuable also

for the differential diagnosis of parkinsonian disorders related to a striatal dopaminergic deficiency from movement disorders not related to a striatal dopaminergic deficiency. DaTSCAN can be used to confirm or exclude a diagnosis of dopamine deficient parkinsonism in cases where the diagnosis is unclear. It can also detect the dopaminergic dysfunction in presymptomatic subjects at risk for PD since the reduced radiotracer binding to DATs in striatum is already present in the prodromal stage of PD [24].

1.4 Background on Dopamine Asymmetry in Parkinson's Disease

Only three studies have thoroughly examined dopamine lateralization in Parkinson's disease patients, using DATSCAN. These studies aimed to classify patients into right- and left-dominant lateralized groups in a specific and distinct manner. However, the choice of cutoffs was purely empirical, while the classification relied entirely on mathematical criteria, lacking a clear biological rationale to guide the stratification process. (2015) In the article, "Ipsilateral deficits of dopaminergic neurotransmission in Parkinson's disease" of Valtteri Kaasinen, 434 PD patients from PPMI composed the dataset. 395 Right-handed, 39 left-handed and 12 ambidextrous. Ambidextrous patients and those with uncertain handedness, as well as patients who had taken medications within six months prior to imaging, were excluded. The Asymmetry Index was calculated from the [^{123} I]FP-CIT SPECT data using the following formula:

$$\text{Asymmetry Index} = \frac{\text{right putamen SBR} - \text{left putamen SBR}}{\text{right putamen SBR} + \text{left putamen SBR}}$$

The significant DAT asymmetry was defined by the range: $0.05 < \text{asymmetry index} < -0.05$. Patients were classified as 'Right' when the Asymmetry Index was > 0.05 otherwise 'Left' it was < -0.05 . The study investigated the prevalence of patients with "wrong-sided" lesions, that is, patients with symptoms on the side ipsilateral to the predominant dopaminergic deficit.

When patients with any asymmetry were included in the analysis, the prevalence of ipsilateral deficits was 15.4% ($n = 65/423$). Right-handed PD patients had predominantly right-sided motor symptoms and left-sided dopamine defects, whereas the effect was opposite in left-handed patients. The findings suggest that the dopaminergic defects and the side of the predominant motor symptoms in PD correspond, directed by brain lateralization and not in a randomized way. But, as Kaasinen

states: "The traditional pathogenetic model of nigral degeneration causing primarily contralateral motor symptoms may be inadequate in many patients." [23]

(2021) Following Kaasinen's asymmetry index, Fiorenzato E. et al., in the paper "Asymmetric Dopamine Transporter Loss Affects Cognitive and Motor Progression in Parkinson's Disease" investigate, the relevance of dopamine transporter asymmetry on cognitive and motor manifestations at onset and at 4-year progression in drug-naïve PD. The goal was to search if right or left asymmetry differently affects cognitive and motor progression. 435 untreated de novo PD with [^{123} I] FP-CIT SPECT at screening visit and 238 HC from the PPMI took part in the study. Right-handed only were selected. [24] Assessed the dominant side of the symptoms, 16 PD with motor symptoms on the side ipsilateral side of the putamen deficit were excluded. HC with MoCA < 26 and normal DAT-SPECT binding were excluded from the study. "The asymmetry index was computed according to the formula described elsewhere, and we considered only those values above 20%". As Kaasinen, Fiorenzato et al. divided the patients by the same asymmetry index while applying a more 'conservative' criteria: 0.1 instead of 0.05 (baseline asymmetry greater than 20%). As a matter of fact they state: "We applied a more conservative criteria compared with previous evidence to ensure clear-cut asymmetry". For the results of the study PD-left group showed worse performance on the Symbol Digit Modality Test (SDMT), an attention and processing-speed test, and lower cerebrospinal fluid β -amyloid levels than the PD-right group. These differences were maintained at follow-up, declining over time in both groups. By contrast, the PD-right group showed greater motor impairment at baseline, which increased over 4 years. Striatal DAT binding decreased over time in both groups, but the PD-right group showed a steeper decline, particularly during the first 2-year follow up. Putaminal asymmetry assessed at baseline was maintained over time [13].

(2022) Moreover, in the paper: "Gastrointestinal Symptoms and Dopamine Transporter Asymmetry in Early Parkinson's Disease" Murtomäki KMert-

salmi TJaakkola E et al. had 90 PD participants that were assessed with ¹²³I-FP-CIT, exclusion/inclusion criteria non available. Mean putamen DAT binding was calculated for both sides as mean putamen = (anterior putamen SBR + posterior putamen SBR)/2. Mean putamen asymmetry index (AI) in DAT uptake was then calculated as :

$$AI = \frac{\text{putamen highest} - \text{putamen lowest}}{\text{putamen highest} + \text{putamen lowest}}$$

The cut-off selected to determine a significantly asymmetric reduction in DAT binding was AI > 0.05.

The terms 'highest' and 'lowest' putamen values are not explicitly defined by the researchers, but it can be reasonably inferred that they refer to the hemisphere with the higher or lower SBR signal, respectively. This implies that 'putamen highest' refers to the hemisphere with greater dopamine transporter binding, while 'putamen lowest' refers to the side where binding is reduced. This reasoning helps explain why the cut-off for asymmetry is AI > 0.05, as it ensures that the asymmetry index remains positive.

Two groups were obtained: Asymmetric (N = 72) Symmetric (N = 18). The aim of this study was to elucidate the association between nigrostriatal DAT binding asymmetry and gastrointestinal symptoms (GISs) in PD. The study initially hypothesized that more symmetrical binding would be associated with increased GISs. However, the results revealed a different outcome, showing no significant association between symmetrical binding and GISs. Instead, their results suggest that not asymmetry per se but rather left-predominant defect is associated with reported GISs in PD. When compared to patients with symmetric or right predominant reduction in mean putamen DAT binding, FGIDs (in particular IBS, irritable bowel syndrome) were significantly more common and Wexner constipation scores higher in patients with left-predominant reduction [25].

Historically the Asymmetry issue in Parkinson's Disease has tradition-

ally been examined from the motor symptoms point of view. However, the key advantage of using DaTSCAN data lies in its ability to provide an objective, accurate, and quantitative measure, which offers a more reliable discriminant compared to the subjective motor symptom questionnaires.

1.5 Aim of the study

The aim of this study was to investigate the diagnostic and prognostic value of dopamine laterality in PD. By using a normative model of dopamine laterality based on healthy controls, this study aims to overcome the limitations of previous research based instead on arbitrary cut-off for definition of dopamine extreme lateralization.

Earlier studies lacked a logical and consistent method for classifying or defining significant lateralization, focusing solely on numerical asymmetries rather than incorporating a clear clinical or biological context. This absence of a uniform method has led to inconsistent findings and reduced comparability across studies, limiting our understanding of the true role of dopaminergic asymmetry in Parkinson's disease.

The novelty of this research is to have identified with objective criteria, a category of PD subjects that based on the asymmetry of dopamine, has a clinical outcome completely different from the others.

Our investigation of dopaminergic lateralization has not only been assessed in terms of direction, whether it is right- or left-sided, but also in its magnitude, distinguishing between "Extreme Lateralized" and "Normal Lateralized" individuals. This dual focus on both direction and magnitude allows for a deeper understanding of how lateralization manifests in Parkinson's disease, providing additional layers of insight beyond the traditional methods. This comprehensive approach will enhance the reliability and clarity of findings in the field, contributing to a more accurate understanding of the disease's progression and characteristics. Moving beyond the empirical classification methods currently in use, this study will provide a new framework for assessing dopaminergic asymmetry, refining diagnostic criteria, and potentially improving clinical outcomes for patients with Parkinson's disease, serving as a potential target for personalized rehabilitation strategies or therapeutic interventions in the future.

Chapter 2

Methods

2.1 PPMI

PPMI is a collaborative effort of Parkinson's disease researchers with expertise in biomarker development, PD clinical study design and implementation, bioinformatics, statistics, and data management. The PPMI is a public-private partnership of academic researchers, The Michael J. Fox Foundation for Parkinson's Research (MJFF), and pharmaceutical and biotech industry partners. The overall goal of PPMI is to investigate novel methods to establish longitudinal PD cohorts to examine clinical, imaging, genetic, and biospecimen PD progression markers. Which individually or in combination will rapidly demonstrate interval change in PD patients in comparison to Healthy Controls or in subsets of PD patients defined by baseline assessments, genetic mutations, progression mile-stones, and/or rate of clinical, imaging, or biospecimen change [26]. PPMI has established standardized protocols for acquisition, transfer, and analysis of clinical, imaging, genetic, and biospecimen data that can be used by the PD research community. Importantly, PPMI is committed to data and biospecimen sharing. PPMI data are available to the research community on the PPMI website as it is collected. As of December 2017, there are more than 1.5 million downloads of data, and more than 100 request applications for PPMI biospecimens reviewed by the PPMI Biospecimen Review Committee. The study is made possible with the partnership of nearly 50 clinical sites in 12 countries and

4 continents and with support from more than 40 public, private and philanthropic investors [27].

Thanks to PPMI, this and thousands of independent researches are possible.

2.2 Dataset

Data used in the preparation of this thesis were obtained from the PPMI database (www.ppmi-info.org/data). For up-to-date information on the study, visit www.ppmi-info.org.ClinicalTrials.gov identifier: NCT0114102.

The patients selected for this study were initially screened based on their availability of a baseline or screening DATSCAN examination, ensuring that dopamine deficiency was assessed during their first visits as conducted by the PPMI doctors. This yielded an initial pool of 1556 participants. Further inclusion and exclusion criteria were applied to refine the dataset:

- Only patients with idiopathic Parkinson's disease (PD), or those first diagnosed with Parkinson's syndrome without additional illnesses or complications, were retained.
- Individuals with other neurological conditions were excluded to avoid confounding effects.
- Only patients with 'good' or 'adequate' quality DATSCAN data were included, based on the quality assessments provided. The 'DATSCAN_QUALITY_RATING' is a variable in the dataset that ranges from 1 to 3, where 1 = lower quality, 2 = adequate, and 3 = good. This rating reflects the overall image quality as determined by the 'Image Quality Control', as described in the PPMI Data Dictionary. Although the specific criteria for this assessment are not elaborated upon in detail, the use of this variable ensures that only participants with sufficiently reliable imaging data are included in the analysis.
- To minimize variability related to brain lateralization, only right-handed participants were selected.

The exclusion of left-handed participants was based on the fact that left-handers tend to have more varied brain lateralization patterns. Some

left-handed individuals show right-hemisphere dominance, while others are similar to right-handers with left-hemisphere dominance. In many laterality studies, it is often assumed that the lower average asymmetry in left-handers is due to a small group with reversed lateralization, while most are lateralized like right-handers. However, it's just as likely that many left-handers have typical lateralization, but the degree of their asymmetry is less pronounced than that of right-handers. [28]. Including left-handed individuals could, therefore, introduce variability in the study, complicating the interpretation of the relationship between dopaminergic asymmetry and Parkinson's disease. By focusing on right-handed participants, the study aims to create a more homogeneous dataset, ensuring that lateralization patterns are more consistent across individuals and reducing variability related to handedness.

After applying these criteria, the final dataset comprised 1029 participants, including 191 healthy controls and 847 Parkinson's disease patients.

2.3 Analysis

All statistical analyses were performed using R (version 4.4.1) and JASP (version 0.18.3.0). R was utilized for data preprocessing, manipulation, and advanced statistical tests, while JASP was employed for conducting and visualizing traditional statistical analyses such as univariate and multivariate analysis.

2.3.1 Substantial Binding Rate comparison

For the first analysis, we examined the levels of Substantial Binding Rate of DAT binding in the striatal region, focusing on the Putamen and Caudate areas. The DATSCAN data from the PPMI include two values for the Putamen: one for the Putamen and one for the Anterior Putamen region. In our analysis, we used the Putamen value, as the Anterior Putamen is considered a subset of the former.

2.3.2 Laterality Index Analysis

The Laterality Index (LI) is a key metric used in this study to quantify the asymmetry of dopaminergic function in the brain. It serves as an indicator of how dopaminergic activity is distributed between the left and right hemispheres, allowing us to identify which side exhibits more or less dopaminergic function. As we already saw, this index was first introduced by Valtteri Kaasinen in “Ipsilateral deficits of dopaminergic neurotransmission in Parkinson’s disease” and later employed by Eleonora Fiorenzato et al. in “Asymmetric Dopamine Transporter Loss Affects Cognitive and Motor Progression in Parkinson’s Disease” [24] [13]. The calculation is simple yet effective:

$$LI = \frac{SBR \text{ Right} - SBR \text{ Left}}{SBR \text{ Right} + SBR \text{ Left}}$$

The formula reflects the ratio of dopaminergic activity between the

right and left hemispheres, as per the referenced studies, we define the laterality as "right minus left," meaning that positive LI values correspond to greater dopaminergic function on the right hemisphere, whereas negative LI values indicate dominance on the left. Moreover, a lower LI reflects a more symmetrical dopaminergic function.

For each participant, Laterality Index values were computed for both the Putamen and Caudate regions. Before comparing the LI distributions across the different groups, we conducted a correlation analysis between the LI and demographic factors.

Next, we compared the LI distributions between the groups and assessed the discriminative power of the Putamen and Caudate LI to classify PD patients from controls, using a Receiver Operating Characteristic (ROC) curve. These results were then compared to the discriminative power of the SBR values themselves, offering insights into the relative effectiveness of the two metrics.

Lastly, a correlation analysis was conducted to explore potential relationships between the absolute values of the LI in both the Putamen and Caudate, and various demographic and clinical variables within the PD cohort. This analysis aimed to assess how these factors may be associated with patterns of lateralization in the disease.

