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DOTTORATO DI RICERCA IN MEDICINA TRASLAZIONALE DELLO SVILUPPO E DELL'INVECCHIAMENTO ATTIVO

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Tesi di Dottorato in:

Analysis of predictive factors of neurodegeneration in patients with Bipolar Disorder and parkinsonism: a nested case-control study

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Abstract

Introduction and aim of study: Bipolar disorder (BD) has been suggested to be a risk factor for the development of Parkinson's disease (PD). Standard treatment of BD includes drugs that are known to induce drug-induced parkinsonism (DIP). Clinical differentiation between PD and DIP is crucial and might be aided by functional neuroimaging of the dopaminergic nigrostriatal pathway. Thus, the aim of this thesis is to perform a clinical and scintigraphic characterization of consecutive BD patients with parkinsonism, the latter by exploring the functional integrity of the dopaminergic nigrostriatal pathway with the use of DaTSCAN, and to analyze any possible predictive factors of neurodegeneration in the BD population.

Methods: We enrolled consecutive BD patients with parkinsonism. Screening for parkinsonism was performed with the ScanMove Instrument. Clinical evaluation was performed using the MDS-UPDRSIII scale.

Abstract

Patients were also screened for REM sleep behavior disorder, using the RBD screening questionnaire, and hyposmia, using the University of Pennsylvania Smell Identification test (UPSIT). A first level cognitive assessment was obtained with the Montreal Cognitive Assessment. Patients underwent ^{123}I-ioflupane dopamine transporter single-photon emission computer tomography (SPECT). A subset of BD patients performed Gait Analysis, and the obtained parameters were compared to those of a population of age-matched PD patients. We employed monovariate and multivariate (machine-learning-based) statistical methods in order to look for possible predictive factors of neurodegeneration.

Results: Forty-one consecutive BD patients were enrolled. Eight of them (19,5%) had abnormal scans (BD+). The two populations significantly differed in terms of age at evaluation, with BD+ population significantly older than the population with normal scan (BD-).

Machine learning-based class discrimination, performed with the PLS-DA, Random Forest and Logistic Regression algorithms, did not reach statistical significance. However, we discovered trends in worst MDS-UPDRSIII “gait” scores, more frequently referred hyposmia and higher RBD scores in the BD+ class, compared to BD- class. Left action tremor

tended to be slightly worse in the BD- class. Moreover, the BD - class tended to report a higher number of episodes and higher doses of antipsychotics.

BD UPSIT scores were compared to those obtained by a population of age-matched PD patents and controls. Difference was statistically significant among the three classes, with the Bipolar population scoring intermediately between PD and controls.

Gait analysis showed an overall worse gait performance in BD patients compared to PD, associated to a higher interference during cognitive dual task. A further trend in worse parameters in the BD+ population, compared to BD-, was also detected.

Conclusions: About 20% of BD patients with parkinsonism might have an underlying dopaminergic deficit, which would not be due to cumulative exposure to offending drugs and is higher than expected in the general population. This supports the evidence that BD may represent a risk factor for subsequent development of neurodegenerative parkinsonism. Trends in more frequent referred hyposmia and higher RBD scores, as well as worse gait features, in the BD+ population, may represent possible

predictive factors of neurodegeneration, which must be verified on a larger cohort.

1. Introduction

1.1. The relationship between Bipolar Disorder and Parkinson's Disease: literature review.

This literature review explores the points of convergence and ongoing controversies surrounding the relationship between Bipolar Disorder (BD) and Parkinson's disease (PD). In particular, it examines whether BD should be conceptualized as a risk factor, a prodromal manifestation, or a comorbid condition in the neurodegenerative trajectory leading to PD. By synthesizing epidemiological, clinical, and neurobiological evidence, this review highlights shared pathophysiological mechanisms, while critically addressing inconsistencies and methodological limitations in the existing literature.

1.1.1. Neurobiological bases

Parkinson's Disease (PD) is characterized by loss of dopaminergic neurons in the substantia nigra pars compacta (Poewe et al. 2017). For this reason, PD motor symptoms (namely bradykinesia, rigidity, rest tremor, postural and gait impairment) are mainly explained by a striatal dopaminergic impairment. Consequently, dopamine pharmacological replacement is related to symptom relief (commonly referred to as the "on" state). In PD, non-motor symptoms such as depression have been classically found to be, at least partially, connected to motor fluctuations, depressive mood being connected to the "off" states and vice-versa (Menza et al. 1990). This clinical observation, as well as pharmacological evidence, has supported the pathophysiological hypothesis of an increased dopaminergic drive in mania and the reverse in depression also in Bipolar Disorder (BD). In these patients, disrupted homoeostatic mechanisms responding to the hyperdopaminergic state of the manic phase would induce an excessive decrease in the function of dopaminergic signaling, rapidly leading to a hypodopaminergic state and depression. In turn, a faulty regulatory response to the hypodopaminergic state would lead again to mania (Ashok et al. 2017). Indeed, compounds which increase dopamine availability, such as levodopa or

amphetamines, may trigger hypomanic or manic states. On the contrary, symptoms of depression can arise in the context of lowered dopamine transmission (e.g. reserpine), while symptomatic relief can be obtained by increasing dopamine concentrations (e.g. pramipexole, buproprion) (Berk et al. 2007).

Dopaminergic neurotransmission has been investigated in patients with BD both through the measurement of metabolites in cerebrospinal fluid (CSF) and through *in vivo* imaging studies of dopaminergic transmission with either positron-emission tomography (PET) or single photon emission tomography (SPECT), using specific tracers for receptor studies.

A study on monoamine metabolites in BD indicates increased levels in CSF homovanillic acid (HVA), a major dopamine metabolite, compared to controls (Pålsson et al. 2017).

Research concerning pre-synaptic dopamine transporter (DAT) binding in bipolar disorder (BD) have conflicting results, showing either state or trait-dependent alterations. A PET study with [^{11}C]d-threo-methylphenidate (MP) showed that manic episodes in BD were associated with decreased striatal (putamen, caudate, nucleus accumbens) DAT density (Yatham et al. 2022). Earlier studies had found increased DAT density (as measured by TRODAT-1 SPECT) in bipolar

and unipolar depressed patients compared to controls (Amsterdam and Newberg 2007). In euthymic BD patients, striatal DAT binding, as measured through TRODAT-1 SPECT, was found to be higher than in control subjects and negatively correlated to valproate serum concentration (Hsueh et al. 2021). On the other hand, a former study conducted on unmedicated BD patients demonstrated significantly lower caudate DAT binding (as measured by [^{11}C]CFT PET) relative to healthy controls in bilateral dorsal caudate (Anand et al. 2011).

Extra-striatal (cortical) DAT alterations have been scarcely studied so far: a postmortem study using [^{3}H]mazindol did not show any difference in frontal DAT availability in BD patients compared to controls.

Post- synaptic dopamine receptor status, as reviewed by (Nikolaus et al. 2019) in psychiatric disorders, revealed that BD patients, both in mania and in depression, were characterized by desensitization of D1 receptors in the frontal cortex, reflecting an increased availability in frontal dopamine. Dopamine transmission is intimately related to serotonin. The same authors have detected neocortical serotonin receptor desensitization in BD mania (reflecting increased serotonin) and the reverse in BD depression (reflecting decreased serotonin). In sum, they found that while increased mesencephalic, limbic and parieto-temporo-occipital serotonin and increased frontal dopamine may underlie mania,

the depressive state would be characterized by decreased frontal and limbic serotonin and increased frontal dopamine (Nikolaus et al. 2017).

Since serotonin stimulates dopamine release via 5-HT1/2 receptors (Ichikawa and Meltzer 1995a), the desensitization of these neocortical binding sites in mania can be assumed to (although not effectively) diminish cortical dopamine concentrations and, together with the desensitization of frontal D1 receptors, to reduce dopaminergic input to the mesolimbic target regions of descending DA neurons. On the contrary, the sensitization of frontal 5-HT1 receptors in BD depression would lead to an augmentation of dopamine release, but, on the other hand, the sensitization of inhibitory 5-HT1 autoreceptors in prefrontal/frontal cortex and limbic system increases the inhibitory action of the negative feedback loop, secondarily leading to a further aggravation of 5-HT shortage (Nikolaus et al. 2017).

Serotonin has also been described for its role in PD. Low serotonin levels have been linked to alterations in mood, such as depression, and changes in sleep architecture. Reductions in serotonin levels of nearly 50% have been reported in the cortex and basal ganglia of patients with PD (Scatton et al. 1983). The globus pallidus and substantia nigra receive a dense serotonin-mediated innervation that originates predominantly from the brainstem raphe nuclei. Serotonin modulates the

excitability of globus pallidus neurons by both pre- and post-synaptic mechanisms (Chen et al. 2008), significantly increasing the spontaneous firing rate of external globus pallidus (Rav-Acha et al. 2008).

Moreover, the loss of dopamine neurons is believed to cause an increase in glutamatergic activity in the basal ganglia. Glutamate receptor antagonists, such as amantadine, have proven to be beneficial for motor symptoms in PD (Rascol et al. 2021). Impairment in glutamate signaling, through its NMDA receptor, is also relevant in depression (Barone 2010). Glutamatergic hyperactivity in terms of elevated brain glutamate has also been described in BD through *in vivo* ^{1}H magnetic resonance spectroscopy studies (Shen and Tomar 2021).