2.4 Relationship between dopamine lateralization and clinical symptoms

A normal model of lateralization was developed from the HC group to serve as a reference for identifying deviations in the PD cohort. This model established cut-off values for lateralization, with PD LI values falling outside the maximum and minimum range of the HC group's LI considered abnormal. Everything classified as 'normal' dopaminergic asymmetry remained within the boundaries of the HC LI distribution range. The analysis of lateralization focused on two key aspects: the magnitude and the direction of dopaminergic asymmetry. First, patients were stratified into two groups based on the absolute value of the HC's LI cut-offs: Normal Lateralized (NL) and Extreme Lateralized (EL). The analysis then went further by examining the direction of this lateralization, dividing the EL group into Left Extreme Lateralized and Right Extreme Lateralized, depending on which side showed greater lateralization. While this classification method might seem simple and straightforward, it is rooted in biological reasoning. The approach has the potential to reveal important insights into PD, by clearly distinguishing between normal and extreme lateralization patterns, both in magnitude and direction, this method could serve as a valuable tool for better understanding the role of dopaminergic asymmetry in disease development and patient stratification. Its simplicity makes it easy to implement, yet its biological basis ensures that the findings could be both reliable and meaningful for clinical practice and research. The two striatal regions under investigation were the Putamen and the Caudate. When comparing the lateralization indices of these regions across different cohorts, only the Putamen exhibited significant differences. The Caudate, on the other hand, did not show notable variability, and its strict cut-off values for extreme lateralization would have limited the number of patients classified as "Extreme Lateralized." This would reduce the impact of potential findings. Therefore, afterwards the study will focus exclusively on the Putamen as the region of interest within the stria-

tum. This decision aligns with previous research, which predominantly emphasizes the Putamen in the analysis of dopaminergic asymmetry, reinforcing the confidence in this decision.

In order to investigate the differences between the subgroups of PD, we compared the values of the most significant scores typically used to assess Parkinson's Disease progression:

- The Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) test, a self-report questionnaire which is divided in four parts: part I, II, III and IV. Each part has multiple points that are individually scored, using zero for normal or no problems, 1 for minimal problems, 2 for mild problems, 3 for moderate problems, and 4 for severe problems [29]. Part I of the MDS-UPDRS focuses on the Non-Motor Experiences of Daily Living and consists of two sections of questions. The section A is focused on cognitive, mood, and behavior symptoms, such as cognitive impairment, hallucinations, depression and anxious mood. The section B assesses other non-motor symptoms such as sleep disturbances, pain, constipation and urinary problems. The MDS-UPDRS Part II concerns the Motor Experiences of Daily Living and evaluates motor symptoms and their impact on daily activities. While the MDS-UPDRS Part III concerns the motor examination, which focuses on clinician-rated assessment of motor symptoms such as tremor, slowness and rigidity. Part IV is about Motor Complications. This score is related to the wearing-off condition. Which is a condition that develops later in the disease and causes the levodopa medication to stop working as it once did, creating motor fluctuations. Fortunately, this score is absent for all patients analysed, considering that we only have PD patients' scores from their initial visit [29].
- The Montreal Cognitive Assessment (MoCA) was assessed. The MoCA is a 10-minute cognitive functional screening tool developed by Nasreddine in 2004. This test is often used to assess

cognitive ability of PD patients [30].

- The Symbol Digit Modalities Test (SMDT) is a cognitive test, which evaluates elements like attention, psycho-motor speed, visive elaboration and working memory. The SMDT is fast, simple and an economical test to screen for cerebral dysfunction. The SMDT has demonstrated remarkable sensitivity in detecting not only the presence of brain damage, but also changes in cognitive functioning over time and in response to treatment [31].
- The Scales for Outcomes in Parkinson's Disease Autonomic (SCOPA-AUT) is a well-validated self-report questionnaire consisting of 23 items assessing autonomic dysfunction in individuals with PD. The SCOPA-AUT examines the frequency of gastrointestinal, urinary, cardiovascular, thermoregulatory, and pupillomotor symptoms [32]. Items 8–13 were summed to create a composite score for urinary-related problems, while items 5–7 were combined to form a score related to gastrointestinal issues, specifically concerning constipation and stool passage. These decisions and their rationale will be explained in more detail in the following chapters [32].
- The State-Trait Anxiety Inventory (STAI) is a self-report scale to measure the presence of current anxiety symptoms and the proneness to anxiety. Responses are measured on a 4-point Likert scale and higher scores indicate more frequent anxiety. The STAI-Y is split into two scales, Y1 and Y2, which respectively assess state anxiety (which consists of questions about the subject's feelings at the time of the assessment) and trait anxiety (which consists of questions about the subject's feelings on a regular basis) [33].
- The Geriatric Depression Scale-Short Form (GDS-SF), is a 15 item self-report measure of depression in older adults. Items assess the presence or absence of depressive symptoms within the past week. Higher scores indicate more severe depression. Both the GDS-SF

and STAI are recommended by the Movement Disorder Society for use with PD samples [34].

- Finally, the Epworth Sleepiness Scale (ESS) consists of a list of eight situations in which the tendency to become sleepy is rated on a scale from 0, indicating no chance of dozing, to 3, indicating a high chance of dozing. After completing the test, all the values are summed, resulting in a total score ranging from 0 to 24. This score helps estimate whether excessive sleepiness is present, potentially requiring medical attention. [35]

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2.4.1 Magnitude of the lateralization

In this section, the analysis focused on comparing the PD patients classified as Extreme Lateralized versus the Normal Lateralized patients. Initially, we assessed differences in the Putamen SBR DATSCAN values between these two groups to determine if lateralization was associated with variations in dopaminergic activity. Subsequently, a series of univariate analyses were conducted to evaluate potential differences across the clinical tests that were just presented. This approach allowed us to explore whether lateralization status had broader implications for motor and non motor function and cognitive performance. Moreover, a longitudinal analysis was performed using data from the 6th, 10th, and 13th visits, which correspond to 2, 4, and 6 years after the initial visit, respectively. This analysis aimed to observe how the disease evolves over time for both the EL and NL groups, providing insights into the progression of the condition across these two classifications.

2.4.2 Direction of the lateralization

In this section, the analysis focused on comparing the Extreme Lateralized groups, PD patients with Right Lateralized against those with Left Lateralized dopaminergic activity. The initial step, again involved assessing potential differences in the SBR DATSCAN values between

these two subgroups. Following this, a univariate analysis was performed to examine variations across the clinical tests. Additionally, a critical verification was conducted to determine whether the observed dopaminergic lateralization deficiency aligned with the lateralization of motor symptoms. The motor symptom lateralization was evaluated according to specific criteria [Tab.2.1] explained in the Kaasinen paper, ensuring that the analysis accounted for clinical manifestations of lateralization.

Variable	Explanation/equation
Tremor asymmetry index	$\frac{(\text{right} - \text{left side score})}{(\text{right} + \text{left side score})}$ Score of lateralized tremor items in MDS-UPDRS Part III was calculated separately for the left and right side (hand postural tremor + hand kinetic tremor + hand rest tremor + foot rest tremor)
Bradykinesia-rigidity asymmetry index	$\frac{(\text{right} - \text{left side score})}{(\text{right} + \text{left side score})}$ Score of lateralized bradykinesia or rigidity items in MDS-UPDRS Part III was calculated separately for the left and right side (rigidity in upper extremity + rigidity in lower extremity + finger tapping + hand movement + pronation/supination + toe tapping + leg agility)

Table 2.1: Explanations and equations of the investigated clinical factors [24].

Chapter 3

Results

Following the data preprocessing, demographic characteristics and key clinical variables of the two cohorts, HC and PD, were analyzed [Tab. 3.1]. This analysis served not only to compare the two groups but also to confirm established evidences, such as the PD cohort exhibiting worse clinical outcomes and having lower SBR levels.

The HC group consists of 191 participants, with a male-to-female ratio of 121:70. The average age at enrollment for this group is 61.67 years (SD = 12.14). A small proportion, 10 participants reported a family history of Parkinson's Disease, while 50 did not. The PD group is significantly larger, with 847 participants, 519 (the 61.3 %) of whom are male and 328 female. The average enrollment age for the PD group is 63.26 years (SD = 9.56). A substantial number of PD participants, 193 (more than the 45%) have a family history of the disease, compared to 232 without such a history. Despite the presence of numerous missing values, the chi-squared test revealed that the PD group had a significantly higher number of individuals with a family history of Parkinson's Disease, $\chi^2(1) = 17.85$, $p < .001$.

As expected, PD patients exhibit worse performances or more severe symptoms compared to the HC cohort in almost all clinical tests. However, no significant differences were found in the first part of the STAI test, which assesses state anxiety, nor in sleep problems. Interestingly, the second part of the STAI test, which measures trait anxiety (anxiety experienced on a regular basis), revealed that HC participants showed

Variable	HC	PD	Comparison
N° of participants	191	847	
Age [years]	61.67 ± 12.14	63.26 ± 9.56	ns
Gender (m/f)	121/70	519/328	ns
Any familiar with PD (y/n)	10/50	193/232	$\chi^2 = 17.85, p < .001^{***}$
Years of education [years]	16.21 ± 3.20	15.83 ± 3.42	ns
Height [cm]	172.19 ± 9.84	171.95 ± 9.90	ns
Weighth [kg]	79.92 ± 16.7	79.95 ± 17.35	ns
SBR Caudate Right	3.04 ± 0.60	2.00 ± 0.63	MW = 144528.5, $p < .001^{***}$
SBR Caudate Left	3.06 ± 0.59	1.99 ± 0.59	MW = 146561.5, $p < .001^{***}$
SBR mean Caudate	3.05 ± 0.57	1.99 ± 0.57	MW = 147580, $p < .001^{***}$
SBR Putamen Right	2.22 ± 0.55	0.88 ± 0.41	MW = 156824.5, $p < .001^{***}$
SBR Putamen Left	2.23 ± 0.54	0.84 ± 0.38	MW = 158234.5, $p < .001^{***}$
SBR mean Putamen	2.23 ± 0.53	0.86 ± 0.34	MW = 158729, $p < .001^{***}$
MDS-UPDRS part I	2.65 ± 2.38	4.86 ± 3.58	MW = 46497.5, $p < .001^{***}$
MDS-UPDRS part II	0.46 ± 1.00	6.33 ± 4.57	MW = 6609.5, $p < .001^{***}$
MDS-UPDRS part III	1.25 ± 1.94	21.87 ± 9.91	MW = 422, $p < .001^{***}$
MoCA	28.00 ± 1.51	26.73 ± 2.64	MW = 101945.5, $p < .001^{***}$
SDMT	47.88 ± 10.91	41.38 ± 10.53	MW = 96808, $p < .001^{***}$
Gastrointestinal related problems	0.42 ± 0.74	1.28 ± 1.53	MW = 48000, $p < .001^{***}$
Urine related problems	0.66 ± 0.97	2.21 ± 2.09	MW = 36384, $p < .001^{***}$
STAI_Y1	47.93 ± 4.10	47.52 ± 4.83	ns
STAI_Y2	46.71 ± 3.20	46.02 ± 4.24	MW = 80909, $p = 0.026^*$
Epworth Sleepiness Scale	5.35 ± 3.44	5.74 ± 3.78	ns
Geriatric Depression Scale	5.17 ± 1.25	5.46 ± 1.47	MW = 64768.5, $p = 0.011^*$
Disease Duration [years]		2.70 ± 3.10	

Table 3.1: Healthy controls and Parkinson's Disease patients demographics and clinical tests. Every variable is represented as (mean ± SD), with the exception of gender and family history of PD, which are categorical variables. The Mann-Whitney U test (MW) was used for continuous variables, and the chi-squared test (χ^2) for categorical variables. Significance levels are indicated as follows: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

higher anxiety levels than PD patients.

Due to the non-normality of the distributions, the Mann-Whitney U test was employed for the univariate analysis. It is also important to note that these patients are likely in the early stages of the disease.

3.1 Substantial Binding Rate comparison

The Shapiro-Wilk test revealed that the distribution of SBR values was not normal in at least one of the two cohorts. Consequently, the Mann-Whitney U test was used for all comparisons. Analyzing the Putamen, the tests revealed that the Right SBR of the HC group was significantly higher (mean = $2.22 \pm \text{SD} = 0.55$) compared to the PD group (mean = $0.88 \pm \text{SD} = 0.41$) $F(1036) = 156824.5$, $p < 0.001$. A similar pattern was observed for the Left SBR Putamen, where the HC group had an SBR of (mean = $2.23 \pm \text{SD} = 0.54$) and the PD group (mean = $0.84 \pm \text{SD} = 0.38$) $F(1036) = 146561.5$, $p < 0.001$. The box-plot in [Fig. 3.1] visually demonstrates this, showing the Left and Right distributions side by side. The difference between the Left and Right Putamen is negligible.

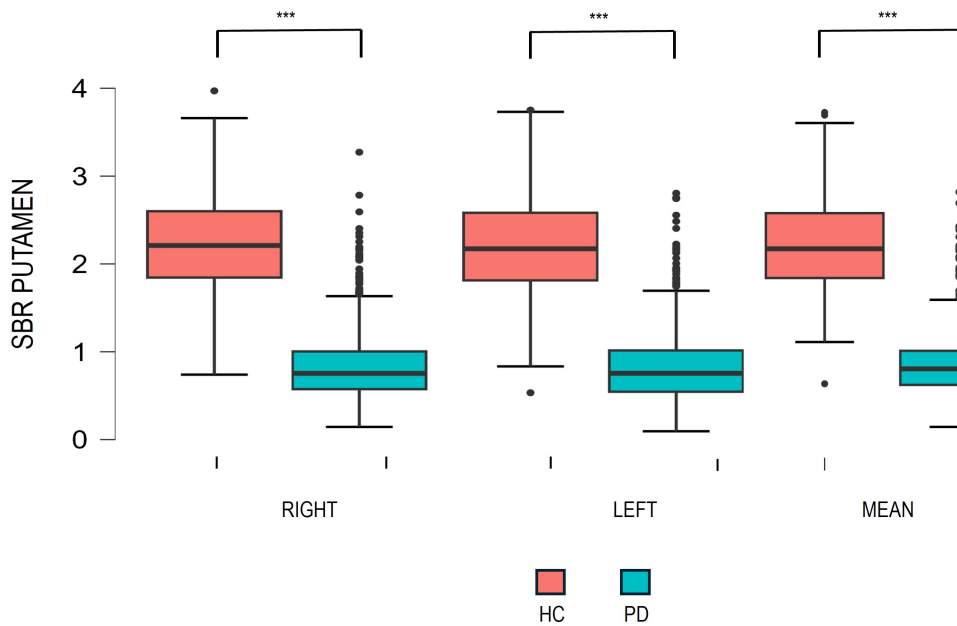


Figure 3.1: Boxplots representing the SBR signal rate of the Right and Left Putamen region between the cohorts.