1.1.2. Premorbid and comorbid traits: focus on the Impulse Control Disorder (ICD)

The Impulse Control Disorder (ICD) category includes compulsive gambling, hypersexuality (including paraphilic manifestations), compulsive

shopping, bulimia, as well as other compulsive behaviours such as aggressive driving, obsession with bricolage, exercise, house cleaning, or gardening (punding). In PD, these disturbances are mainly triggered or precipitated by the use of dopamine agonists (Vargas et al. 2019; Bastiaens et al. 2013) or even levodopa (Voon et al. 2011). Classical risk factors for ICD development in the context of PD include male sex, younger age or younger age at PD onset, a pre-PD history of ICD symptoms, personal or family history of substance abuse or bipolar disorder, and a personality style characterized by impulsiveness (Weintraub 2009). As a consequence, an early development of ICD, also occurring in the context of a low dopaminergic drug burden, can be seen in genetic forms of PD such as glucocerebrosidase (GBA)-related PD (Petrucci et al. 2020). In turn, premorbid (i.e. preceding motor symptom onset) ICD have been described in genetic forms of PD, such as parkin-related PD (Morgante et al. 2016). The fifth version of the Diagnostic and Statistic Manual of Mental Disorders (DSM-5) (American Psychiatric Association 2013) does not present a specific section for the ICD (apart from gambling which is included in the “Non-Substance-Related Disorders” section). However, identical altered behaviours are observed in patients with bipolar disorder during manic/hypomanic or mixed states; indeed, an increase in goal-directed activity (either socially, at work or

school, or sexually), and/or an excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments) are amongst the diagnostic criteria for a manic or hypomanic episode (American Psychiatric Association 2013). It must be emphasised that these symptoms fail to configure a manic-hypomanic episode in BD when occurring within the physiological effects of a potentially culprit medication; this seems to contrast with the strict relationship between dopaminergic medication use and impulsive behaviours when regarding PD. However, despite the relatively high prevalence rates of ICD in medicated PD patients, a large proportion of them do not develop ICD. This indicates that ICD develops due to an interaction between dopamine replacement therapy and a certain neurobiological vulnerability (Vriend 2018).

1.1.3. Epidemiological studies

A systematic review and meta-analysis (Faustino et al. 2019) suggested an increased risk of developing PD in patients with a diagnosis of BD, compared to the general population (odds ratio, 3.35; 95%CI, 2.00-5.60;

I^2 = 92%). It was conducted on 7 studies and more than 4 million participants. The studies included were the following:

The cohort study by Lin et al. (Lin et al. 2014) included 73.597 patients with an established psychiatric disorder who were recruited between 2001 and 2003, among whom 1203 had BD, and these individuals were matched with 220.971 controls. The selection was made using medical records of hospitalizations and ambulatory care. Patients were observed for 6 years to identify PD. In this 6-year follow-up, patients with BD were at an increased risk of developing PD compared with the control group (adjusted hazard ratio, 5.02; 95%CI, 3.85-6.55). This result was adjusted for age and sex.

The use of lithium and PD diagnosis was assessed in a study by Marras et al. (Marras et al. 2016) that used data from the Ontario administrative health care database between 2002 and 2011. The results showed that compared with antidepressant therapy (285.154 patients), lithium monotherapy (1749 patients) was associated with an increased risk of antiparkinsonian drug use or PD diagnosis (adjusted hazard ratio, 1.68; 95%CI, 1.13-2.48).

Nilsson et al. (Nilsson et al. 2001) assessed psychiatric admissions between 1977 and 1993 among 164.722 patients with multiple psychiatric and nonpsychiatric disorders. Patients with the diagnosis of mania at

discharge were compared with a control group who had osteoarthritis or diabetes. The difference in the risk of PD diagnosis in the mania vs. control groups was not statistically significant, but among 2007 patients with mania, 7 patients (0.3%) developed PD.

A cohort study by Huang et al. (Huang et al. 2019) conducted with data from 2001 to 2009 and with follow-up until 2011, was designed to assess the risk of developing PD among people with BD. A total of 56.340 patients with BD and 225.360 healthy controls were included. Excluding the diagnosis of PD within the first year of the observation period, the study found an increased risk of PD among patients with BD during the follow-up period (hazard ratio, 5.82; 95% CI, 4.89-6.93).

Forty et al. (Forty et al. 2014) conducted a cross-sectional study that enrolled 1720 patients with BD who were interviewed regarding their history of multiple medical conditions, among which PD was included. The data were compared with data from a similar population who had unipolar mood disorders (1737 patients) and a control group (1340 patients). In the BD group, a 0.6% lifetime rate of self-reported PD was found, while in both the unipolar mood disorder and control groups, the rate of self-reported PD was 0.1%. This study also found a significant difference between BD types 1 and 2, with those with BD type 2 having a greater self-reported proportion of PD.

Another cross-sectional study by Smith et al (Smith et al. 2013), conducted on patients from primary care practices in Scotland, identified a higher prevalence of PD or parkinsonism for patients with BD compared with the control group (OR, 3.05; 95% CI, 1.83-5.09).

Conversely, a cross-sectional study by Kilborune et al. (Kilbourne et al. 2004) enrolled 4310 patients with BD receiving care in veteran centers and retrospectively analyzed these patients for PD. This study found a significantly lower number of patients with PD in the BD group compared with controls.

More recently, a study by (Yoon et al. 2024) have addressed the differential risk for early-onset PD (EOPD) vs late-onset PD (LOPD) in a 9 year longitudinal study involving people with mental illness. The BD population resulted in a higher risk for EOPD than for LOPD (OR 10.58 vs 3.74, respectively).

Finally, a prospective study (Xu et al. 2024) involving 501,233 UK Biobank participants, found that antipsychotic use as an independent predictor was strongly associated to PD risk compared to the BD status alone (hazard ratios 4.62 vs 1.54, respectively).

1.1.4. Genetic studies

A number of recent papers investigated whether the relationship between BD and PD be mirrored by a shared genetic background. However, results are conflicting.

A recent work by Hossain et al (Hossain et al. 2022), conducted using RNA-Seq gene expression datasets from brain tissue samples from patients with PD and BD, identified 45 common genes (32 upregulated and 13 downregulated) that are abnormally expressed in both diseases. Upregulated genes were *RPL21, TNFRSF10A, TMC4, TM4SF1, SRGN, SNORD3A, RPL34, PLAC8, MT1M, MT1G, MT1 F, MT1E, MT1A, MS4A6A, LST1, LOC554223, LILRB1, IL18R1, HLADPA1, HLA-B, HCG25, FGF23, DTX2, CYSLTR2, CLIC1, CLEC2B, CKS2, CCDC102A, CASP4, CARD16, BRDT, and B2M).* Down-regulated genes were *VEPH1, TAPBP, PBX2, MOG, MIR4516, MDC1, LOC107985075, LOC100507091, KRTAP5-AS1, GRID2IP, DNAH10, CYP2D6, and ATP2A3.* Gene ontology (GO) and molecular pathway analysis (BioCarta, KEGG, Reactome) revealed altered pathways, including mineral absorption, Epstein-Barr virus infection, and antigen presentation. Protein-protein interaction analysis identified nine significant hub proteins (RPL21, RPL34, CKS2, B2M, TNFRSF10A, DTX2, HLA-B, ATP2A3, and TAPBP).

Furthermore, transcription factors (IRF8, SPI1, RUNX1 and FOXA1) and post-transcriptional regulatory microRNAs (hsa-miR-491-3p and hsa-miR-1246) that interact with shared genes were identified.

Moreover, (Nashiry et al. 2023) found 8 shared genes between PD and BD, including *KCNA3, C3, GPRIN3, RIPK3, ANKRD1, BGN, LHX9, and GATA6.* They also found Small leucine–rich proteoglycan (SLRP) molecules and Activation of C3 and C5 as the two top significant signalling pathways in PD and BD interaction.

Another work consisting in a bidirectional Mendelian randomization study using large GWAS datasets, found a statistically significant causal effect of genetically predicted PD on increased risk of BD (odds ratio 1.053, 95% CI 1.02–1.09, p=0.001). However, the authors but did not find evidence for a causal effect in the reverse direction (i.e., BD increasing risk for PD) (Wu et al. 2023).

On the other hand, a very recent work by (Smeland et al. 2025) analysed nearly one million cases across 10 neurological and 10 psychiatric disorders, finding that while common genetic variants impact risk for multiple disorders, the pleiotropic signal between BD and PD was not significant, and no shared loci were highlighted for this pair.

1.1.5. Controversies: drug - induced parkinsonism

Large scale epidemiological studies exploring the risk of developing PD for BD patients were mainly conducted on disease records, insurance records, GPs registers, self-reported diagnoses. Thus, PD diagnosis was detected through the related International Classification of Diseases (ICD) code, without any instrumental confirmation. Another limitation is that a subgroup analysis conducted by (Faustino et al. 2019) showed a greater likelihood of PD diagnosis in shorter studies. All these aspects raise concern about the reliability of PD diagnosis in the above-described studies: indeed, actual diagnoses of drug-induced parkinsonism may have been included.

Iatrogenic or drug-induced parkinsonism (DIP) is the second most frequent cause of parkinsonism after PD. It typically, but not selectively, occurs in patients treated with dopamine receptor blocking agents. Indeed, the drugs commonly associated to the risk of developing DIP are summarized in Table 1:

POTENTIAL RISK OF DIP	PHARMACHOLOGICAL GROUP	DRUG
HIGH	Dopamine D2 receptor antagonists	Typical antipsychotics: phenothiazines (chlorpromazine); butyrophenones (haloperidol); thioxanthene (flupenthioxol). Atypical antipsychotics (at higher doses): benzamides (sulpiride); diphenylbutylpiperazines (pimozide); dibenzyldiazepines (clozapine).
	Dopamine depleters	Tetrabenazine, reserpine.
	Dopamine synthesis blockers	Alfa-methyldopa.
	Calcium channel antagonists (P-channel)	Flunarizine, cinnarizine.
INTERMEDIATE	Atypical antipsychotics	Ziprasidone.
	Antiemetic and gastric motility agents	Prochlorperazine, metoclopramide, substituted benzamides.
	Calcium channel antagonists (L-channel)	Verapamil, diltiazem.
	Others	Lithium, valproate, phenytoin.
LOW	Antidepressants	Selective serotonin reuptake inhibitors, SSRI (fluoxetine, sertraline); tricyclic (amitriptyline); Monomamine oxidase inhibitors, MAO-I (moclobemide, phenelzine).
	Others	Amiodarone, procaine, tacrolimus, ciclosporin.

Table 1. Drugs potentially responsible for DIP (adapted from Erro R, Bhatia KP, Tinazzi M. Parkinsonism following neuroleptic exposure: A double-hit hypothesis? Mov Disord. 2015 May;30(6):780-5. doi: 10.1002/mds.26209. Epub 2015 Mar 18. PMID: 25801826)(Erro et al. 2015).