A similar analysis was conducted for the Caudate region, where SBR values were slightly higher than those in the Putamen but followed the same pattern. The SBR of the right Caudate was significantly higher in the HC group (mean = $3.04 \pm \text{SD} = 0.60$), compared to the PD group

(mean = $2.00 \pm \text{SD} = 0.63$). The Mann-Whitney U test confirmed these differences $F(1036) = 144528.5$, $p < 0.001$.

The situation remained consistent across hemispheres. For the left Caudate, the SBR values were (mean = $3.06 \pm \text{SD} = 0.59$) in the HC group and (mean = $1.99 \pm \text{SD} = 0.59$) in the PD group, with statistical confirmation via the Mann-Whitney U test $F(1036) = 146561.5$, $p < 0.001$. These differences are visually evident in [Fig. 3.2].

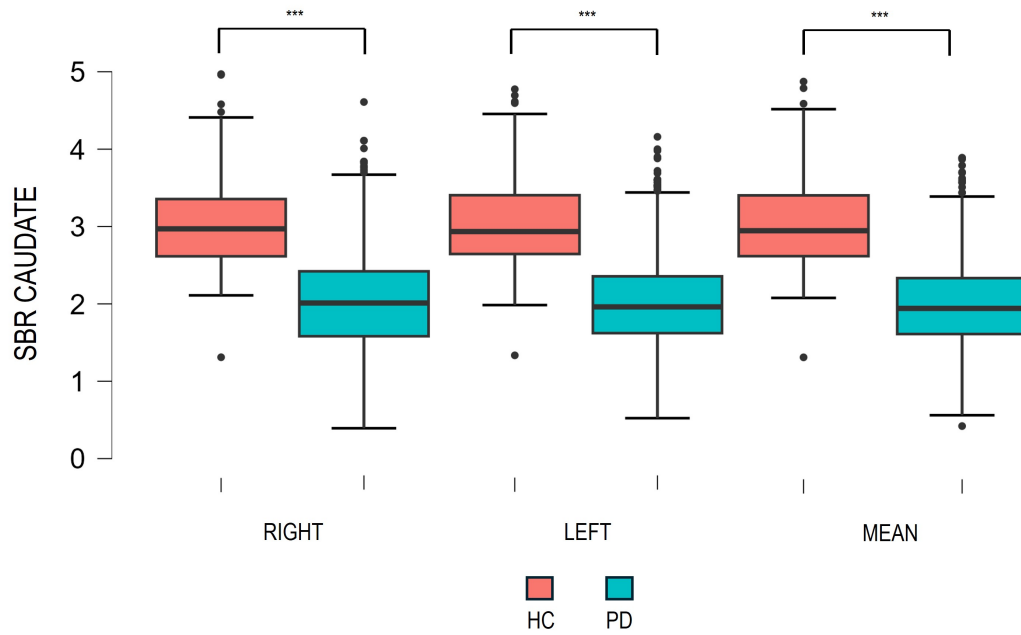


Figure 3.2: Boxplots representing the SBR signal rate of the Right and Left Caudate region between the cohorts.

The analysis of SBR values in both the Putamen and Caudate regions confirmed previously established findings. Dopamine levels in the striatum were significantly lower in PD patients compared to the HC group.

3.2 Laterality Index Analysis

After calculating the Laterality Indexes for both the Putamen and Caudate, initial visual inspection suggested that the variance within the PD group was notably larger than that of the HC group [Fig. 3.3].

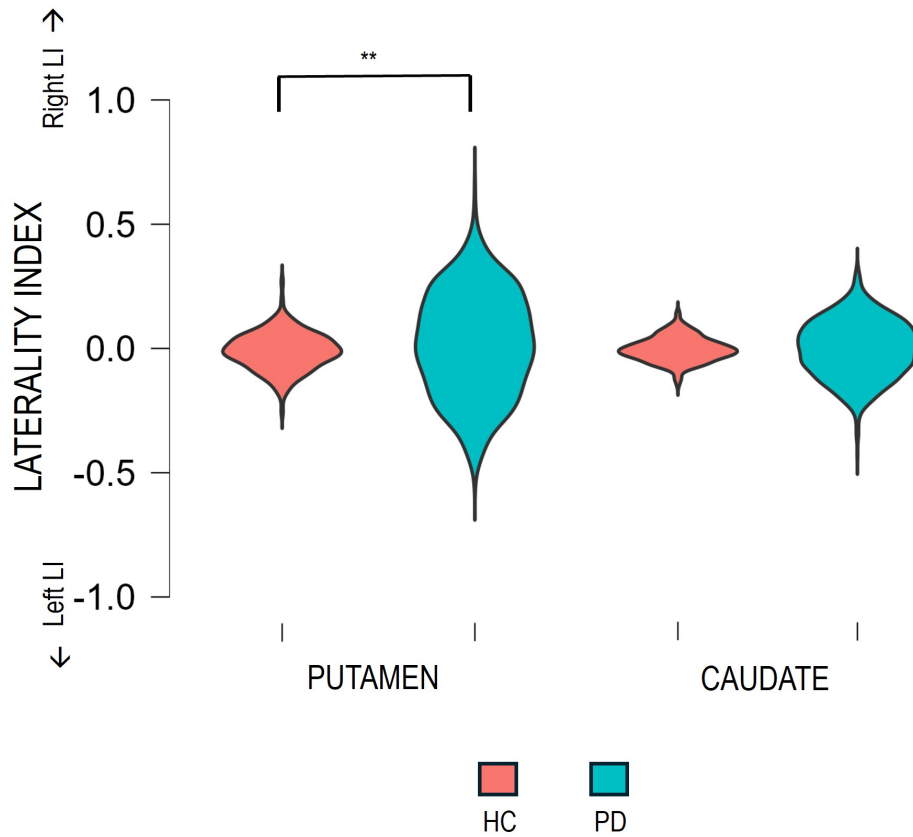


Figure 3.3: Violin plots representing the Laterality Index of Caudate between cohorts, the only significant difference present is between HC and PD in Putamen

This observation was confirmed through Levene's test, which indicated significant inequality of variance in the LI distributions for both the Putamen and Caudate regions between the two cohorts. Specifically, for the Putamen, Levene's test yielded $F(1,1036)=179.72$, $p < 0.001$, and for the Caudate, $F(1,1036)=126.8$, $p < 0.001$.

Given the violation of the assumption of homogeneity of variances, an independent t-test with Welch's correction was applied, as this test adjusts for unequal variances while comparing the means between groups.

For the Putamen, the Welch-corrected t-test revealed a significant difference between the PD cohort (mean = $0.02 \pm \text{SD} = 0.21$) and the HC cohort (mean = $-0.005 \pm \text{SD} = 0.07$), $F(855.04) = -2.819$, $p = 0.005$, indicating a statistically significant divergence in their LI distributions.

In contrast, no significant differences were found in the Caudate's Laterality Index between the two cohorts. The mean LI for the PD group was (mean = $0.0004 \pm \text{SD} = 0.114$), while for the HC group, it was (mean = $-0.004 \pm \text{SD} = 0.049$), and the Welch's t-test reported $F(696.83) = -0.78$, $p = 0.436$.

Thanks to the Welch correction we saw that the LI group means for the Putamen show significant differences between cohorts, while no such difference is observed for the Caudate. However, when we assessed distribution differences, again using the Mann-Whitney U test (rank-based test that examines if one group tends to have higher values than the other), no significant differences were found. Moreover, a visual comparison of the distributions reveals substantial overlap between the PD and HC groups. These evidences explains the limited discriminative power of the LI between the cohorts. This was confirmed by a quick assessment using ROC curves [Fig. 3.4].

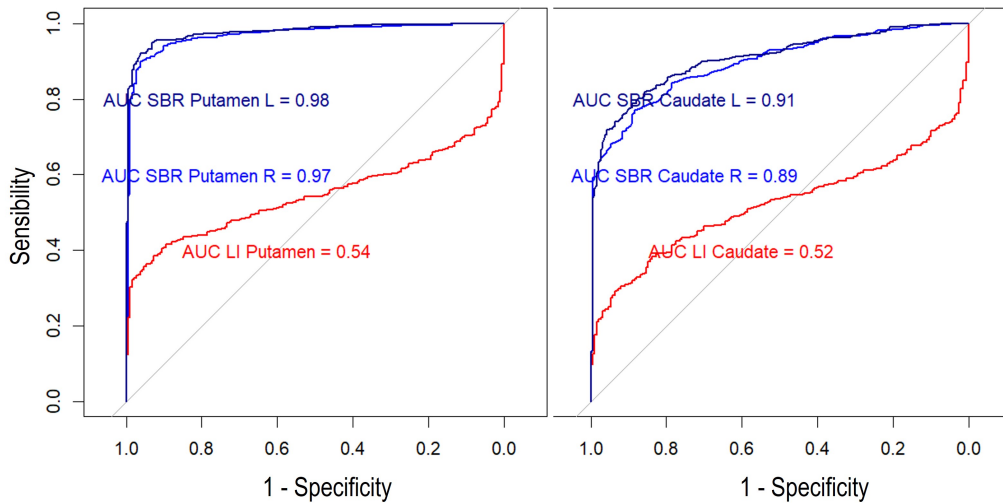


Figure 3.4: ROC curves comparing the Area Under the Curve (AUC) of SBR and LI. The AUC for the LI is close to the chance level of discrimination (0.5), indicating a random or near-random discriminative capability.

The Laterality Index has minimal discriminative power, meaning that

with a random LI value, it is difficult to determine whether it belongs to the PD or HC cohort. In contrast, the SBR values for both the Putamen and Caudate demonstrate much better discriminative power. For instance, ROC curve parameters such as Sensitivity and Specificity, which respectively measure the ability to correctly identify PD patients and correctly exclude HC participants, highlight this. The SBR in the Left Putamen achieves a Sensitivity of 0.92, while the Right Putamen reaches 0.9, compared to a mere 0.55 for the LI. Similarly, the Specificity for the Left and Right Putamen's SBR is 0.96, compared to 0.55 for the Putamen LI.

These results suggest that the LI is not suitable as a diagnostic biomarker. However, the most notable characteristic of the PD group's LI are the extended distribution's tails. As we will explore in the following sections, the Laterality Index potential relevance as a prognostic biomarker in the stratification process cannot be dismissed.

The results of the correlation analysis between the absolute values of the Putamen and Caudate LI with demographics and clinical variables are summarized below [Tab. 3.2]. Given that normality assumptions were violated, Spearman's rank correlation was employed to assess the relationships. Before delving into the specific findings, it's important to emphasize that all significant correlations were weak, with Spearman's absolute rho values remaining below 0.3, indicating that the relationships identified were present but not strong enough to be considered moderate or robust.

A significant negative correlation between the absolute value of the Putamen LI and age indicates that as the laterality increases, the age decreases. This might suggest that younger patients tend to have more pronounced asymmetry in dopamine activity. Moreover, the negative correlations with the MDS-UPDRS I and II scores and Autonomic Functions (GDI and Urine problems) implies that higher laterality is associated with less severe symptoms in these domains. Positive significant correlations of the LI of Putamen with the SBR values of the Putamen and Caudate, except for the SBR of the Left Putamen, suggests that

higher laterality is related to increased SBR values, indicating higher dopamine transporter activity. Additionally, a positive correlation between Putamen LI and SDMT cognitive test scores implies that greater lateralization is linked to better cognitive performance.

While higher laterality in the Putamen is linked to higher SBR, the Caudate shows the opposite pattern. That is, higher laterality in the Caudate is associated with lower SBR values across all regions.

These patterns suggest complex relationships between laterality, dopamine activity, and disease symptoms. This divergence might offer insights into the underlying pathophysiology of Parkinson's disease and the functional role of dopamine lateralization.

Variables	Correlation Putamen LI absolute value	Correlation Caudate LI absolute value
Putamen LI absolute value		$\rho = -0.26, p < 0.001^{***}$
Age [years]	$\rho = -0.16, p < 0.001^{***}$	$\rho = -0.13, p < 0.001^{***}$
Gender (m/f)	ns	ns
Any familiar with PD (y/n)	ns	ns
Years of education [years]	ns	ns
Height [cm]	ns	Ns
Weighth [kg]	ns	Ns
SBR Caudate Right	$\rho = 0.16, p < 0.001^{***}$	$\rho = -0.13, p < 0.001^{***}$
SBR Caudate Left	$\rho = 0.07, p = 0.048^*$	$\rho = -0.15, p < 0.001^{***}$
SBR mean Caudate	$\rho = 0.11, p = 0.002^{**}$	$\rho = -0.14, p < 0.001^{***}$
SBR Putamen Right	$\rho = 0.13, p < 0.001^{***}$	ns
SBR Putamen Left	ns	$\rho = -0.12, p < 0.001^{***}$
SBR mean Putamen	$\rho = 0.08, p = 0.026^*$	$\rho = -0.08, p = 0.02^*$
MDS-UPDRS part I	$\rho = -0.11, p = 0.002^{**}$	ns
MDS-UPDRS part II	$\rho = -0.11, p = 0.002^{**}$	ns
MDS-UPDRS part III	ns	ns
MoCA	ns	ns
SDMT	$\rho = 0.12, p < 0.001^{***}$	ns
Gastrointestinal related problems	$\rho = -0.13, p < 0.001^{***}$	ns
Urine related problems	$\rho = -0.13, p < 0.001^{***}$	ns
STAI Y1	ns	ns
STAI Y2	ns	ns
Epworth Sleepines Scale	ns	ns
Geriatric Depression Scale	ns	ns
Disease Duration [years]	ns	ns

Table 3.2: Parkinson's Disease patients demographics and clinical tests correlated with the absolute value of the LI of Putamen and Caudate. Every variable is represented with the respective rho and pvalue of the Pearson's correlation. Significance levels are indicated as follows: $^*p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

3.3 Relationship between dopamine lateralization and clinical symptoms

The previous analysis revealed that the PD cohort's laterality might reach both greater and lower values than the other group (i.e., higher left and higher right lateralization). Given the greater variance observed in the PD cohort's Laterality Index compared to the HC group, we propose introducing the concept of 'Normal Laterality'. The HC distribution can serve as a reference to establish cut-off points that define the expected range of normal lateralization. By doing so, we create boundaries for classifying LI values within the PD group, facilitating a logical stratification based on deviations from these established norms.