Drug-induced parkinsonism usually develops subacutely over days to months, most commonly when the drug is started or when the dose is increased. By definition, DIP should resolve within 6 months after the causative agent has been suspended (Bower et al. 1999); however, it can take several months, or even years to resolve after the culprit drug is stopped. There are no clinical characteristics that can reliably distinguish drug-induced parkinsonism from Parkinson's disease: however, the former is most commonly characterized by subacute onset, absence of tremor, symmetric signs at onset (Factor et al. 2019). Moreover, non-motor symptoms, such as hyposmia and REM behavioral sleep disorder (RBD) are usually absent in DIP (Brigo et al. 2014).

Real life studies (Ghaemi et al. 2006) report that over half of BD patients treated with atypical antipsychotics experience extrapyramidal side effects. For parkinsonism, these findings are not correlated to age, gender, neuroleptic dose or potency, duration of neuroleptic treatment (Ghaemi et al. 2006). Bipolar patients, especially in depression, are more vulnerable to have acute antipsychotic-induced movement disorders than those with schizophrenia (Gao et al. 2008).

The mechanisms associated with the appearance of DIP have a common final result: diminished D2 receptor stimulation in the striatum. This occurs primarily with the blockade of D2 receptors by antipsychotics and related

drugs, but also occurs with decreased dopamine release produced by compounds that deplete dopamine storage vesicles (tetrabenazine), with medications that block dopamine synthesis (alpha-methyldopa) or with compounds that block dopamine entry into the vesicles that are released into the synapse (reserpine) (López-Sendón et al. 2012). With dopamine D2 receptors blockade in the striatum, striatal neurons containing GABA and encephalin are disinhibited, affecting the indirect pathway and ultimately leading to a relative decrease in the activity of thalamocortical circuits (Vaiman et al. 2022).

Drugs that are not primarily targeted to the dopamine receptor can cause parkinsonism by an indirect effect on dopamine transmission, such as calcium channel blockers (Mena et al. 1995).

Furthermore, a linkage between serotoninergic and dopaminergic systems has been described: treatment with SSRIs such as fluoxetine inhibits the nigrostriatal dopaminergic neurons through the increase in serotonin activity in the raphe nuclei. SSRIs potentiate the inhibitory action of serotonin on both production and release of dopamine by neurons of the basal ganglia (Govoni et al. 2001; Ichikawa and Meltzer 1995b).

The association between lithium exposure and parkinsonism is controversial, since some authors associated lithium use with improved parkinsonian features, on and off phenomenon, impulsiveness, and

levodopa-induced mania, as reviewed by (Barros et al. 2025). However, both acute and chronic exposure to lithium were associated with the development of parkinsonism in several reports (Barros et al. 2025). The pathophysiological mechanism behind lithium-induced parkinsonism is unclear: it might be related to lithium-induced modulation of signalling pathways downstream of dopamine receptors (Ashok et al. 2017).

The use of lamotrigine and valproate has been associated to higher risk of incident PD (Belete et al. 2023). Several pathophysiological mechanisms, including altered gene expression, neurotransmitter signalling (i.e., an increase in afferent-to-nigral dopaminergic neurons GABAergic inhibition (Tepper and Lee 2007)), enhanced neurodegeneration or unmasking subclinical dopaminergic degeneration, have been addressed to explain valproate-associated parkinsonism (Brugger et al. 2016).

1.1.6. Persistent or tardive parkinsonism following neuroleptic exposure

As anticipated in the previous section, a number of patients (nearly 30%) develop a persistent parkinsonism following neuroleptic exposure (Erro et al. 2015).

DAT imaging using SPECT conducted on schizophrenic patients showed that a number of DIP patients carried abnormal uptake values (Tinazzi et al. 2012, 2014)[1]. In these patients, motor symptoms did not recover after the culprit drug had been withdrawn (Tinazzi et al. 2014).

Moreover, a 15-year prospective population-based study has shown that long-term risk of incident PD was increased by 3.2-fold after past exposure to neuroleptics, with only 30% of the case developing probable PD during the exposure (Foubert-Samier et al. 2012).

This supports the hypothesis that neuroleptic exposure may represent a risk factor for subsequent development of degenerative parkinsonism.

[1] Single-photon emission computed tomography (SPECT) imaging using ligands of the pre-synaptic Dopamine Transporter (DaT), such as ^{123}I-Ioflupane (^{123}I-FP-CIT-SPECT), known as DaTSCAN, allows the study of the functional integrity of the dopaminergic nigrostriatal pathway. Indeed, this nuclear medicine exam may be useful in differentiating DIP from neurodegenerative parkinsonism (PD), since it is expected to be normal in DIP patients, being DIP a form of postsynaptic parkinsonism due to D2-receptor blockade. Several studies suggest that SPECT DaTSCAN can be a reliable technique to differentiate between PD and DIP patients with relatively good sensitivity and specificity values (Vlaar et al. 2008; Cuberas-Borrós et al. 2011; Bajaj et al. 2013).

Indeed, available evidence support the notions that neuroleptic exposure can produce neurotoxic effects on dopaminergic neurons through inhibition of mitochondrial respiratory chain, increased dopamine turnover, and enhanced production of neurotoxic free radicals (Rollema et al. 1994; Meredith et al. 2004; Burkhardt et al. 1993).

Thus, it is reasonable to conclude that in a subset of predisposed subjects, drug-induced neurotoxic effects could enhance irreversible consequences on the presynaptic dopaminergic pathway. This would explain the appearance of “unmasked PD” in formerly DIP patients, as well as the development of PD in those subjects exposed to neuroleptics who do not manifest parkinsonism during the exposure (Erro et al. 2015; Brigo et al. 2014).

1.1.7. Longitudinal observations

A study by (Bacciardi et al. 2022), retrospectively evaluated a population of consecutive PD patients, carrying a positive SPECT DaTSCAN exam, for the prevalence of a mood disorder consistent with the bipolar spectrum. Out of 100 patients, 32 were classified as having a bipolar spectrum disorder, including drug-induced hypomania. Compared to the others,

patients with comorbid bipolar disorder had an earlier age of onset of PD and more motor fluctuations and involuntary movements, despite a homogeneous exposure to dopaminergic drugs. A higher prevalence of lifelong ICD was also observed in this subclass. Nearly two thirds of the “bipolar spectrum disorder” patients had experienced psychiatric symptoms before the onset of PD. The limitations of this study are the Inclusion of drug-induced hypomania (which is an exclusion criterion for bipolar disorder); the lack of SPECT criteria for dopaminergic denervation; the risk of inaccuracy in a retrospective lifelong assessment of psychiatric signs and symptoms.

A study by (Onofrj et al. 2021) performed a longitudinal evaluation of patients with levodopa-responsive PD with and without preexisting BD features. Group comparison showed a higher prevalence of positive family history for psychiatric and neurological disease in the BD group, as well as a higher prevalence of dopamine agonist withdrawal syndrome and higher exposure to neuroleptics. Longitudinal assessment confirmed higher prevalence of ICD both before and during the administration of dopaminergic drugs, earlier motor fluctuations, earlier onset of cognitive decline. In sum, this study shows that preexisting BD features influence disease course in patients with a diagnosis of PD.

1.2. Aim of study

The previous section has tried to analyze the common ground between BD and PD, which probably concerns a shared neurobiological dysfunction which may be, in turn, triggered by a shared genetic background.
However, it is still less clear whether the two diseases may be somewhat temporally connected (i.e. whether BD may represent a true risk factor for the development of PD): as highlighted, the influence of pharmacotherapy on the development of parkinsonian motor symptoms which may resemble those of PD is of primary importance.

With these premises, the aims of this study are:

1. To perform a clinical and instrumental characterization of consecutive BD patients with parkinsonism, the latter by exploring the functional integrity of the dopaminergic nigrostriatal pathway and by quantifying stratal uptake with the use of ^{123}I-FP-CIT-SPECT.

2. To analyze possible predictive factors of neurodegeneration in BD patients, including the evaluation of non-motor symptoms, such as REM sleep behavior disorder and hyposmia, as well as gait features.
3. To compare gait parameters to those of age-matched PD patients and healthy controls.

2. Materials and methods

2.1. Patients' enrollment: anamnestic and clinical evaluation

Participants were enrolled from the BD outpatient clinic of the Department of Medicine "Scuola Medica Salernitana", University of Salerno, Italy. The study protocol was approved by the local ethics committee and written informed consent was obtained from all participants. Study protocol strictly adhered to the guidelines outlined in the Declaration of Helsinki.

Consecutive patients were eligible for inclusion if they had a BD diagnosis according to DSM-5 criteria (Diagnostic and Statistical Manual of Mental Disorders, Fifth edition) (American Psychiatric Association 2013). Screening for parkinsonian symptoms was performed through the use of the ScanMove Instrument, a 31-item scale for the screening of antipsychotic-associated movement disorders for use by mental health nurses (Balint et al. 2018). Sub scores of the The ScanMove Instruments were subsequently obtained as follows: "bradykinesia-rigidity" (items 1-2-3-25-26-27-28-33), "tremor-myoclonus-appendicular dystonia" (items 7-9-

15-17-22-36-38), “abnormal posture” (items 4-5-13-20-34), “facial movement disorders” (items 6-14-21-29-35), “dyskinesia-akathisia” (items 10-11-18-24).

The presence of comorbid psychiatric disorders, such as psychotic disorders, anxiety disorders, and eating disorders was an exclusion criterion. All patients were euthymic at the study inclusion as assessed by total scores of ≤8 at the Young Mania Rating Scale (Young et al. 1978) and ≤6 at the Montgomery Asberg Depression Rating Scale (Montgomery and Asberg 1979). They were assessed to collect the following data: age at BD onset, BD type, family history for psychiatric and neurological disorders, polarity at disease onset, number of total episodes, number of depressive, hypomanic and manic episodes, pharmacological status. Specifically, current and previous antipsychotic therapy was converted into Chlorpromazine Equivalent Doses (CED) (Andreasen et al. 2010; Rothe et al. 2018) and used to estimate the cumulative exposure to antipsychotic drugs in dose/years. Similarly, we calculated the cumulative exposure of lithium in dose/year, the definition of 1 lithium dose/year being equivalent to taking lithium 450 mg daily for one year.