By establishing these cut-offs, it will be possible to determine what is above "Normality" and determine if lateralization over these values classifies as "Extreme." Consequently, the minimum and maximum values of the distribution, which correspond to the higher 'normal' Left Lateralization value and the higher 'normal' Right Lateralization value of the HC's LI, respectively, of -0.247 and 0.273, have been chosen as the cut-offs [Fig. 3.5]. Although the HC group played a crucial role in the development of this model, the following analysis focuses solely on the PD's group laterality.

In the next step, the PD group was classified by examining dopamine laterality. First, the absolute values of the Putamen LI were used to assess the magnitude of lateralization, classifying any value above 0.273 as "Extreme" Lateralization (EL). The second classification, based on the direction of lateralization, divided this extreme lateralization into two subgroups: Extreme Left Lateralization (EL_{Left}) for values below -0.247, and Extreme Right Lateralization (EL_{Right}) for values above 0.273.

Based on this classification, nearly 26% of PD patients fall into the EL category. In the classification based on the magnitude of lateralization, the distribution of participants is 675 in the NL group and 172 in the EL group. For the classification based on the direction of lateralization, the

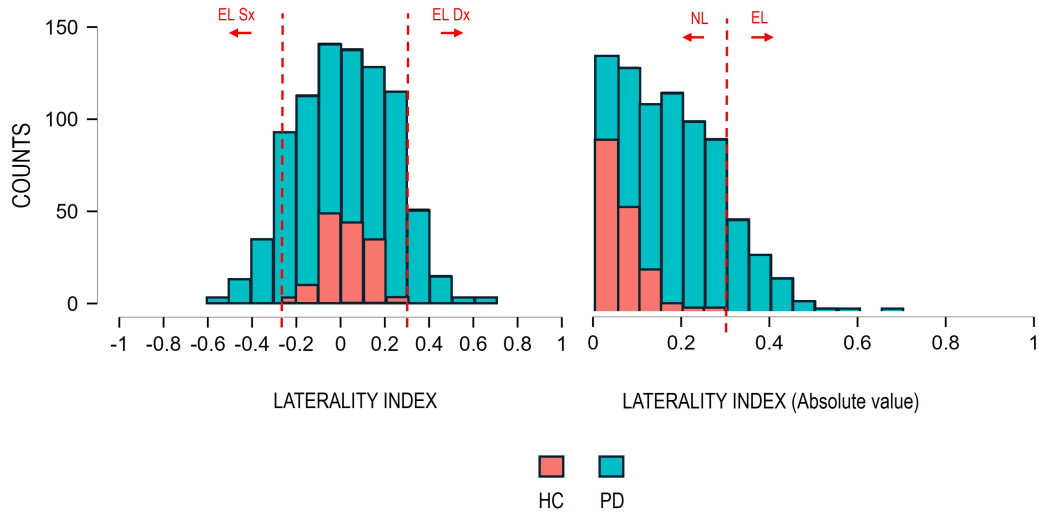


Figure 3.5: Histograms showing the distribution of the LI for the Putamen. Left Image: The normal LI distribution comparison, illustrating the direction of lateralization (right or left). Right Image: The absolute value of the LI, from which the magnitude of lateralization is examined. This histogram aids in distinguishing between "Extreme Laterality" (EL) and "Normal Laterality" (NL), based on the magnitude of LI, regardless of direction.

EL group is subdivided in 104 as EL_{Right} and 91 as EL_{Left}, 652 participants are categorized as NL.

3.3.1 Extreme and Normal Lateralized comparison

In this section, we analyze the Magnitude of lateralization using an univariate analysis, where the Mann-Whitney U test was applied due to the non-normal distribution of variables. As presented in [Tab. 3.3] we compare the demographics, SBRs, and clinical features of the EL and NL groups. Among the demographics, the only difference is the age at enrollment. The NL group is significantly older (mean = $63.98 \pm \text{SD} = 9.26$) compared to the EL group (mean = $60.50 \pm \text{SD} = 10.21$), with the Mann-Whitney test showing a significant result: $F(810) = 42950.5, p < 0.001$.

The next course of action was, investigate the SBR data on the EL vs NL.

In the Putamen, the right SBR values were significantly higher in the EL group (mean = $1.00 \pm \text{SD} = 0.47$) compared to the NL group

Variable	NL	EL	Comparison
N° of participants	675	172	
Age [years]	63.98 ± 9.26	60.50 ± 10.21	MW = 42950.5, $p < .001^{***}$
Gender (m/f)	409/266	110/62	ns
Any familiar with PD (y/n)	157/182	36/50	ns
Years of education [years]	15.71 ± 3.51	16.27 ± 3.02	ns
Height [cm]	171.61 ± 9.86	173.26 ± 9.97	ns
Weight [kg]	79.79 ± 17.48	80.56 ± 16.87	ns
SBR mean Caudate	1.97 ± 0.57	2.10 ± 0.55	MW = 67093.5, $p = 0.002^{**}$
SBR Putamen Right	0.85 ± 0.38	1.00 ± 0.47	MW = 68939, $p < .001^{***}$
SBR Putamen Left	0.84 ± 0.37	0.86 ± 0.43	ns
SBR mean Putamen	0.85 ± 0.35	0.93 ± 0.31	MW = 70111, $p < .001^{***}$
MDS-UPDRS part I	4.92 ± 3.46	4.61 ± 4.01	MW = 52295.5, $p = 0.046^*$
MDS-UPDRS part II	6.41 ± 4.58	5.99 ± 4.55	ns
MDS-UPDRS part III	22.03 ± 9.99	21.24 ± 9.56	ns
MoCA	26.65 ± 2.69	27.06 ± 2.42	ns
SDMT	40.75 ± 10.65	43.84 ± 9.66	MW = 62923.5, $p = 0.001^{**}$
Gastrointestinal related problems	1.35 ± 1.55	1.02 ± 1.46	MW = 47520, $p = 0.006^{**}$
Urine related problems	2.31 ± 2.10	1.83 ± 2.00	MW = 46963.5, $p = 0.002^{**}$
STAI_Y1	47.59 ± 4.82	47.25 ± 4.86	ns
STAI_Y2	45.94 ± 4.28	46.33 ± 4.11	ns
Epworth Sleepiness Scale	5.68 ± 3.81	5.97 ± 3.66	ns
Geriatric Depression Scale	5.44 ± 1.48	5.54 ± 1.43	ns
Disease Duration [years]	2.67 ± 3.19	2.66 ± 2.91	ns

Table 3.3: NL vs EL patients demographics and clinical tests. Every variable is represented as (mean ± SD), with the exception of gender and family history of PD, which are categorical variables. The Mann-Whitney U test (MW) was used for continuous variables, and the chi-squared test (χ^2) for categorical variables. Significance levels are indicated as follows: $*p < 0.05$, $**p < 0.01$, $***p < 0.001$.

(mean = $0.85 \pm \text{SD} = 0.38$), with a Mann-Whitney U test result of $F(845) = 68939$, $p < 0.001$. However, the left Putamen SBR did not show significant differences. Despite this, the mean SBR values still suggest a difference: the EL group had higher values (mean = $0.93 \pm \text{SD} = 0.31$) compared to the NL (mean = $0.85 \pm \text{SD} = 0.35$), with the test reporting $F(845) = 70111$, $p < 0.001$.

The boxplot in [Fig. 3.6] visually demonstrates the differences in SBR distributions between the groups.

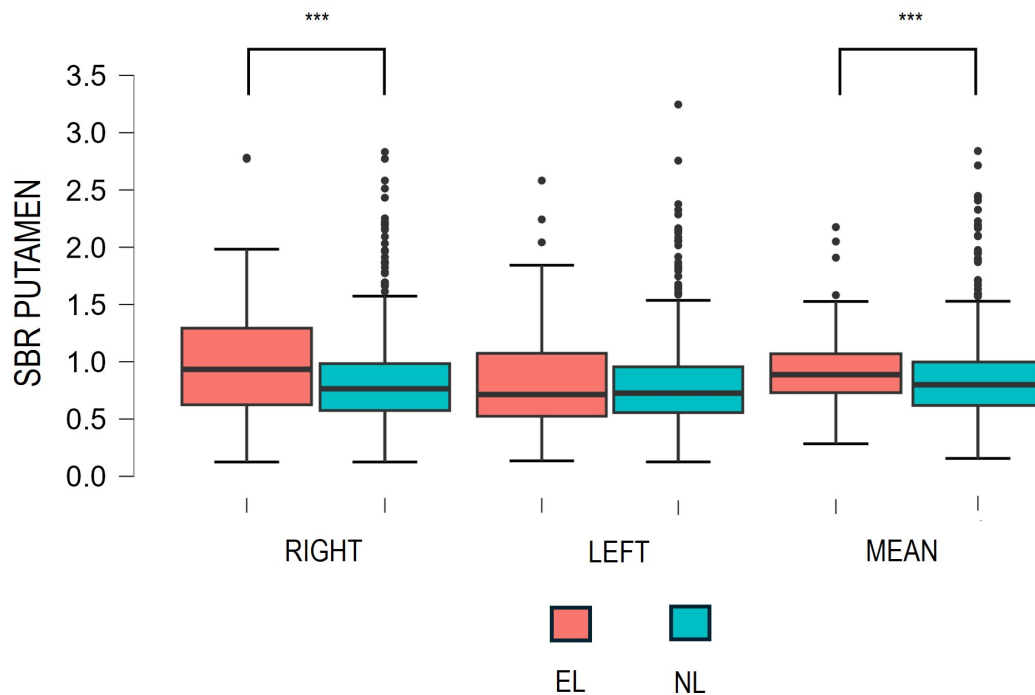


Figure 3.6: Boxplots representing the Right, Left and average SBR signal rate of the Putaminal region between the EL and NL subgroups.

Next, the clinical variables of the EL and NL groups were analyzed. While the t-test focuses on comparing mean values, the Mann-Whitney U test evaluates differences in median values. However, to better illustrate the disparities between groups, mean values and raincloud plots will be displayed. The analysis began with MDS-UPDRS scores, starting with MDS-UPDRS part I [Fig. 3.7]. The Mann-Whitney U test showed a significant difference with $F(844) = 52295.5$, $p = 0.046$. This indicates that the Extreme Lateralized group have less severe cognitive and non-motor symptoms (mean = $4.61 \pm \text{SD} = 4.01$) compared to the Normal

Lateralized (mean = $4.92 \pm \text{SD} = 3.64$).

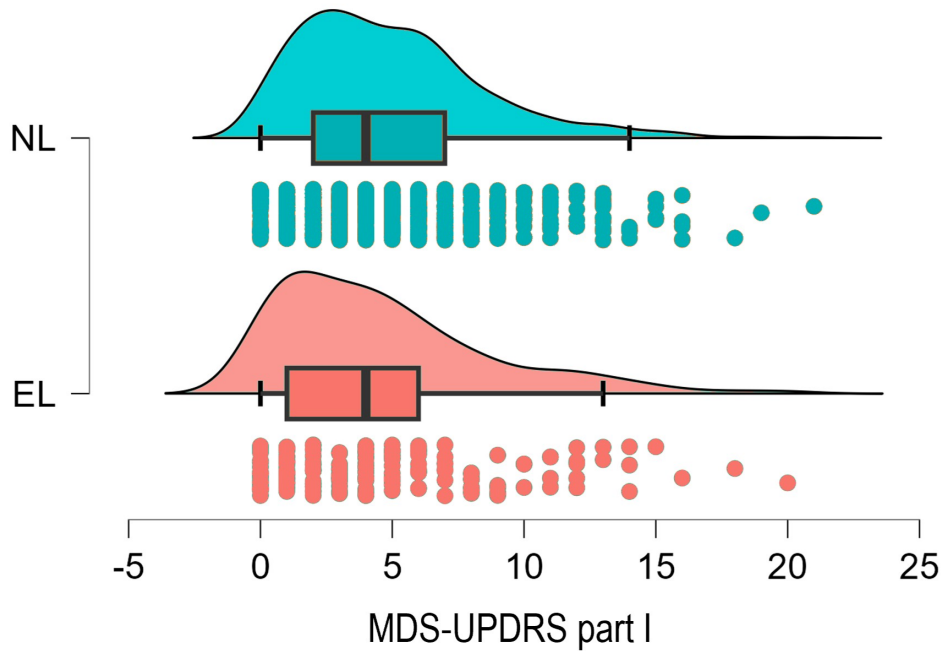


Figure 3.7: Raincloud plot of EL vs NL on MDS-UPDRS part I.

Although the EL group exhibited slightly lower scores in the MDS-UPDRS part II and III, with means of (mean = $5.99 \pm \text{SD} = 4.55$) and (mean = $21.24 \pm \text{SD} = 9.56$), respectively, compared to the NL group's means of (mean = $6.41 \pm \text{SD} = 4.58$) and (mean = $22.03 \pm \text{SD} = 9.99$), these differences were not statistically significant in both tests.

Next, the cognitive tests were analyzed, MoCA was the first one. The test didn't present statistical difference among the groups, but a very interesting insights could be extrapolated [Fig. 3.8]. The Mann-Whitney results were $F(841) = 61970.5$, $p = 0.109$, with an average MoCA score lower for the NL (mean = $26.65 \pm \text{SD} = 2.69$) than the EL average score (mean = $27.06 \pm \text{SD} = 2.42$).

As a matter of fact, the average MoCA scores for the NL are closer to the 26-point cutoff point for mild cognitive impairment. To determine how many participants for each group fell below the cut-off, a quick check was conducted. It was discovered that, compared to 29.55% for the Extreme Lateralized, 40% of the Normal Lateralized were below the threshold for mild cognitive impairment.

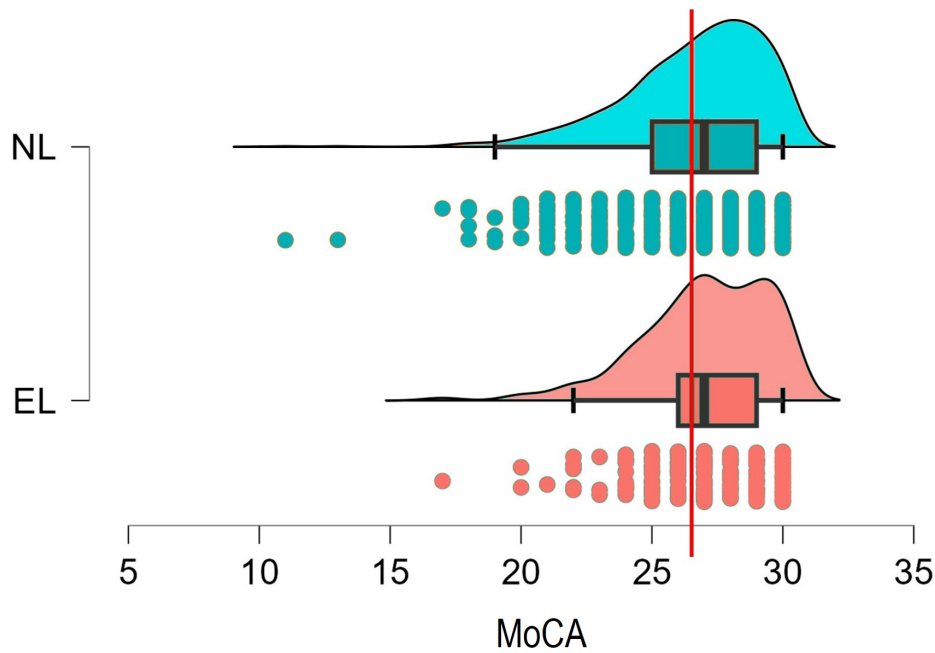


Figure 3.8: Raincloud plot of EL vs NL on MoCA. The red line represents the cutoff point, below which the patient is considered in mild cognitive impairment.

The Mann-Whitney test, with $F(815) = 62923.5$ and $p = 0.001$, then demonstrated that the NL had a more severe cognitive score (mean = $40.75 \pm SD = 10.65$) than the EL (mean = $43.84 \pm SD = 9.66$) based on the Symbol Digit Modalities Test. Furthermore, as shown in Fig. 3.9, the average SDMT score for the NL is again, in closer proximity to the cutoff of 34.2. Additionally, a check has been done here too, and the proportion of participants falling below the EL limit was considerably lower than that of the NL. While the NL is 37.34%, the EL below the threshold is 20.29%.

Afterwards, the gastrointestinal and urinary related problems derived from the SCOPA-AUT have been addressed. In this case, there were statistically significant differences in both the two tests. To be more specific, the Normal Lateralized ranked poorer.

The Mann-Whitney test parameters for the GDI were $F(820) = 47520$ and $p = 0.006$, and for the urine-related issues, $F(823) = 46963.5$ and $p = 0.002$. What emerged from these tests is that NL patients have more gastrointestinal related problems (mean = $1.35 \pm SD = 1.55$) than the EL

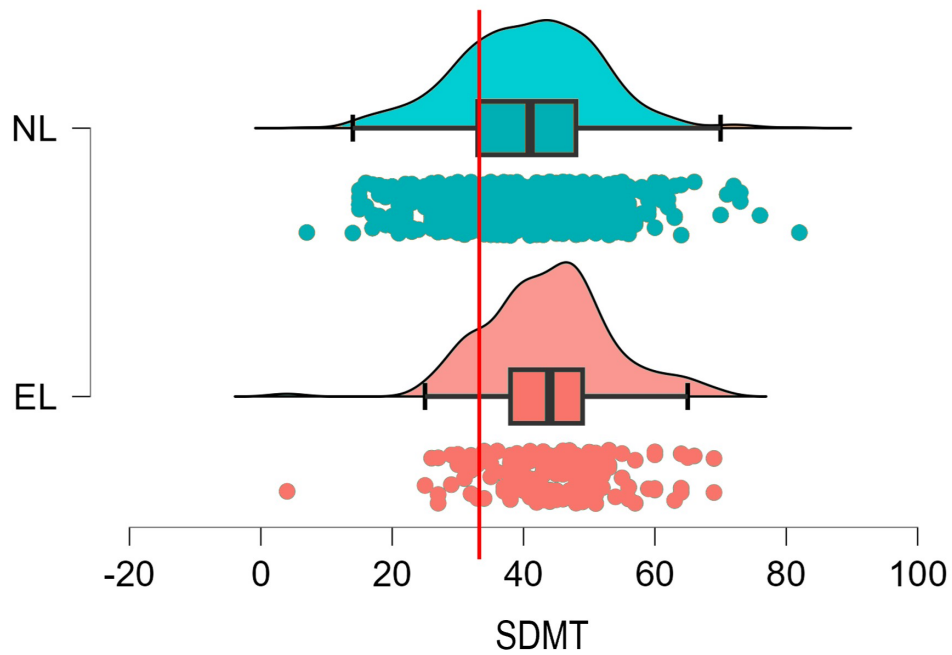


Figure 3.9: Raincloud plot of EL vs NL on MoCA. The red line represents the cutoff point, below which the patient is considered in mild cognitive impairment.

(mean = $1.02 \pm \text{SD} = 1.46$), the distribution are shown in Fig. 3.10.

Moreover, about the Urinary problems again, derived from the SCOPA-AUT, the Normal Lateralized have significantly worse issues, as proven by the rank test, (mean = $2.31 \pm \text{SD} = 2.10$) than the Extreme Lateralized (mean = $1.83 \pm \text{SD} = 2.00$) [Fig. 3.11].

To conclude, the Depression score taken from the Geriatric Depression Scale, the State and Trait Anxiety scores and the Sleep related problems from the Epworth Sleep Scale, didn't highlight differences among the groups.

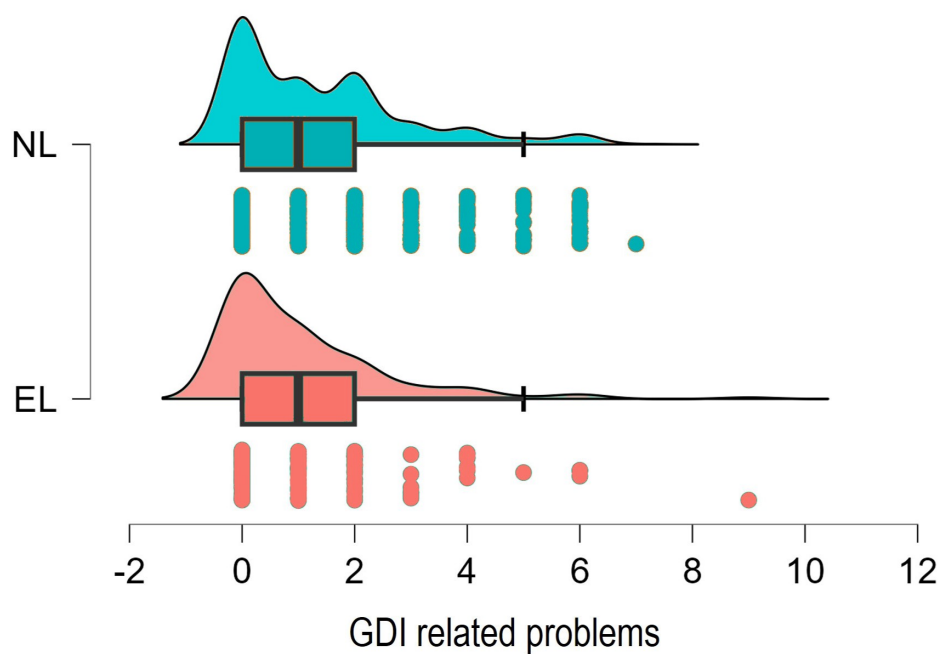


Figure 3.10: Raincloud plot EL vs NL in Gastro Intestinal related problems score, derived from the SCOPA-AUT.

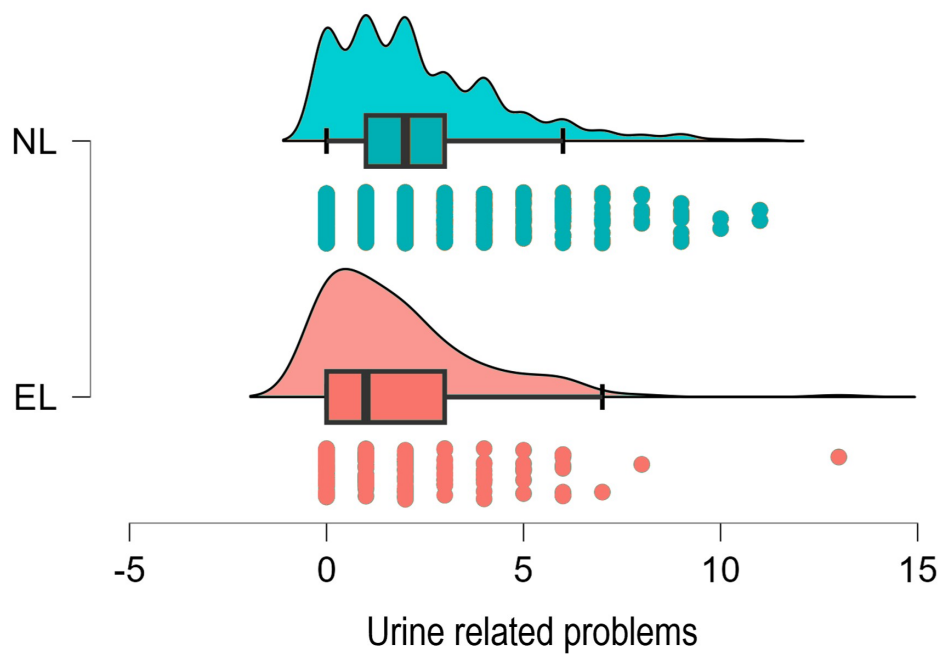


Figure 3.11: Raincloud plot EL vs NL in Urine related problems score, derived from the SCOPA-AUT.

3.3.2 Longitudinal Analysis

First of all, as mentioned, 'the overall goal of PPMI is to investigate novel methods to establish longitudinal PD cohorts to examine clinical, imaging, genetic, and biospecimen PD progression markers'. Therefore the data is periodically updated and released, allowing ongoing monitoring of the disease progression in patients. However, one significant limitation is the rate of dropout, as many participants abandon of the study for various reasons. Consequently, as time progresses, the available dataset shrinks. For instance, DATSCAN imaging data is available only up to the 10th visit (V10), which corresponds to four years after the initial visit.

Due to this limitation, we constructed the first analysis, focusing on the evolution of Putamen SBRs up to V10, accompanied by the clinical tests where significant group differences were observed [Tab. 3.4]. In this analysis, we calculated the difference in scores between different visits, choosing to compare V10 and V06 (2 years). Following this, an ANOVA was conducted, considering both the lateralization classification (EL vs. NL), the time points when the measurements were taken, and the interaction between these factors. The three p-values presented in the results are: First p-value (p_1): refers to the effect of LI classification on the average clinical test score or SBR value. Second p-value (p_2): indicates whether the visit time point (when the measurements were taken) has an effect on the average clinical test score or SBR value. Third p-value (p_3): represents the interaction effect, showing whether the combination of Putamen LI classification and timepoint has an additional impact beyond their individual effects. In other words, it checks if the effect of Putamen asymmetry on the average clinical test score or SBR value changes over time.

Variable N° of participants [NL - EL]	NL	EL	Comparison
SBR Putamen Right V6. [401 - 100] V10. [236 - 58]	V1. 0.85 ± 0.38 V6. 0.67 ± 0.31 V10. 0.56 ± 0.27	V1. 1.00 ± 0.47 V6. 0.73 ± 0.30 V10. 0.57 ± 0.22	$p1 < .001^{***}$ $p2 = 0.002^{**}$ $p3 = 0.043^*$
SBR Putamen Left V6. [401 - 100] V10. [236 - 58]	V1. 0.84 ± 0.37 V6. 0.66 ± 0.30 V10. 0.57 ± 0.29	V1. 0.86 ± 0.43 V6. 0.65 ± 0.22 V10. 0.54 ± 0.173	$p1 < .001^{***}$ $p2 = ns$ $p3 = ns$
SBR mean Putamen V6. [401 - 100] V10. [236 - 58]	V1. 0.85 ± 0.35 V6. 0.67 ± 0.28 V10. 0.57 ± 0.26	V1. 0.93 ± 0.31 V6. 0.69 ± 0.21 V10. 0.57 ± 0.16	$p1 = ns$ $p2 < .001^{***}$ $p3 = ns$
MDS-UPDRS part I V6. [418 - 99] V10. [300 - 75]	V1. 4.92 ± 3.46 V6. 1.89 ± 2.27 V10. 2.45 ± 2.73	V1. 4.61 ± 4.01 V6. 1.88 ± 2.47 V10. 1.89 ± 2.31	$p1 = ns$ $p2 < .001^{***}$ $p3 = ns$
SDMT V6. [324 - 81] V10. [281 - 72]	V1. 40.75 ± 10.65 V6. 38.72 ± 11.20 V10. 37.89 ± 11.90	V1. 43.84 ± 9.66 V6. 42.80 ± 11.03 V10. 43.11 ± 13.43	$p1 < .001^{***}$ $p2 = 0.056$ $p3 = ns$
Gastrointestinal related problems V6. [414 - 97] V10. [300 - 74]	V1. 1.35 ± 1.55 V6. 1.63 ± 1.70 V10. 1.88 ± 1.69	V1. 1.02 ± 1.46 V6. 1.34 ± 1.63 V10. 1.26 ± 1.50	$p1 < .001^{***}$ $p2 = 0.002^{**}$ $p3 = ns$
Urine related problems V6. [416 - 98] V10. [300 - 74]	V1. 2.31 ± 2.10 V6. 2.78 ± 2.32 V10. 3.20 ± 2.35	V1. 1.83 ± 2.00 V6. 2.30 ± 2.14 V10. 2.20 ± 1.84	$p1 < 0.001^{***}$ $p2 < 0.001^{***}$ $p3 = ns$

Table 3.4: EL vs NL patients SBRs values and clinical tests evolution over time. ANOVA was used to assess differences in the groups. Significance levels are indicated as follows: $p1$: effect of LI classification on the average clinical test score or SBR value. $p2$: the visit time point (when the measurements were taken) has an effect on the average clinical test score or SBR value. $p3$: it checks if the effect of LI classification on the average clinical test score or SBR value changes over time. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$.

If the first two p-values are significant, it indicates that both the LI classification and the time points of the visits independently influence the clinical test scores or SBR values. In other words, each have an effect on their own. However, if the third p-value is also significant, this suggests a synergistic effect. Essentially, the interaction between these factors has a cumulative effect on the clinical test scores or SBR values. Based on the results, nearly all variables show that either the LI classification or the visit timepoints independently have a significant effect.