Motor symptoms duration and item-per-item and total score of the MDS-Unified Parkinson’s Disease Rating Scale (MDS-UPDRS), part III, were collected (Goetz et al. 2008). MDS-UPDRSIII sub items were also grouped

into the following sub scores: “axial score”, including axial rigidity, gait, posture, postural stability, arise from chair, freezing of gait, speech, facial expression, global spontaneity of movements; “left action tremor” and “right action tremor” including postural and kinetic tremor for each hemisome; “right bradykinesia” and “left bradykinesia” including all items evaluating appendicular bradykinesia for each hemisome; “right rigidity” and “left rigidity”, including all items evaluating appendicular rigidity for each hemisome. Further, we computed lateralized MDS-UPDRS-III sub scores for the most affected (MA) and least affected (LA) body side to calculate the clinical asymmetry index [(CAI)= (MA-LA)/(MA+LA)], where lower CAI values indicated a decrease of the degree of clinical asymmetry; (i.e., CAI = 0 when MAS = LAS)(Plotnik et al. 2005).

Longitudinal motor assessment was performed 1 to 6 months after in those patients who were dopaminergic drug naïve at baseline and started a dopaminergic treatment with either levodopa or monoamine oxidase inhibitors. A follow up MDS-UPDRSIII score was collected in ON state for these patients.

First level cognitive evaluation was performed using the Montreal Cognitive Assessment, Italian version, and we recorded total scores corrected for age and education (Santangelo et al. 2015).

2.2. Non-motor symptoms assessment

We explored the presence of two of the most common and specific non-motor symptoms of PD: REM sleep behavior disorder (RBD) and hyposmia.

The former was evaluated using the RBD screening questionnaire (Stiasny-Kolster et al. 2007), in the Italian validated version (Marelli et al. 2016). RBD screening questionnaire total score was recorded. Also, we recorded the percentage of patients having a score >8, as established by the cut-off values for the Italian version (Marelli et al. 2016).

Anamnestic information about a history of referred hyposmia was recorded. In a subset of patients, we evaluated smell using the University of Pennsylvania Smell Identification Test (UPSIT), Italian validated version. The University of Pennsylvania 40-item Smell Identification test is the most frequently used identification test to evaluate olfaction worldwide (Doty et al. 1984), and has been adapted and administered in several countries as a diagnostic tool in the diagnosis of PD (Doty et al. 1995). A cut-off point of ≤21/40 has been recognized as relatively accurate (82 % sensitivity and 88.2 % specificity) in differentiating PD patients from controls in an Italian cohort (Picillo et al. 2014b). The obtained total score was compared to the one obtained by an age-matched population of

subjects affected by PD and healthy controls (Picillo et al. 2014b). For the purpose of comparing motor scores, UPDRSIII scores computed for the PD class were converted into MDS-UPDRSIII scores using the formula described in (Goetz et al. 2012).

2.3. SPECT studies

All subjects underwent ^{123}I-FP-CIT SPECT study (DaTSCAN, GE Healthcare). It is a nuclear medicine exam aimed at showing the location and concentration of dopamine transporters (DaTs) in the synapses of striatal dopaminergic neurons (Grabher 2019). Patients received an intravenous injection of 185 MBq of ^{123}I-ioflupane after thyroid block with oral administration of Lugol solution. SPECT studies were performed using a dual-head system equipped with low-energy high-resolution collimators (e.cam, Siemens Medical systems, USA). The acquisition started between 3.45 and 4.15 h after the radiotracer injection and lasted 40 min (Djang et al. 2012). Images were acquired with a 128 × 128 matrix (zoom: 1.23; pixel size: 3.90 × 3.90mm), reconstructed using a Butterworth filter (cutoff 0.5, order 10) and corrected for attenuation using Chang's algorithm (μ = 0.06 cm^{-1}). After acquisition, images were analyzed with DaTQUANT (GE Healthcare), a software that uses a predefined voxel-of interest (VOI)

template for automatic asymmetry measurements and putamen-to-caudate uptake ratios and that further provides *z* scores of single VOIs (i.e., right and left striata, putamina, and caudates) (Brogley 2019). These values are based on a database of 196 age-matched healthy subjects from the Parkinson Progression Markers Initiative (PPMI) (Marek et al. 2018). The subjects involved in this study were scanned at the Department of Diagnostic Imaging and Radiotherapy of the University of Salerno, which is an authorized PPMI site and has undergone a program for technical qualification, quality assurance, and ongoing camera quality control, as per protocol guidelines (Marek et al. 2018). We used a striatal specific binding ratio (SBR) *z* score of <-2 (Kreyszig 1979) to classify BD patients with dopaminergic deficits (BD+), whereas SBR *z* scores of −2 or more were considered normal and used to classify patients as BD– (i.e., without dopaminergic deficits).

2.4. Gait Analysis

A subset of patients underwent quantitative assessment of gait parameters (“gait analysis”).

Spatio-temporal gait parameters were assessed in all participants using the SMART DX-400 motion capture system (BTS Bioengineering). This

optoelectronic setup is composed of two force plates, two video cameras, six infrared cameras, a set of passive reflective markers, and a central computer for data acquisition and biosignal processing. Data collection followed the Davis Heel protocol (Davis et al. 1991), which involves several standardized steps: recording anthropometric measurements (e.g., weight, height, pelvic width, and leg length); placing 22 reflective markers on predefined anatomical landmarks; conducting a static calibration trial while the participant stood still on the force plate; and performing dynamic walking trials along a straight 10-meter walkway. During gait assessment, each participant completed three experimental conditions, each one repeated at least four times: GAIT (single task), consisting of normal walking; MOT (motor dual task), which required carrying a tray with two glasses filled with water while walking; and COG (cognitive dual task), which involved performing serial subtractions of seven from 100 (e.g., 100–7, 93–7, 86–7, etc.) during walking.

Gait cycle phases and subphases are depicted in figure 1.

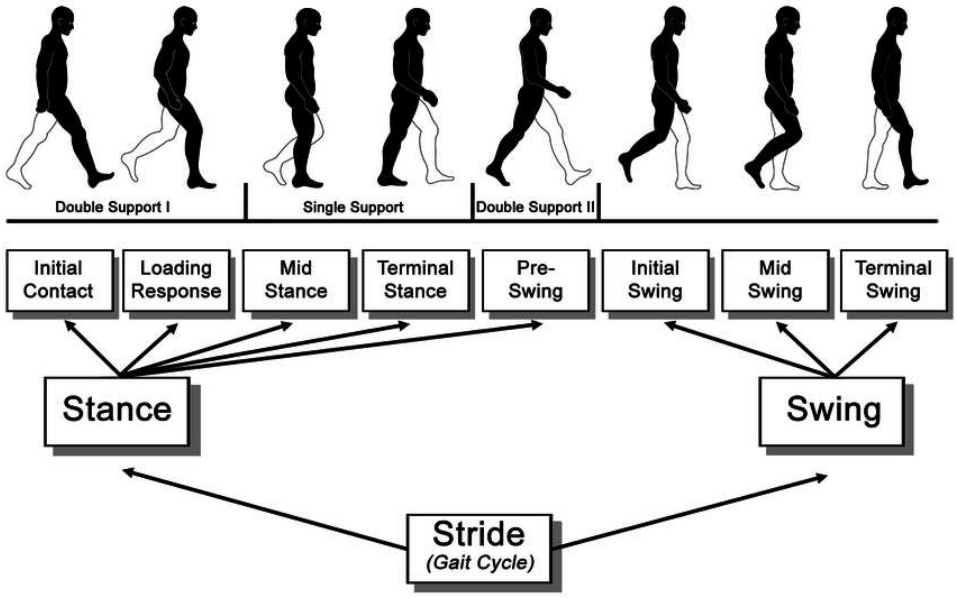


Fig. 1. Gait Cycle phases and sub-phases. the gait cycle is defined as the interval between two successive heel strikes of the same foot (step). It is also known as stride and consists of two phases: the stance phase and the swing phase which alternate for each leg. The stance phase includes the heel-to- toe contact sequence of the foot. The swing phase proceeds with the foot suspended in the air. On average stance phase accounts for 60% of the gait cycle, whereas the swing phase for 40%. Furthermore, each phase includes a sequence of Double Support (both feet are in contact with the ground) and Single Support (only one foot is in contact with the ground) sub-phases (sources: ("Gait Analysis" 2010; Cicirelli et al. 2022)).

The extracted spatio-temporal gait parameters included: Cycle Duration (s), the time for a full gait cycle; Stride Length (m), the distance between two successive placements of the same foot; Cycle Length (m), and its normalization by body height (Cycle Length [% height]), reflecting walking

efficiency; Step Length (m) and Step Length Variability, indicating step size and consistency; Stride Time (s), the duration of a complete gait cycle; Stance Duration (s) and Swing Duration (s), denoting the time spent in contact with the ground or in the air, respectively; Stance Phase (%), Swing Phase (%), Single Support Phase (%), and Double Support Phase (%), capturing relative proportions of each gait component; Step Width (m), the lateral distance between feet during walking; Swing Time Variability (%) and Stride Time Variability (%), reflecting gait stability and regularity; Velocity (m/s) and Velocity normalized to height (% height/s), representing walking speed; and Cadence (steps/min), the number of steps taken per minute.

Subjects were excluded from gait acquisition if they had clinically significant diseases including neurologic disorders other than parkinsonism, orthopedic diseases, cardiovascular/respiratory diseases.

Gait parameters were compared to those of age-matched PD and healthy controls (HC).

2.5. Statistical analysis

Normality of continuous variables was assessed using the Shapiro–Wilk test. For univariate analysis, comparisons between two groups of normally distributed continuous variables were performed using the Student's *t*-test, while one-way ANOVA was applied for comparisons among more than two groups. When the assumption of normality was not met, the Mann–Whitney *U* test was used instead. For variables showing significant differences, Bonferroni post hoc corrections were performed to identify pairwise group differences.

Associations between categorical variables were evaluated using the chi-square test. Correlation analyses were conducted with Spearman's rank correlation for non-normally distributed continuous variables, Pearson's correlation for normally distributed continuous variables, and Cramer's *V* for categorical variables.

For longitudinal data, a linear regression analysis was performed to evaluate the relative contribution of two dichotomous predictors—modification of neuroleptic treatment (yes/no) and disease status (BD+/BD-)—on the percentage change of the motor score (MDS-UPDRS

III) after treatment. The percentage change was computed as [(post treatment score – baseline score)/ baseline score x 100]. Both predictors were simultaneously entered into the model using the Enter method. The regression analysis provided estimates of unstandardized coefficients with their 95% confidence intervals, as well as model fit indices (R^2). Standardized beta coefficients were reported to allow direct comparison of the relative impact of each predictor on the outcome.

Multivariate statistical approaches, in terms of supervised machine learning-based statistical methods, were employed in order to test for possible variable interaction in class discrimination. For this purpose, the "diagnostic" label (i.e. ^{123}I-FP-CIT SPECT DaTSCAN results, which defined the class labels) was excluded from the set of predictors.

For multivariate analysis, we employed three machine learning approaches: Logistic Regression, Random Forest, and Partial Least Squares-Discriminant Analysis (PLS-DA). Logistic Regression models the probability of a binary outcome as a function of predictor variables through a logistic function (Hosmer Jr et al. 2013). Random forest is a supervised ensemble learning method based on the aggregation of multiple decision trees (Breiman 2001). SHAP (SHapley Additive exPlanations) values were depicted to explain model output by attributing each feature's contribution to the final prediction. PLS-DA, a supervised variant of partial least squares

regression, projects predictors into a lower-dimensional space that maximizes the separation between predefined groups (Boulesteix and Strimmer 2007). In the context of PLS-DA, variable importance in projection (VIP) scores were calculated to identify the predictors that contributed most strongly to class discrimination, with higher VIP values indicating greater relevance.

Additionally, a post-hoc analysis was conducted to examine the distribution of variables identified as relevant within each classification model. Their distributions were visualized using violin plots, which allowed for a detailed representation of both the probability density and variability across groups.

Spatio-temporal gait parameters were analyzed using generalized linear mixed models (GLMMs) to examine the effects of task (GAIT, MOT, COG), clinical condition (BD, PD, HC), and their interaction, accounting for within-subject correlations arising from repeated measures. When appropriate, post hoc comparisons were adjusted for multiple testing.

Within-group comparisons between experimental conditions were additionally performed using the Wilcoxon signed-rank test for paired samples, in order to assess task-related differences in spatio-temporal gait parameters within each clinical group.

The Dual Task Effect (DTE) was calculated to quantify the relative change in gait performance between the single-task and dual-task conditions. The calculation was performed separately for both the motor dual-task and the cognitive dual-task conditions. The DTE was calculated using the following formula:

$$DTE(\%) = \frac{Dual\ Task\ Performance - Single\ Task\ Performance}{Single\ Task\ Performance} \times 100$$

where *Dual Task* represents the value of the parameter measured during the dual-task condition and *Single Task* represents the value measured during the single-task condition.

To compare the DTE values across the three groups, a Kruskal–Wallis test was performed. When significant differences were observed, post hoc pairwise comparisons with Bonferroni correction were conducted to identify differences between groups.

The same statistical approach was subsequently applied in a subgroup analysis within the BD group, comparing patients with (DAT+) and without (DAT−) evidence of striatal dopaminergic denervation, in order to explore potential differences in gait features.

Statistical significance was set at $p < 0.05$.

3. Results

3.1. Demographic and clinical features of the studied BD cohort.

A total of 41 patients affected by bipolar disorder were recruited. Eight of them (19,5%) had abnormal SPECT DaTSCAN results and were classified as BD+. Demographic, clinical and pharmacological characteristics of our cohort are summarized in tables 3.1. and 3.2.:

Table 3.1. Demographic and clinical comparisons between BD patients with (BD+) and without (BD-) evidence of dopaminergic deficits. Normally distributed data are expressed as mean±standard deviation; not normally distributed data are expressed as median (interquartile range). [BD, bipolar disorder].

	BD+ (n=8)	BD-(n=33)	p-value
Age (years)	71.12±5.11	65.15±9.28	**0.02**
Sex (M/F)	4/4	27/6	0.06
Age at BD onset (years)	45.5±15.65	35.93±14.91	0.14
Disease duration (years)	25.62±11.57	29.21±16.08	0.48
Family history for psychiatric disorders (yes/no)	3/5	16/17	0.31
Family history for neurological disorders (yes/no)	4/4	12/21	0.47
BD type (type 1/type 2)	3/5	22/11	0.12
No. of depressive episodes	3 (7)	3 (11)	0.57
No. of mania-hypomania episodes	3 (7)	3 (10)	0.29

Table 3.2. Pharmacological and clinical comparisons between BD patients with (BD+) and without (BD-) evidence of dopaminergic deficits. Normally distributed data are expressed as mean±standard deviation; not normally distributed data are expressed as median (interquartile range) [BD, bipolar disorder; CED, chlorpromazine equivalent dose; CPZ, chlorpromazine; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin–norepinephrine reuptake inhibitors; MDS–UPDRS, Movement Disorder Society–Unified Parkinson's Disease Rating Scale; RBD, REM sleep behavior disorder; UPSIT, University of Pennsylvania Smell Identification Test].

	BD+ (n=8)	BD-(n=33)	p-value
Lithium (yes/no)	4/4	22/11	0.38
Lithium dose/year	4 (12.39)	1.38 (4)	1.00
Antipsychotic drugs (yes/no)	5/3	19/14	0.8
Current CED (mg/day)	50 (125)	37.5 (200)	0.64
CPZ dose/year	200 (2522)	56.38 (198.96)	0.55
Exposure to valproate (yes/no)	6/2	21/12	0.54
Exposure to SSRI/SNRI drugs (yes/no)	6/2	18/15	0.29
MDS-UPDRSIII total score	27.65±11.24	21.57±10.29	0.15
Motor symptom duration (months)	30 (36)	24 (24)	0.68
Clinical asymmetry index	0.23 (0.22)	0.14 (0.20)	0.40
RBD score	5 (4)	3 (3)	0.32
Patients with RBD score >8 (yes/no)	1/7	3/30	0.77
Referred Hyposmia	4/4	6/27	0.06
UPSIT score	21 (12)	19 (12)	1.00

The two populations significantly differed in terms of age at evaluation, with BD+ population significantly older than BD- population. However, they were homogeneous in terms of age at BD onset and disease duration. The two classes were uniform for all other demographic, clinical and pharmacological characteristics, except for a trend in referred hyposmia (more frequent in the BD+ population), and in sex distribution (the BD- class being mostly represented by men).

Spearman's rank correlation, Pearson's correlation, and Cramer's V were employed to evaluate potential associations among the variables; nevertheless, none of these analyses indicated statistically significant relationships.

3.2. Smell identification performances of BD patients compared to Parkinson's Disease and Healthy Controls

UPSIT scores of a subgroup of 31 BD patients were compared to those obtained by an age-matched population of subjects affected by PD and healthy controls (Picillo et al. 2014a).

Study population was composed of 31 euthymic BD patients, 30 PD patients, 28 Healthy Subjects. Populations were homogeneous in terms of

age and ever smoking status. Moreover, PD and BD population were homogeneous in terms of motor burden. Coherently with disease-specific age prevalence (Pagano et al. 2016; BALDESSARINI et al. 2012), disease duration was longer in the BD population compared to the PD population (see Table 3.3).

	HS (N= 28)	**BD (N=31)**	**PD (N=30)**	**P Value**
Age as mean ± sd	65,03 ± 7,57	66,74 ±7,68	66,56 ±7,95	0,65
SEX (M/F)	14/14	24/7	16/14	0,059
Smoking status (yes/no)	5/23	12/19	7/23	0,169
MDS-UPDRSIII score as mean ± sd		23,19 ± 11,10	19,98 ± 8,98	0,21
Disease duration in years as median (IQR)		24 (39,5-15)	4,5 (6,25-3)	<0,01

Table 3.3. Demographic and clinical characteristics of the three studied classes. Abbreviations. HS: Healthy Subjects; BD: Bipolar Disorder; PD: Parkinson's Disease; sd: standard deviation; IQR: interquartile range.

Table 3.4 shows mean UPSIT scores for the three studied population. Difference was statistically significant among the three classes (as reported by one-way ANOVA and post hoc t-tests), with the Bipolar population scoring intermediately between PD and HS.

	UPSIT scores as mean (CI 95%)	**P value (post-hoc T-test)**
HS	25,64 (27,64-23,64)*	<0,01
BD	19,77 (21,74-17,81) *	0,014
PD	16,00 (17,75-14,25) *	

Table 3.4. Mean total UPSIT scores in the 3 classes. * represents a statistically significant difference (p<0,05) as calculated with one-way ANOVA. The right column shows the results of post-hoc T-test with Bonferroni correction. Abbreviations. CI: confidence interval

3.3. Multivariate statistical approaches

3.3.1 Partial Least Square-Discriminant Analysis (PLS-DA)

The PLS-DA model shows partial group separation, but with significant overlap (fig.2). Permutation test did not reach significativity (p≈0.67) (fig.3).

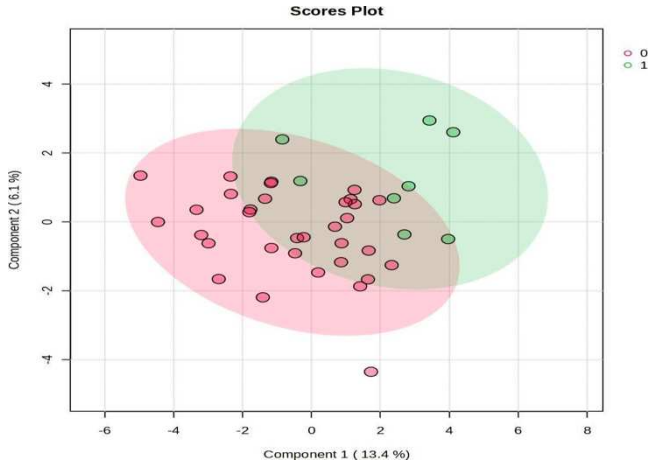


Fig.2: PLS-DA-based scores plot showing partial group separation.

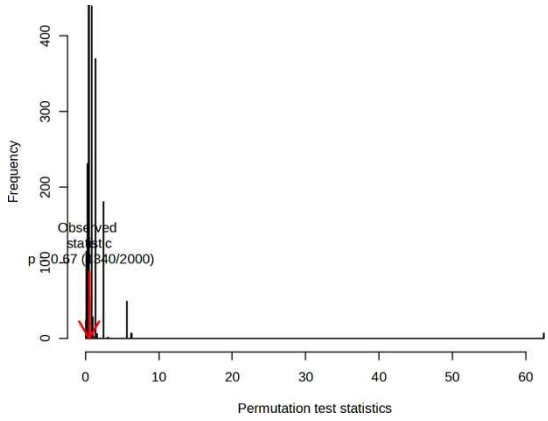


Fig.3. PLS-DA-based permutation test.