However, for the SBR signal in the Right Putamen, the interaction between these two factors is also significant. This means that the effect of lateralization on the Right Putamen's dopamine transporter signal changes depending on the timepoint of the visits. Essentially, how much the Right Putamen's SBR value is affected by lateralization depends on when the measurements were taken. This points to a more dynamic relationship between disease progression, time, and lateralization in this specific region.

Building upon the earlier analysis, we extended the longitudinal approach by including data from the 13th visit (V13), which corresponds to six years after the first visit. Unfortunately, only clinical variables were available for this timepoint, and missing data remained a challenge. To ensure the focus remained on the most meaningful metrics, we selected the key clinical tests from the prior group of tests for further examination [Tab. 3.5].

Variable N° of participants [NL - EL]	NL	EL	Comparison
MDS-UPDRS part I V6. [418 - 99] V10. [300 - 75] V13. [225 - 58]	V1. 4.92 ± 3.46 V6. 1.89 ± 2.27 V10. 2.45 ± 2.73 V13. 2.76 ± 2.89	V1. 4.61 ± 4.01 V6. 1.88 ± 2.47 V10. 1.89 ± 2.31 V13. 1.88 ± 2.00	$p1 = 0.015^*$ $p2 < .001^{***}$ $p3 = ns$
MDS-UPDRS part II V6. [416 - 99] V10. [301 - 75] V13. [224 - 58]	V1. 6.41 ± 4.58 V6. 8.11 ± 5.79 V10. 10.15 ± 6.78 V13. 11.59 ± 7.07	V1. 5.99 ± 4.55 V6. 6.98 ± 4.95 V10. 8.40 ± 5.86 V13. 8.93 ± 5.83	$p1 < .001^{***}$ $p2 < .001^{***}$ $p3 = 0.098$
MDS-UPDRS part III V6. [370 - 87] V10. [255 - 68] V13. [202 - 53]	V1. 22.03 ± 9.99 V6. 26.63 ± 11.93 V10. 29.85 ± 12.84 V13. 33.22 ± 14.47	V1. 21.24 ± 9.56 V6. 25.41 ± 10.90 V10. 28.74 ± 11.35 V13. 29.70 ± 11.87	$p1 < .001^{***}$ $p2 < .001^{***}$ $p3 = ns$
SDMT V6. [324 - 81] V10. [281 - 72] V13. [198 - 55]	V1. 40.75 ± 10.65 V6. 38.72 ± 11.20 V10. 37.89 ± 11.90 V13. 37.25 ± 12.63	V1. 43.84 ± 9.66 V6. 42.80 ± 11.03 V10. 43.11 ± 13.43 V13. 42.31 ± 9.41	$p1 = 0.028^*$ $p2 < .001^{***}$ $p3 = ns$
MoCA V6. [407 - 98] V10. [278 - 72] V13. [205 - 57]	V1. 26.65 ± 2.69 V6. 26.23 ± 3.28 V10. 26.04 ± 3.72 V13. 25.96 ± 3.84	V1. 27.06 ± 2.42 V6. 26.71 ± 3.51 V10. 27.40 ± 3.58 V13. 27.39 ± 2.91	$p1 < .001^{***}$ $p2 = ns$ $p3 = 0.098$
Gastrointestinal related problems V6. [414 - 97] V10. [300 - 74] V13. [226 - 59]	V1. 1.35 ± 1.55 V6. 1.63 ± 1.70 V10. 1.88 ± 1.69 V13. 2.01 ± 1.73	V1. 1.02 ± 1.46 V6. 1.34 ± 1.63 V10. 1.26 ± 1.50 V13. 1.39 ± 1.62	$p1 < .001^{***}$ $p2 < .001^{***}$ $p3 = ns$
Urine related problems V6. [416 - 98] V10. [300 - 74] V13. [226 - 59]	V1. 2.31 ± 2.10 V6. 2.78 ± 2.32 V10. 3.20 ± 2.35 V13. 3.46 ± 2.43	V1. 1.83 ± 2.00 V6. 2.30 ± 2.14 V10. 2.20 ± 1.84 V13. 2.34 ± 2.08	$p1 < 0.001^{***}$ $p2 < 0.001^{***}$ $p3 = ns$

Table 3.5: EL vs NL patients clinical tests evolution over time. ANOVA was used to assess differences in the groups. Significance levels are indicated as follows: $p1$: effect of LI classification on the average clinical test score or SBR value. $p2$: the visit time point (when the measurements were taken) has an effect on the average clinical test score or SBR value. $p3$: it checks if the effect of LI classification on the average clinical test score or SBR value changes over time. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$.

The results of this extended analysis reveal an increase in the presence of significant effects across several clinical variables after 6 years from the first visit. There is also a greater divergence between the average

scores of the EL and NL groups in the tests, highlighting the evolving differences between these groups as the disease progresses. However, no interaction or cumulative effect between the LI classification and timepoint was found, indicating that while both factors influence clinical outcomes, they do so independently rather than synergistically. Despite this, the findings remain intriguing.

To better illustrate these results, visual plots of some tests are shown. For instance, the MDS-UPDRS part II score variations clearly demonstrate how both the LI classification and the timepoint of measurements significantly influence these scores [Fig. 3.12]. Daily motor symptoms, progress differently in the EL and NL groups over a span of 6 years.

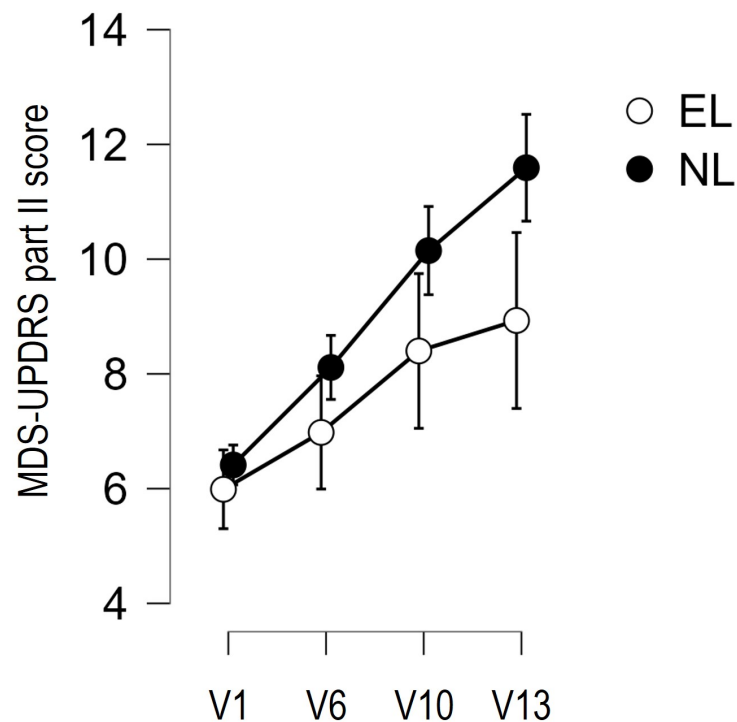


Figure 3.12: Line plot illustrating the evolution of MDS-UPDRS Part II scores over time for both the EL and NL groups. The timepoints represent follow-up visits conducted every two years, starting from the baseline (V1).

A similar trend is observed in the Urine-related problems score [Fig. 3.13], as well as the Symbol Digit Modalities Test [Fig. 3.14]. Particularly in the V13 of the SDMT, the average score for the NL group approaches the threshold for mild cognitive impairment (mean = $37.25 \pm$

SD = 12.63), while the the average EL score stays further (mean = $42.31 \pm$ SD = 9.41).

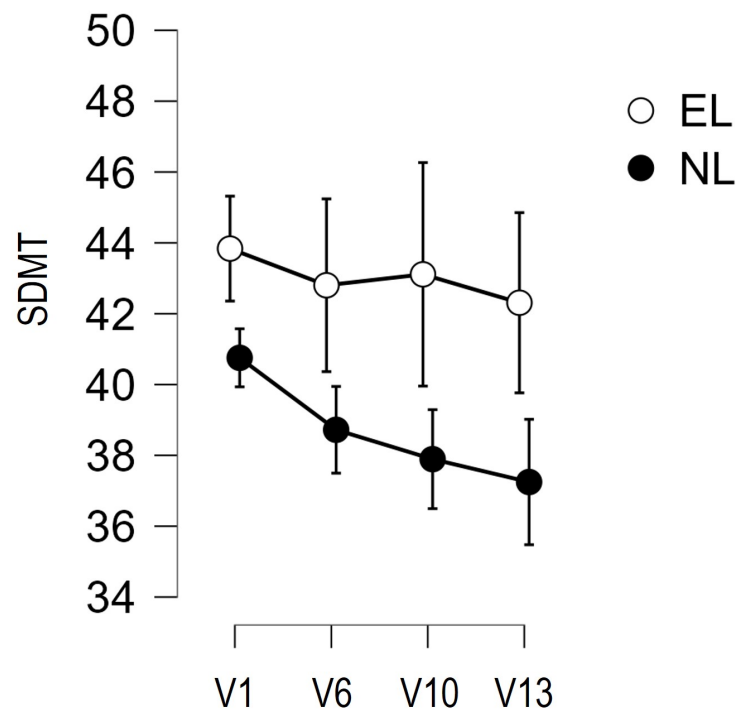


Figure 3.13: Line plot illustrating the evolution of the SDMT scores over time for both the EL and NL groups. The timepoints represent follow-up visits conducted every two years, starting from the baseline (V1).

Moreover, in the MoCA, only the LI classification has a significant effect on cognitive test scores. But is also noteworthy that the average MoCA scores of the EL groups at the V13 (mean = $25.96 \pm$ SD = 3.84) falls below the cutoff point of 26, while the NL does not (mean = $27.39 \pm$ SD = 2.91) [Fig. 3.15].

The results indicates a disparity in cognitive performance progression between the groups, with the NL group showing a decline that edges closer to the MCI threshold, whereas the EL group appears to maintain a greater cognitive buffer.

They also suggest that while the impact of being in the EL or NL group and the timing of assessments both play significant roles in disease progression, their effects do not reinforce each other, but still reveal important patterns over time. These findings will be further analyzed

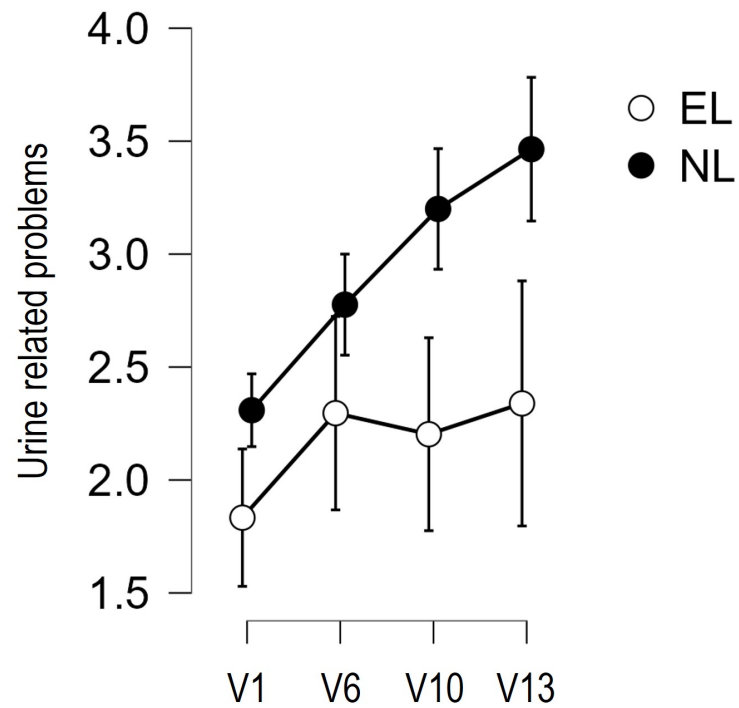


Figure 3.14: Line plot illustrating the evolution of the Urine related problems scores over time for both the EL and NL groups. The timepoints represent follow-up visits conducted every two years, starting from the baseline (V1).

and discussed in the concluding chapter.

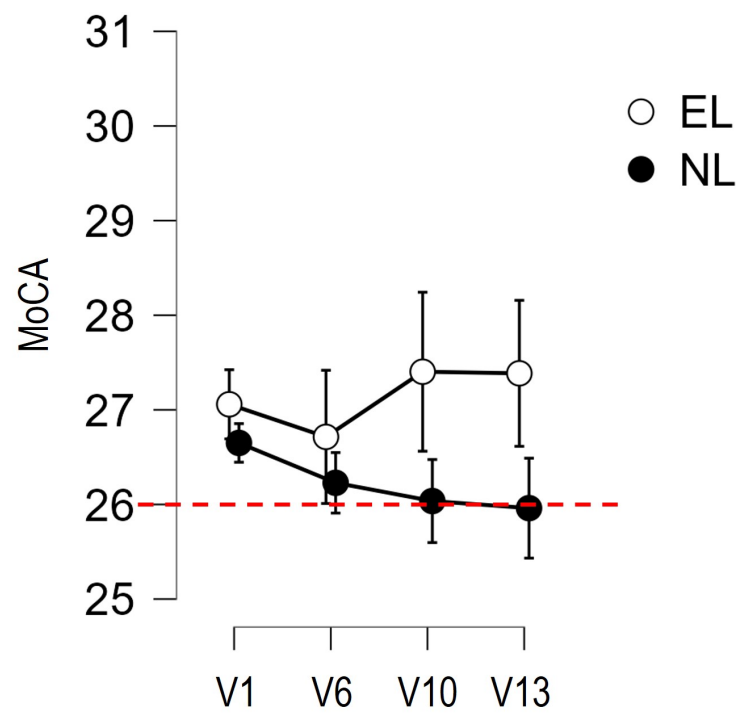


Figure 3.15: Line plot illustrating the evolution of the MoCA scores over time for both the EL and NL groups. The timepoints represent follow-up visits conducted every two years, starting from the baseline (V1).

3.3.3 Direction of the lateralization

According to the findings, when looking at the Right Putamen, it is not surprising that the EL_{Right} patients have the highest dopamine levels compared to the other groups, even higher than those of the NL. When ANOVA is performed on the three groups, it can be observed that while the SBR of the EL_{Right} (mean = $1.27 \pm SD = 0.40$) is significantly greater than the SBR of the NL (mean = $0.86 \pm SD = 0.39$), the SBR of the EL_{Left} (mean = $0.62 \pm SD = 0.21$) is significantly lower. When we move to the Left Putamen, the situation is the opposite. Here, the SBR of the EL_{Left} (mean = $1.21 \pm SD = 0.40$) is much higher than the SBRs of the EL_{Right} (mean = $0.63 \pm SD = 0.23$) and the NL (M = 0.83, SD = 0.38). Once more, the NL dopamine levels are significantly higher than those of the EL_{Right} .