Referred hyposmia, sex, the “gait” sub-item of the MDS-UPDRSIII score and age had the highest VIP score (>1.5) and, thus, were selected as the main variables for class discrimination.

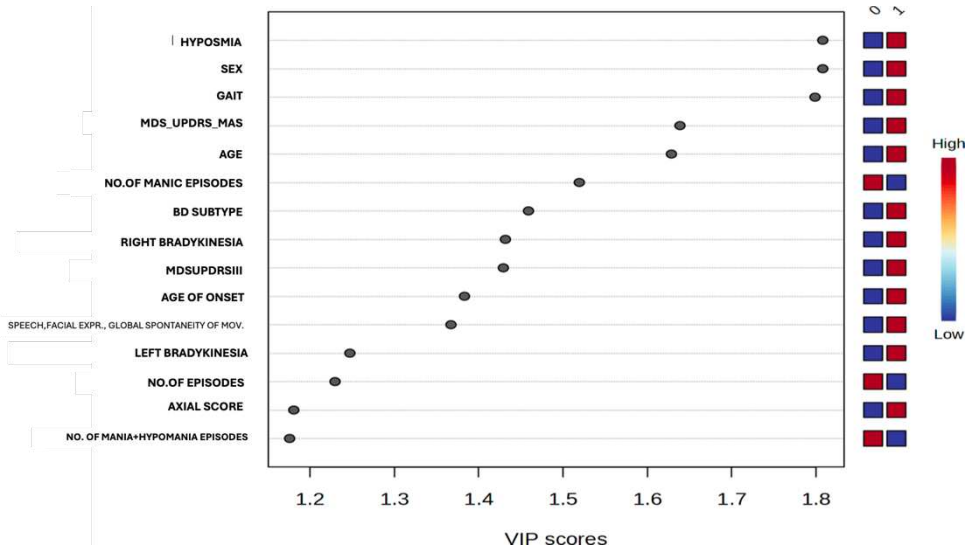


Fig. 4. VIP graph showing the main features in class (BD+ vs. BD-) discrimination. Abbreviations: VIP, Variable importance in projection; MAS, most affected side.

3.3.2 Random Forest

As shown in figure 5, the Random Forest algorithm showed a good performance into classifying BD- patients, but a scarce performance into correctly classifying BD+ patients.

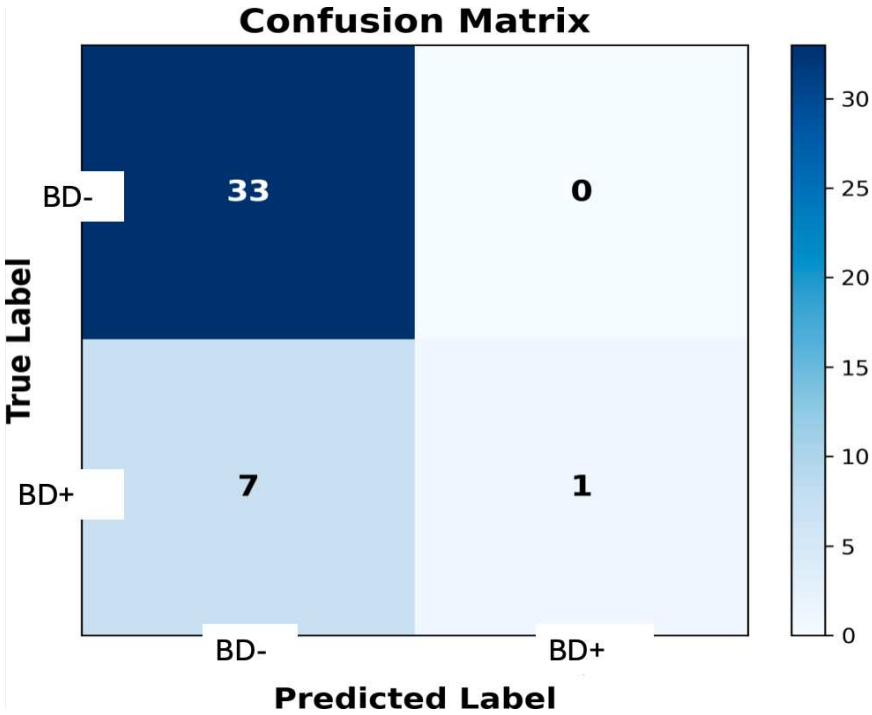


Fig 5: Confusion Matrix showing Random Forest Model performance in class (BD- vs BD+ classification).

However, the model identified no. of episodes, CED and RBD score as the main features in class discrimination (fig. 6).

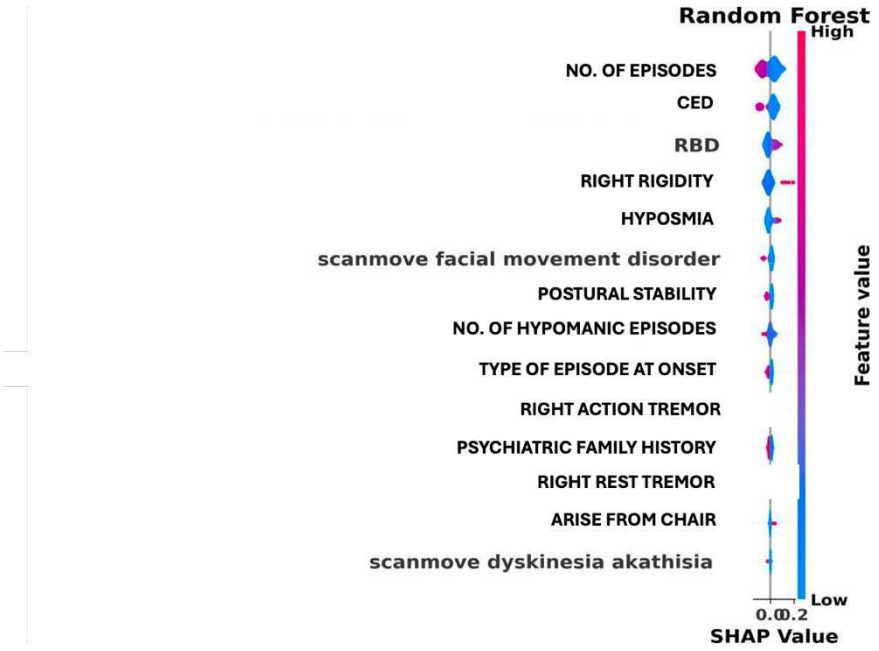


Fig.6. SHAP (SHapley Additive exPlanations) violin plots showing variables with the greatest impact in class discrimination.

3.3.3 Logistic Regression

Like the Random Forest Model, the Logistic Regression Model showed good performance into classifying BD- patients, but worst performance into correctly classifying BD+ patients (see fig.7).

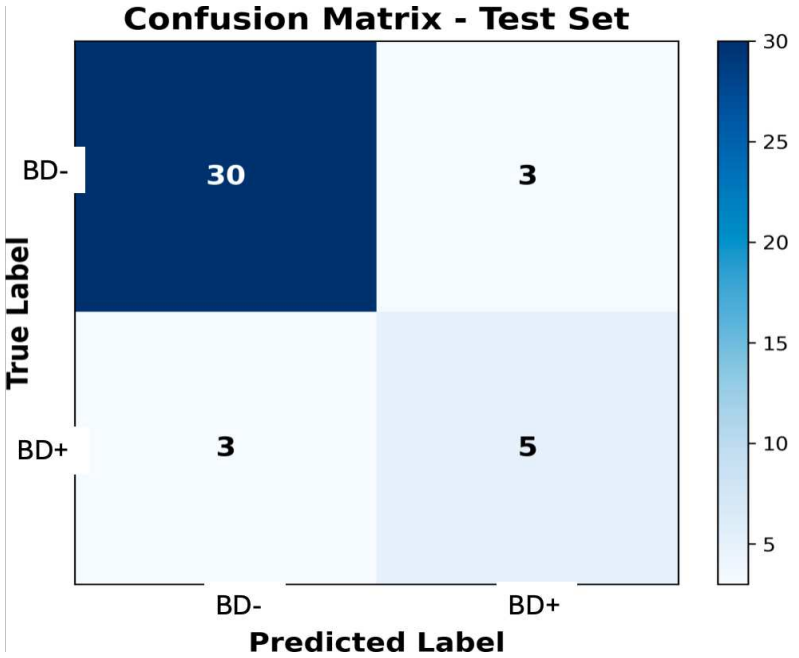


Fig 7. Confusion Matrix showing Logistic Regression Model performance in class (BD- vs BD+ classification).

However, the model identified left action tremor, age, sex, psychiatric family history and postural stability as the main features in class discrimination (fig. 8).

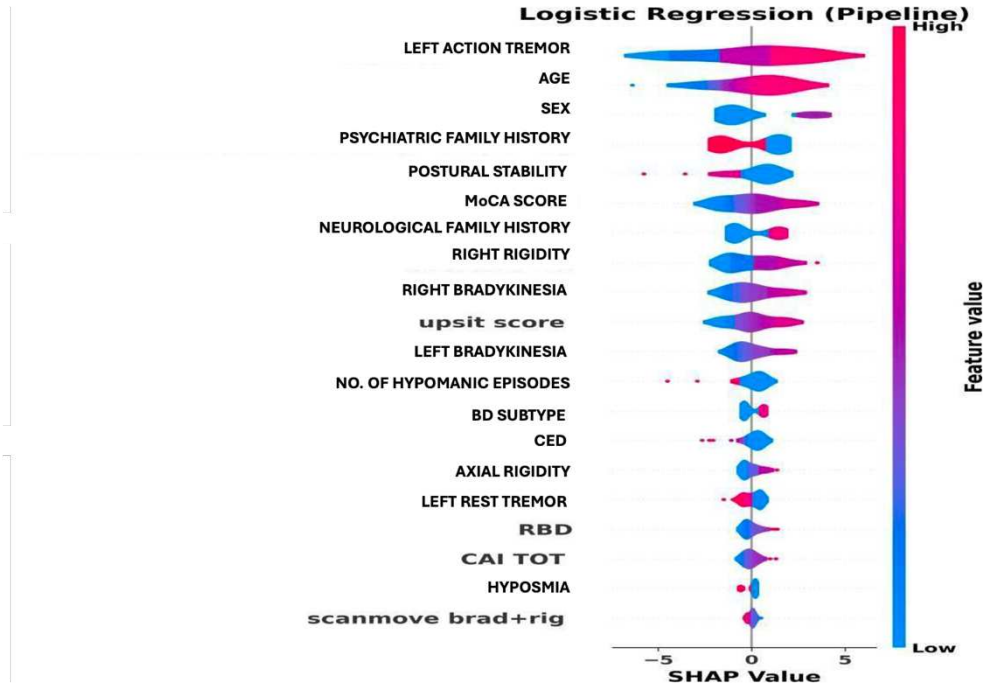


Fig.8. SHAP (SHapley Additive exPlanations) violin plots showing variables with the greatest impact in class discrimination.

3.3.4. Post-hoc evaluations

Overall, machine learning-based class discrimination, performed with the PLS-DA, Random Forest and Logistic Regression algorithms, did not reach statistical significance. However, we studied the distribution of the variables which emerged as the most interesting in class discrimination, such as referred hyposmia, the gait sub-item of the MDS-UPDRSIII scale, left action tremor, the RBD score, the total number of episodes and the antipsychotic burden in terms of chlorpromazine equivalents, comparing them between the two classes of interest. As shown in figure 9, there is a trend in worst gait scores and more frequently referred hyposmia in the BD+ class, compared to BD- class, as well as a slightly higher percentage of patients with worse RBD scores. Left action tremor showed a trend for higher scores in the BD- class.

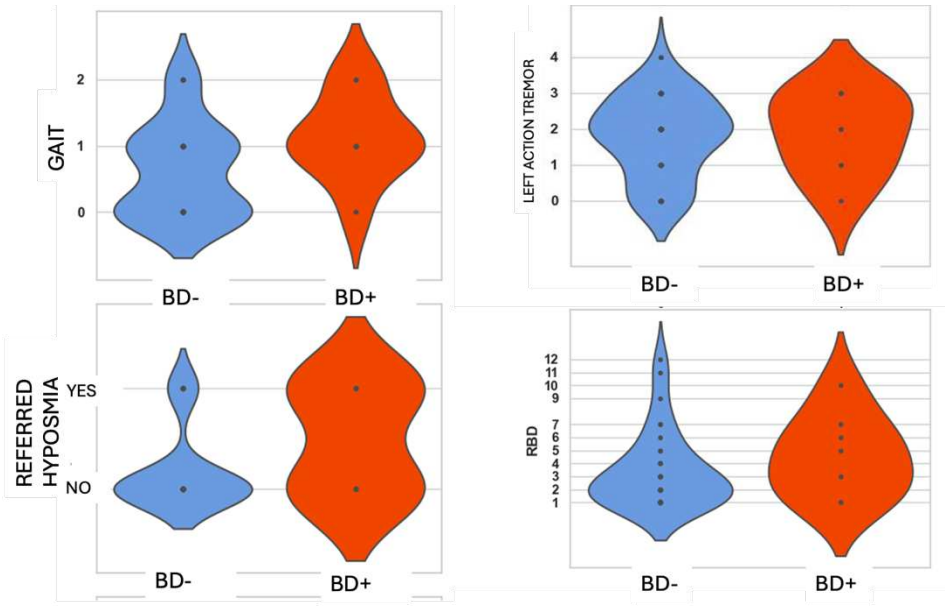


Fig.9. Violin plots showing feature (referred hyposmia, the gait sub-item of the MDS-UPDRSIII scale, left action tremor, the RBD score) distribution in the two studied classes.

Moreover, the BD- class tended to report a higher number of episodes and higher doses of antipsychotics (Fig.10).

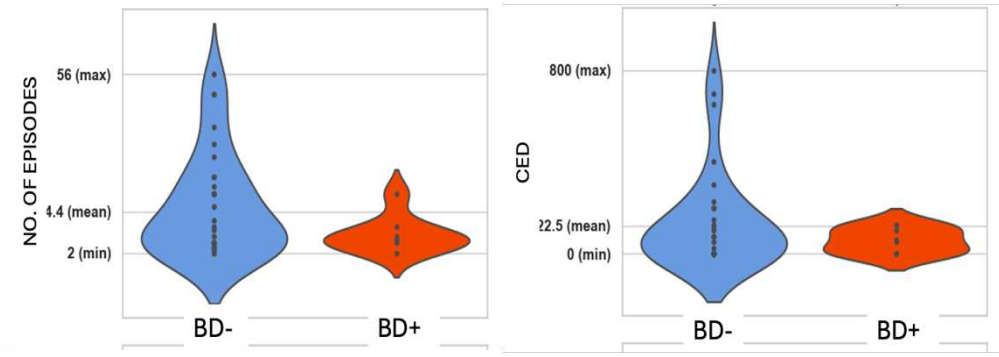


Fig.10. Violin plots showing feature (the total number of episodes and the antipsychotic burden in terms of chlorpromazine equivalents) distribution in the two studied classes. Abbreviations: CED, chlorpromazine equivalent dose.

3.4. Dopaminergic drug response in longitudinal assessment

Longitudinal (performed 1 to 6 months after) motor (MDSUPDRSIII) evaluation after the introduction of levodopa (max 300 mg/die) or selegiline (max 10 mg/die) in patients previously dopaminergic drug naïve is available for 8 patients (4 BD+, 4 BD-). Three patients had had changes in psychiatric therapy between baseline and follow-up motor assessments.

Figure 11 shows percentage changes in MDSUPDRSIII score between basal and follow up evaluation.

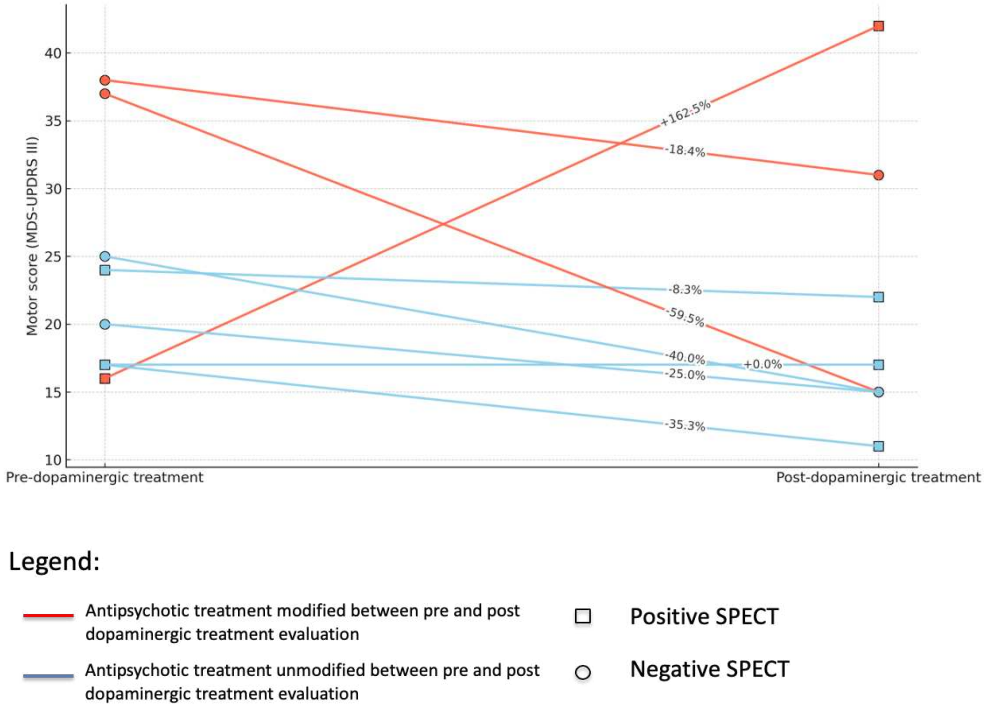


Fig.11. Spaghetti plot depicting MDSUPDRSIII score variation in 8 patients from basal (left) to first follow up (right) evaluation.

The regression model explained approximately 52% of the variance in the percentage change of motor scores ($R^2 = 0.52$). Neither variable reached statistical significance, likely due to the limited sample size. However, both predictors showed positive associations with the outcome. Modification of neuroleptic treatment was associated with an estimated 72% higher change in motor scores, while disease status (BD+ vs. BD-) showed an estimated 83% higher change. Although not statistically significant, the standardized coefficients suggested that disease status exerted a slightly greater relative impact on the percentage change compared to neuroleptic modification.

3.5. Gait analysis study: gait features in BD patients, compared to PD patients and healthy controls

Gait study population included a total sample of 80 participants, divided into three groups: 27 patients affected by BD, 27 patients affected by PD, and 26 HC. In addition, a subgroup analysis was conducted within the BD group, comparing 8 patients with evidence of striatal dopaminergic denervation (DAT+) and 8 without (DAT−), alongside further characterization of gait features in the PD group.

In the first comparison (Table 3.5) among patients with BD (n=27), PD (n=27), and HC (n=26), motor symptom duration was significantly shorter in the BD group compared with PD (BD: 2.33 ± 2.32 years; PD: 3.68 ± 2.10 years; p=0.029). Cognitive performance assessed with the MoCA was significantly lower in BD patients compared with PD (BD: 17.87 ± 3.86; PD: 21.52 ± 4.09; p=0.002). Motor severity, measured with the MDS-UPDRS III, age and sex did not differ significantly among groups.

Clinical demographic Variables	**BD (n=27)**	**PD (n=27)**	**HC (n=26)**	**p**
Age (years)	67,70 ± 7,27	66,89 ± 4,58	65,04 ± 7,48	0.260
Sex	M=19 F=8	M=19 F=8	M=13 F=13	0.207
Motor Disease duration (years)	2,33 ± 2,32	3,68 ± 2,10	-	**0.029**
MoCA	17,87 ± 3,86	21,52 ± 4,09	-	**0.002**
MDS-UPDRS III score	24,07 ± 11,27	25,26 ± 9,54	-	0.372

Table 3.5. Comparison on demographic and clinical characteristics among patients with BD, PD, and HC. Data are expressed as mean ± SD or frequencies, as appropriate. Statistical significance was set at 0.05, and significant results are shown in bold.