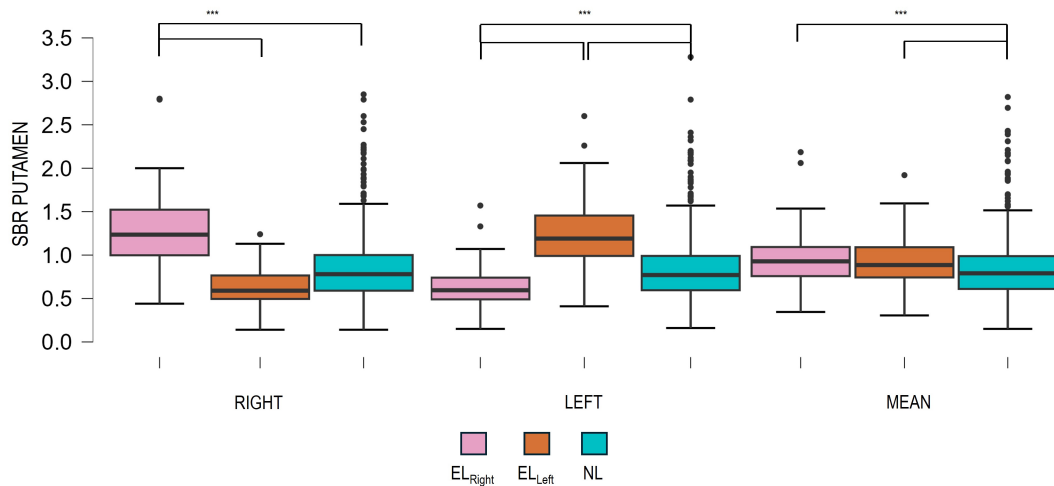


Figure 3.16: Boxplots representing the Right, Left and the average of the SBR signal rate of the Putaminal region, investigating the Direction of the lateralization.

What we find when we compute the Mean of the SBR of the Left and Right Putamen (mPut) is quite interesting. We acknowledge that the Normal Lateralized group has much lower SBR signal than both the Extreme Lateralized group based on the evidence $p < 0.001$, $F(2, 844) = 5.56$. First, the Normal Lateralized patients have the lowest SBR (mean = $0.84 \pm SD = 0.35$) of the average SBR and are substantially lower than both EL_{Right} and EL_{Left} . Lastly, the Right Lateralized patients have

Variable N° of participants	NL 652	EL _{Right} 104	EL _{Left} 91	Comparison EL _{Right} vs EL _{Left}
Age [years]	63.98 ± 9.26	59.87 ± 10.25	61.76 ± 9.80	ns
Gender (m/f)	409/266	68/36	57/34	ns
Any familiar with PD (y/n)	157/182	23/31	19/25	ns
Years of education [years]	15.71 ± 3.51	16.44 ± 3.02	16.07 ± 3.03	ns
Height [cm]	171.61 ± 9.86	173.47 ± 10.58	172.94 ± 8.95	ns
Weigth [kg]	79.79 ± 17.48	80.64 ± 17.24	80.78 ± 16.62	ns
SBR mean Caudate	1.95 ± 0.57	2.14 ± 0.53	2.09 ± 0.59	ns
SBR Putamen Right	0.86 ± 0.37	1.27 ± 0.40	0.86 ± 0.39	MW(193) = 8917.5, $p < .001^{***}$
SBR Putamen Left	0.83 ± 0.37	0.63 ± 0.23	1.21 ± 0.40	MW(193) = 4925, $p < .001^{***}$
SBR mean Putamen	0.84 ± 0.35	0.95 ± 0.31	0.92 ± 0.30	ns
MDS-UPDRS part I	4.92 ± 3.46	4.24 ± 3.86	4.88 ± 3.94	ns
MDS-UPDRS part II	6.41 ± 4.58	5.85 ± 4.35	5.78 ± 4.66	ns
MDS-UPDRS part III	22.03 ± 9.99	19.55 ± 8.89	23.25 ± 9.57	MW(166) = 2491.5, $p = 0.004^{**}$
MoCA	26.65 ± 2.69	27.14 ± 2.35	26.87 ± 2.50	ns
SDMT	40.75 ± 10.65	44.04 ± 9.58	43.40 ± 10.21	ns
Gastrointestinal related problems	1.35 ± 1.55	0.95 ± 1.35	1.19 ± 1.64	ns
Urine related problems	2.31 ± 2.10	1.64 ± 1.75	2.18 ± 2.26	ns
STAI_Y1	47.59 ± 4.82	47.58 ± 4.53	46.92 ± 5.12	ns
STAI_Y2	45.94 ± 4.28	46.24 ± 4.04	46.06 ± 4.34	ns
Epworth Sleepines Scale	5.68 ± 3.81	6.14 ± 3.76	5.36 ± 3.51	ns
Geriatric Depression Scale	5.44 ± 1.48	5.47 ± 1.34	5.52 ± 1.49	ns
Disease Duration [years]	2.67 ± 3.19	2.57 ± 2.58	2.63 ± 3.01	ns

Table 3.6: EL_{Right} vs EL_{Left} patients demographics and clinical tests. NL are taken as reference. Every variable is represented as (mean ± SD), with the exception of gender and family history of PD, which are categorical variables. The Mann-Whitney U test (MW) was used for continuous variables, and the chi-squared test (χ^2) for categorical variables. Significance levels are indicated as follows: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

the highest SBR values (mean = $0.95 \pm \text{SD} = 0.31$), followed by the Left Lateralized patients (mean = $0.92 \pm \text{SD} = 0.30$).

After having assessed potential differences in the SBR signal between the groups, the idea was to proceed in analysing the subgroup of the Extreme Lateralized. Having divided this class in Right and Left. First of all, the main thing was to check the implicit hypothesis that dopamine lateralization is closely linked to the lateralization of motor symptoms in Parkinson's disease. Specifically, that the hemisphere of the brain with lower dopamine levels, typically the contralateral side to the more affected body side, corresponds to the side of the body where motor symptoms are most pronounced. This relationship was explored by comparing the degree of dopamine asymmetry, with the lateralization of motor symptoms such as tremors, rigidity, and bradykinesia. The Tremor Asymmetry Index (TRMAI) and the Bradykinesia-Rigidity Asymmetry Index (BrdykAI), have been calculated. This motor symptom asymmetry indexes give us a hint on which side of the body the disease is more prominent. All the data have been taken from the already cited Kaasinen V. paper [24].

If the motor asymmetry index is positive, it indicates that the right side of the body is more severely affected by the symptoms; if it is negative, the left side of the body is more afflicted. For example, for the Right Extreme Lateralized patients, with higher dopamine levels on the right and lower dopamine in the left hemisphere, it is expected that the side of the body with more prominent symptoms, is the right one. The results of the check showed that, out of the 94 valid Right EL patients, 84 (or slightly less than 90%) had positive TRMAI, and only 10 had more noticeable symptoms on the "wrong" side of the body. Only 6 of the 81 valid Left EL had a positive TRMAI score, and 75 (about 93%) had a negative score, meaning that the left side of the body had more symptoms. Instead, the TRMAI scores of the Normal Lateralized patients were equally distributed, 269 patients with positive scores of and 258 with negative scores, respectively. Examining the BrdykAI, the circumstances are comparable. Out of 102 valid EL_{Right}, 94 (more than

92%) adhered to the implicit hypothesis, while 8 had a BrdykAI score that was negative. Additionally, out of the 89 valid EL_{Left}, 83 (more than 93%) had a negative BrdykAI score, while 6 had a positive score. Once more, the NL were divided equally, with 328 having a BrykAI < 0 and 308 having a BrdykAI > 0. The violin plots distributions are shown in the Fig. 3.16. With this check, we can deduce that the implicit hypothesis was supported and that it is reasonable to assume that the side of the body that is worst affected by the motor symptoms is the side opposite the side of the brain where the imaging data highlights the dopaminergic deficit.

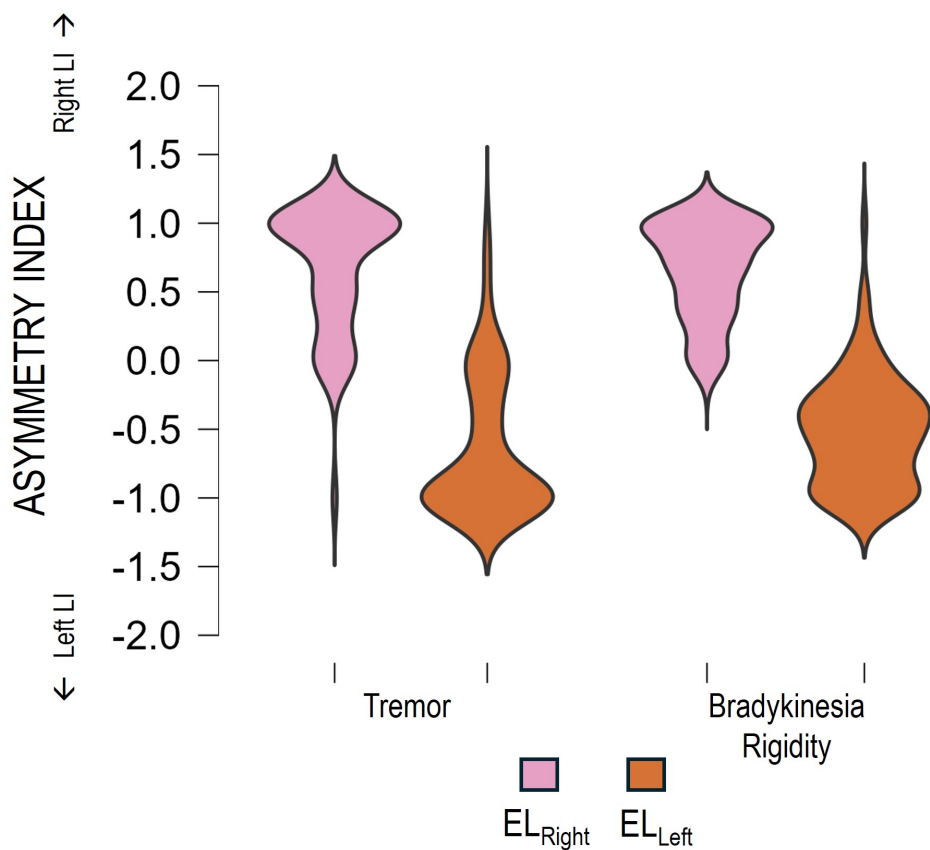


Figure 3.17: Violin plot of the Tremor and Bradykinesia-Rigidity AI that show the correspondence between motor symptoms and dopamine asymmetry

Also the Mann-Whitney U test was performed between the EL_{Right} and the EL_{Left} on the TRMAI and BrydkAI, again due to non-normality. Both resulted significant, precisely the EL_{Right} (mean = $0.73 \pm SD = 0.43$)

and the EL_{Left} (mean = $-0.72 \pm SD = 0.48$) on the Tremor Asymmetry Index $F(193) = 8975.0$ with $p < 0.001$. While for the EL_{Right} (mean = $0.67 \pm SD = 0.34$) and the EL_{Left} (mean = $-0.53 \pm SD = -0.39$) concerning the Bradykinesia-Rigidity Asymmetry Index $F(193) = 9255.5$ and $p < 0.001$. After the check, was possible to move on searching differences between these subgroups in their clinical profile. No differences in the clinical profile were expected. Was expected that these groups would have the same profile in terms of motor, cognitive performance. So, again an univariate analysis was performed. No differences were found between the groups, that means that the symptoms are consistent among the groups. However, one exception was found in the MDS-UPDRS part III, where a notable difference was detected. Again the Mann-Whitney U test, $F(166) = 2491.5$ and $p = 0.004$, shows that the difference in the groups is statistically significant. With the Left Extreme Lateralized having more severe general motor symptoms (mean = $23.86 \pm SD = 10.04$) than the Right (mean = $19.55 \pm SD = 8.89$) [Fig.3.18].

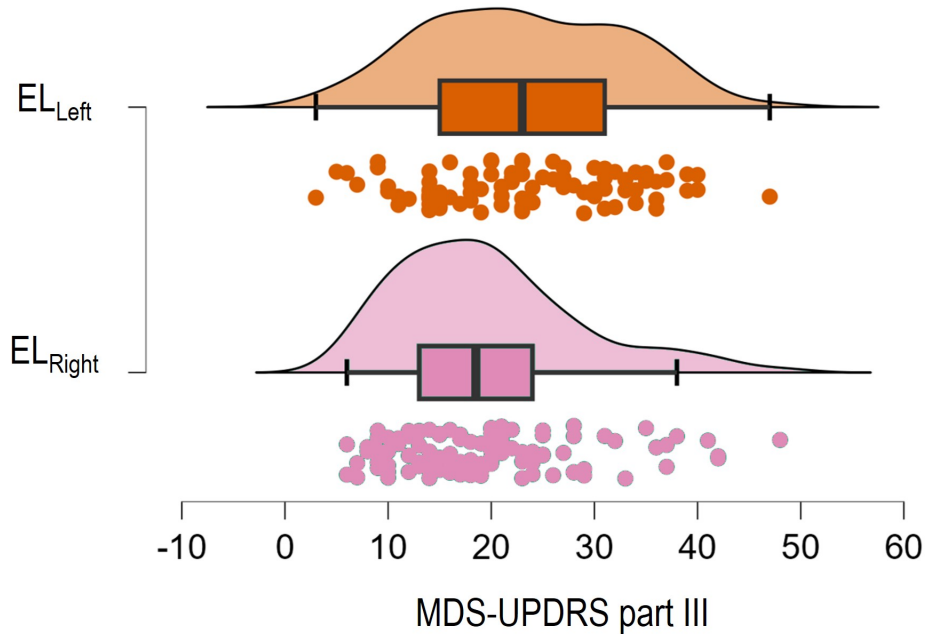


Figure 3.18: Raincloud plot EL_{Right} vs EL_{Left} in the MDS-UPDRS part III

We'll discuss this further in the Discussion section to explore the

broader implications of these findings and how they relate to existing research.

Chapter 4

Discussion

This study shows that in a healthy human brain, the striatum exhibits a normal range of dopamine lateralization. However, in some Parkinson's disease patients, this lateralization becomes more pronounced, exceeding the normal boundaries. From the start, the correlation analysis reveals that increased asymmetry in dopaminergic activity in the Putamen is associated with higher SBR values, milder motor symptoms, improved autonomic functions, and better cognitive performance. The asymmetry in the Caudate does not follow the same pattern as in the Putamen, which could have implications for understanding disease progression in different brain regions. To enforce this results, the analysis of the SBR signal in both the 'Magnitude' and 'Direction' of lateralization between the cohorts reveals key findings. Extreme Lateralized groups, exhibit higher SBR values compared to the Normal Lateralized group. Every comparison yields statistically significant results, demonstrating that lateralization harbors more clinically relevant information than initially assumed. These findings suggest that rather than being indicative of pathology, increased asymmetry in the Putamen's DAT could potentially have a protective or compensatory effect, providing benefits, against the progression of these symptoms and in certain cognitive aspects of Parkinson's disease patients.

The clinical profile that results from the statistical analysis supported this theory. The Extreme Lateralized group outperformed the Normal

Lateralized group, in some of the clinical tests presented. The MDS-UPDRS part I, which examines the patients' non-motor and cognitive symptoms and functions, is where the statistical significant differences in scores initially appeared. The test accounts for issues with sleep, urination, constipation, pain, fatigue, and so on. The ratings for urinary and gastrointestinal-related issues obtained from the SCOPA-AUT actually support this. The results of both tests, again statistically significant, indicate that the Normal Lateralized group's symptoms are worse. When it comes to cognitive disorders, disparities continue. According to the Symbol Digit Modalities Test, the NL performs poorer than other groups in a number of cognitive domains, such as information processing speed, lexical access speed, and memory. Apart from having the lowest scores, around 37.4% of the individuals in the group fall below the cutoff. This could indicate executive function, attention, and cognitive slowness, which could make daily tasks more challenging. Extreme Lateralized participants below the cutoff parameter are nearly half of the NL, or roughly 20% of the total. If the MoCA scores are examined, the same circumstances occur. About 40% of the NL fall within the category of cognitive impairment. Whatever the case, despite the fact that the NL's average score is lower, the test does not reveal statistically significant differences. The scores for the motor symptoms did not differ significantly, which was not what had been expected. It is not sufficient to conclude that the Normal Lateralized have more severe motor symptoms than the Extreme Lateralized on the MDS-UPDRS parts II and III, even if the NL's average scores were still about one point lower than the EL's.

However, the longitudinal analysis presents a different perspective. Over time, the gap between the EL and NL groups becomes more pronounced, also in motor symptoms. The analysis underscores the progressive nature of the differences between the EL and NL groups. Over time, the gap between these groups widens. For example, tests like the SDMT and MoCA, show that cognitive decline is more gradual in the

EL group, while the NL group's scores approach clinical thresholds for mild cognitive impairment over the years. This favorable trend for the EL group extends to motor and autonomic symptoms as well, where the differences in MDS-UPDRS part II and III scores become much more pronounced over time, particularly as the disease progresses. Despite the challenges of missing data and participant dropout over time, the trends observed suggest that lateralization could serve as a valuable marker for predicting the future trajectory of Parkinson's disease symptoms.

Additionally, there was no apparent disparity in the groups' depression, sleep scores and in anxiety levels derived from the Geriatric Depression Scale, the Epworth Sleepiness Scale and the State-Trait Anxiety Inventory, respectively.

Even though the earlier studies that were referenced in the Background chapter had previously been regarded as defective, it's still interesting to observe how their findings compare to ours.

In the paper "Gastrointestinal Symptoms and Dopamine Transporter Asymmetry in Early Parkinson's Disease" by Murtoimäki et al., the researchers aimed to explore the connection between functional gastrointestinal disorders, particularly constipation, and symmetrical SBR signal in early PD. One of their hypothesis aligns with what emerged from our study: that patients with more symmetrical DAT binding, or lower lateralization, tend to have fewer gastrointestinal symptoms. Specifically, in our own research, the NL group exhibited significantly lower scores on gastrointestinal-related symptom scales, as well as on the MDS-UPDRS Part I, which also assesses non-motor symptoms including gastrointestinal disorders.

Interestingly, Murtoimäki et al. observed an association between more severe gastrointestinal symptoms and the 'Left Lateralized' group. Possibly their classification might have influenced these findings.

Moreover, from the paper 'Asymmetric Dopamine Transporter Loss Affects Cognitive and Motor Progression in Parkinson's Disease' by Fiorenzato E. et al., three differences between the lateralized subgroups

were found. At first, the group classified as Left Lateralized performed worse on the SDMT test and had lower levels of cerebrospinal fluid beta-amyloid than the Right Lateralized group. Moreover, Fiorenzato E. et al., found that the Right had greater motor impairment than the Left Lateralized, which is in direct opposition to our research.

The fact that only one significant difference emerged between the lateralized groups in this research can be somewhat reassuring. It's important to highlight that this difference pertains to motor symptoms, where unexpectedly, the EL_{Left} group exhibited more severe motor symptoms than the EL_{Right} group in the MDS-UPDRS score part III. Despite this, the overall clinical profile remains similar between the two subgroups. What the literature says about this is also different from what has been found. The Parkinson patients with symptoms on their dominant side (ex: right-handed people with symptoms on their right side of the body), usually have more severe symptoms than the one with symptoms on their nondominant side [36]. Which means that in our dataset being only right-handed, the EL_{Right} should have shown worse motor symptoms, while was the opposite in our case. First of all, is important to say that the two groups, Extreme Right and Left Lateralized, represent small subgroups of the PD patients. The NL are still lateralized and are not represented in this analysis. On the fact that the results show that the EL_{Left} have more severe motor symptoms than the EL_{Right}, it can be said that most research studies relating laterality of symptoms to handedness have to some degree suffered from a potential of recall bias. These studies can be flawed because they rely on patients' memories of where their symptoms started. Since people pay more attention to their dominant hand (the one they use more frequently), they are likely to notice symptoms there more quickly than in their non-dominant hand. Therefore, there is a possibility that patients with Parkinson's disease with initial and predominant dysfunction of the right nigrostriatal system might have longer latencies between onset of neurodegeneration and subjective awareness of motor deficits in the non-dominant hand or limb [37]. In other words, neurodegeneration might have progressed more

by the time they come to medical attention, leading to potential recall bias. This bias affects the reliability of the study results. This issue can complicate the understanding of how Parkinson's disease symptoms manifest in relation to handedness [37].

Unfortunately for the nature of the hypothesis this was not proved in the research, primarily due to biases inherent in the data concerning the potential disease onset. Additionally, MDS-UPDRS part III, is focused on the patient's motor symptoms in general while MDS-UPDRS part II, which assesses motor symptoms' impact on daily life activities, did not show any significant differences between the groups. This suggests that while EL_{Left} patients may experience more severe motor impairments, these differences might not translate into a noticeable impact on their daily functioning.

Future research may go deeper into all of these questions.

4.1 Limitations and future works

The findings of this study are very interesting and can emphasize a point for the future but the generalizability of these results is subject to certain limitations.

First off, almost all of the assessments and tests are questionnaires or self-reports. Such as the Geriatric Depression Scale, the Epworth Sleepiness Scale, the SCOPA-AUT, the STAI and the MDS-UPDRS tests. The cognitive tests (MoCA, SDMT) instead measure the patient performance in a specific contest and task. Consequently, these subjectively felt and verbalized ratings that correlate with an impairment level and measure the severity of the disease, are biased by the doctor's interpretation. The PPMI's data were the only ones that were utilized, no objective investigations of the gastrointestinal, urinary, sleep, depression, anxiety or motor scores were carried out.

Going on, another important limitation regarding the SCOPA-AUT is worth noting. The parameters used to assess gastrointestinal and urinary disorders in this study were extracted from the broader SCOPA-AUT questionnaire, specifically focusing on the most relevant items for this research. In particular, gastrointestinal symptoms were evaluated using questions from the first seven items of the 23-item questionnaire. The first four items concentrate on specific symptoms related to saliva production, choking, feelings of fullness after meals, and difficulties with swallowing. For the assessment of gastrointestinal problems, only questions 5, 6, and 7 were considered in generating the relevant score, as did by Jones JD et. al in his research [32]. These questions inquire about specific issues experienced in the past month, including: "Have you had problems with constipation?", "Did you have to strain hard to pass stools?", and "Have you experienced involuntary loss of stools?" [38]. This focused approach highlights significant gastrointestinal symptoms, although it may not capture the full range of gastrointestinal dysfunctions that could be present in Parkinson's disease patients.

Every question on urine in the SCOPA-AUT was taken into consid-

eration because they all dealt with issues including involuntary loss of urine, holding urine, and incontinence. The items pertaining to urine range from 8 to 13. This selective approach, while aimed at highlighting the most significant symptoms, may impact the overall assessment of autonomic dysfunction in Parkinson's disease. Future studies should consider a more comprehensive evaluation of all gastrointestinal symptoms to ensure a more thorough understanding of their impact on patient quality of life .

As mentioned in the second chapter, only participants with 'good' and 'discrete' quality imaging data from DaTSCAN were included in the analysis, while those with 'poor' quality data were excluded. However, the specific criteria for defining 'discrete' SPECT image quality remain unclear, as only the PPMI staff, who established these parameters, possess that knowledge. This uncertainty raises the possibility that some conclusions may be affected by noise levels in the data. The decision to retain participants with 'discrete' DaTSCAN quality aimed to maximize the volume of usable data for the study. Future research should strive for more transparency in quality assessment criteria to better understand their impact on study outcomes.

Additionally, it has been chosen to operate exclusively with Putamen data for the previously stated reasons. Nevertheless, this study lacks in information outside the Striatum because it is restricted to DAT binding in the Putamen.

It is also important to note that the cutoffs established for the Extreme Lateralization classification are currently based solely on the available HC data. This limitation suggests that expanding the HC dataset could potentially improve the robustness and accuracy of the classification. To conclude the discussion on limitations, two significant confounders should be acknowledged: age and medication intake. The influence of age on motor and cognitive symptoms is well documented, as older individuals may exhibit different disease progression and symptom severity and the EL group was significantly younger. Moreover, unlike the studies by Kaasinen and Fiorenzato, [24] [13] which included only untreted

de novo PD or patients who didn't took medications within six months prior to imaging, the medication intake was not considered in this paper, yet it can significantly affect the presentation of Parkinson's disease symptoms. Addressing these confounding variables in future research could provide a more comprehensive understanding of lateralization and its implications in Parkinson's disease.

A bigger and more detailed picture of what dopamine lateralization in Parkinson's disease is, may be obtained in the future by supplementing the study with additional tests, analysis and more data.

Additional tests should be taken into consideration. One particularly intriguing test is the MDS-UPDRS part IV, which displays data on Wearing-off (Woff) events. These occurrences occur later in the disease when tolerance changes and levodopa medications no longer function as they once did. Uncontrollably violent spasms are a serious side effect of Woff that makes patients stay at home rather than take the chance of experiencing these events in public or, worse, while driving [39]. Fortunately, the patients in the dataset are still in the early phases of the illness, therefore, few of them have Woff events and MDS-UPDRS part IV available data. These tests' may provide some extremely fascinating information about the EL and the NL. Do the two subgroups truly experience distinct effects from the shift in tolerance?

Other PD specific tests not considered in this analysis are the Hoehn and Yahr Scale and the The University of Pennsylvania Smell Identification Test (UPSIT) test. The first is used along with Unified Parkinson's Disease Rating Scale for a better assessment of Parkinson's disease. It helps in describing the progression of the disease through various stages, thus allowing us to measure the severity of the case [40]. While the (UPSIT) it is the most reliable and accurate olfactory test available, the worldwide standard for olfactory testing. Provides an absolute indication of smell loss (anosmia; mild, moderate, or severe microsomia) [41].

An additional interesting investigation that could be conducted is the analysis of the structural imaging data from magnetic resonance imaging

(MRI). What can be done is to try to determine whether the Dopamine deficit that is shown in the DaTSCAN imaging is associated with a potential structural loss. Alternatively, whether this Putamen dopamine lateralization reflects a more general lateralization of the brain. All of these questions can be examined because the MRI data are available in the PPMI dataset. Sadly, there aren't many people who underwent MRI analysis, therefore the amount of data is limited.

It would be valuable to apply this methodology to a completely new dataset. Exploring different populations could yield insights into the robustness and generalizability of the findings, helping to establish whether the observed patterns hold true across various contexts and conditions.

This knowledge might help in comprehending an additional feature of the extremely complicated Parkinson disease. It may also result in a more effective therapeutic plan and customized, personalized therapy that tackles the disease differently for NL and EL patients.

4.2 Conclusion

In this study, we investigated dopamine lateralization in PD and found that HC exhibit a clear lateralization of dopaminergic function. Intriguingly, some PD patients demonstrated higher levels of lateralization, therefore were categorized as Extreme Lateralized. Our approach was straightforward yet data-driven, contrasting sharply with previous studies that relied on arbitrary cutoffs lacking biological relevance and grounded solely in mathematical conclusions.

The results indicated that the Extreme Lateralized patients exhibited superior cognitive and autonomic functions scores compared to those categorized as Normal Lateralized. Furthermore, EL patients had, on average, higher dopamine levels than their NL counterparts. Longitudinal analyses revealed differing disease trajectories between the two groups: while EL patients experienced a slighter worsening of symptoms, NL patients showed a more rapid decline.

This finding challenges the traditional view that extreme lateralization signifies dysfunction. Instead, it suggests that patterns of dopamine distribution may indicate a more favorable neurobiological mechanism within the context of PD. Specifically, the less affected striatal putamen in the EL group may compensate for dopamine loss on the more affected side, leading to pronounced lateralization. This compensatory mechanism may be an effort to restore equilibrium by enhancing dopaminergic output.

In contrast, the NL group exhibited a more symmetrical progression of the disease, with neither hemisphere retaining significantly more dopamine than the other. This symmetry may indicate that both hemispheres are equally affected, reflecting a more advanced stage of the disease.

For sure, even if some test corroborate the idea, for now this remains just an hypothesis. Future studies and future research should lead to a more vast comprehension, understanding better what is an extreme and what is a normal dopamine lateralization and what does this means in

the PD clinical profile.

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