In the subgroup analysis (Table 3.6) including BD patients with abnormal DAT-SPECT (BD+), BD patients with normal DAT-SPECT (BD−), and PD

patients. No significant differences were observed in age, gender, motor disease duration, MoCA, MDS-UPDRS III and drug exposure between groups.

Clinical demographic Variables	**BD+ (n=8)**	**BD- (n=8)**	**PD (n=8)**	**p**
Age (years)	71,12 ± 5,11	68,38 ± 3,85	68,00 ± 3,35	0.235
Sex	M=4 F=4	M=5 F=3	M=6 F=2	0.587
BD duration (years)	25,62 ± 11,57	28,42 ± 17,72		0.686
Motor symptom duration (years)	2,18 ± 1,36	1,60 ±0,73	2,87 ± 1,12	0.098
MoCA	19,21 ± 5,20	18,04 ± 2,64	20,70 ± 3,06	0.329
MDS-UPDRS III score	27,63 ± 11,25	25,88 ± 13,40	28,00 ± 13,84	0.859
Lithium exposure	Yes=4 No=4	Yes=5 No=3		0.61
Lithium dose/year	2 (12.13)	1.03 (3.76)		0.721
Antipsychotic drug exposure	Yes=5 No=3	Yes=3 No=5		0.317
Clorpromazine equivalent daily dose (mg/day)	55 (119)	0 (563)		1.00
Clorpromazine dose/year	160 (2096)	14.58 (78.13)		0.234
Exposure to valproate	Yes=6 No=2	Yes=7 No=1		0.52
Exposure to SSRI/SNRI drugs	Yes=6 No=2	Yes=4 No=4		0.302

Table 3.6. Comparison on demographic and clinical characteristics between BD+, BD- and PD patients. Data are expressed as mean ± SD, median (interquartile range) or frequencies, as appropriate, Statistical significance was set at 0.05.

The results of the first analysis between BD, PD, and HC are summarized in Table 3.7.

Regarding the spatio-temporal gait parameters, significant group differences were found for cycle duration ($p < 0,001$). Post-hoc comparisons revealed that BD patients exhibited a significantly longer cycle duration than PD patients ($p = 0,018$) and HC ($p = 0,015$). This was accompanied by a reduced cycle length, both in absolute (m) terms and normalized to height (%) ($p=0.035$, and $p< 0.001$, respectively), as well as a reduced step length ($p<0.001$), with BD patients differing significantly from both PD patients and HC (as shown by the post-hoc analysis).

Furthermore, BD patients showed a longer stance duration compared with PD ($p = 0,009$) and HC ($p = 0,006$), reflected in an increased stance phase (%) and, consequently, reduced swing phase (%) and single support phase (%) compared with both groups (all $p < 0,001$).

These alterations were accompanied by an increased double support phase (compared with PD: $p < 0,001$; with HC: $p = 0,009$), reduced gait

velocity (both in absolute terms and normalized to height), as well as shorter cycle and step lengths (all $p < 0,001$).

In addition, the three groups showed a significant difference also in gait cadence ($p= 0.009$), with BD patients demonstrated a lower cadence compared with PD ($p = 0,016$) and HC ($p=0.015$).

No significant group differences were observed for swing duration or swing variability ($p > 0,05$).

Regarding the effect of task, significant differences were observed between the single-task and dual-task conditions across several spatio-temporal gait parameters. Notably, the parameters that showed significant between-group differences were also significantly affected within each group when comparing task conditions.

These task-related differences were predominantly observed in the two pathological groups (BD and PD), highlighting a substantial modulation of gait performance not only between single- and dual-task conditions, but also between the motor and cognitive dual-task paradigms. In detail, temporal gait parameters such as cycle duration, stance duration, and swing duration decreased during the motor dual-task condition, whereas they increased during the cognitive dual-task condition across all three groups (all $p<0.001$).

Regarding spatial parameters, including cycle length (m) and step length (m), a reduction was observed in both motor and cognitive dual-task conditions in all groups (all $p < 0.001$).

Spatio-temporal parameters such as gait velocity (m/s) decreased under both dual-task conditions ($p < 0.001$), while for the cadence (steps/min) an increased trend was showed during motor dual-task and decrease trend during cognitive dual-task in all three groups ($p=0.009$). Finally, swing duration (s) showed a significant effect of task across all three groups ($p < 0.001$). As reported in Table 3.7, most of these comparisons reached statistical significance ($p < 0.005$).

However, no significant task-related differences were observed for step length (%) and swing variability (%), or step width (m).

Finally, regarding the group × task interaction, statistically significant effects were observed for cycle duration (s), stance duration (s), and swing duration (s). Consequently, DTE analyses were performed only for these variables. PD patients showed a significantly lower cognitive DTE in cycle duration compared with both BD and HC ($p = 0.037$ and $p = 0.048$, respectively). Although cycle duration increased during the cognitive dual-task condition, this increase was smaller in PD than in BD and HC, indicating that BD tended to increase cycle duration during cognitive dual-tasking more than PD. A similar pattern was observed for stance duration,

with PD patients showing a significantly lower cognitive DTE compared with BD and HC ($p = 0.029$ and $p = 0.049$, respectively). While stance duration increased during the cognitive dual-task condition, the increase was smaller in PD than in the other groups, suggesting a greater stance duration increase in BD during cognitive dual-tasking. For swing duration, PD patients showed a significantly negative cognitive DTE compared with both BD and HC ($p = 0.009$ and $p < 0.001$, respectively). In contrast to BD and HC, who exhibited an increase in swing duration during the cognitive dual-task condition, PD patients showed a slight reduction in the swing phase.

The results of the sub-analysis are summarized in Table 3.8. Regarding the spatio-temporal gait parameters, significant group differences were observed for cycle duration and cycle length, stance duration and phase, swing phase, single and double support phase and velocity ($p < 0,05$). Post-hoc comparisons indicated that BD+ patients exhibited a significant difference with the PD group. In particular, BD+ showed longer cycle duration and length compared with PD patients ($p < 0,001$, $p = 0,012$, respectively). Moreover, BD+ patients demonstrated a longer stance duration than PD patients ($p < 0,001$), reflected in an increased stance phase (%) and, consequently, a reduced swing phase in BD+ patients

compared with PD (all $p < 0,001$). These gait alterations were accompanied by an increased double support phase (compared with PD, $p = 0,025$), reduced gait velocity (both in absolute terms ($p = 0,007$) and normalized to height ($p = 0,002$)), as well as shorter step length (all $p < 0,001$). No significant effects were found for task conditions or for the interaction between group and task.

Spatio-temporal Parameters (u.m.)	Group	Task			Group		Task		Group * Task
		GAIT	MOT	COG	p-value	Post -hoc	p-value	Post-hoc	p-value
Cycle duration (s)	**BD** **PD** **HC**	1,25 ± 0,20 1,14 ± 0,14 1,16 ± 0,11	1,22 ± 0,18 1,12 ± 0,13 1,09 ± 0,08	1,38 ± 0,24 1,21 ± 0,17 1,23 ± 0,13	**0.001**	**0.018 (BD-PD)** **0.015 (BD-HC)**	**<0.001**	BD: 0.004 (GAIT-MOT); < 0.001 (GAIT-COG. MOT-COG) PD: 0.009 (GAIT-MOT); 0.014 (GAIT-COG); < 0.001 (MOT-COG) HC: < 0.001 (GAIT-COG. MOT -COG)	**0.007**
Stance duration (s)	**BD** **PD** **HC**	0,80 ± 0,16 0,69 ± 0,10 0,68 ± 0,09	0,78 ± 0,14 0,68 ± 0,10 0,66 ± 0,07	0,91 ± 0,20 0,76 ± 0,13 0,76 ± 0,09	**<0.001**	**0.009 (BD-PD)** **0.006 (BD-HC)**	**<0.001**	BD: <0.001 (GAIT-COG; MOT-COG) PD: 0.007 (GAIT-COG); <0.001 (MOT-COG) HC: <0.001 (GAIT-COG; MOT-COG)	**0.014**
Swing duration (s)	**BD** **PD** **HC**	0,45 ± 0,05 0,45 ± 0,05 0,44 ± 0,03	0,44 ± 0,05 0,43 ± 0,04 0,44 ± 0,03	0,47 ± 0,05 0,45 ± 0,05 0,47 ± 0,04	0.294	-	**<0.001**	BD: 0.013 (GAIT-MOT); 0.001 (GAIT-COG; MOT-COG) PD: < 0.001 (GAIT-MOT; GAIT-COG; MOT-COG) HC:<0.001 (GAIT-COG; MOT-COG)	**0.019**
Swing variability	**BD** **PD** **HC**	0,04 ± 0,06 0,03 ± 0,02 0,04 ± 0,02	0,04 ± 0,02 0,04 ± 0,08 0,03 ± 0,02	0,04 ± 0,02 0,03 ± 0,02 0,04 ± 0,02	0.269	-	0.339	-	0.396
Stance phase (%)	**BD** **PD** **HC**	63,52 ± 2,99 60,76 ± 1,76 60,36 ± 1,84	64,00 ± 3,12 61,31 ± 1,98 60,28 ± 1,96	65,37 ±3,15 62,45 ±2,27 61,53 ±1,66	**<0.001**	**< 0.001 (BD-PD;BD-HC)**	**<0.001**	BD:<0.001 (GAIT-COG); 0.006 (MOT-COG) PD: 0.025 (GAIT-MOT); 0.004 (GAIT-COG); 0.029 (MOT-COG) HC: <0.001 (GAIT-COG; MOT-COG)	0.429
Swing phase (%)	**BD** **PD** **HC**	36,34 ± 2,94 39,24 ± 1,76 39,82 ± 1,65	36,44 ± 2,84 38,69 ± 1,98 39,72 ± 1,96	34,71 ±3,27 37,69 ±2,18 38,48 ±1,68	**<0.001**	**< 0.001 (BD-PD;BD-HC)**	**<0.001**	BD: <0.001(GAIT-COG; MOT-COG) PD: 0.025 (GAIT-MOT); <0.001(GAIT-COG); 0.014 (MOT-COG) HC: <0.001(GAIT-COG; MOT-COG)	0.230
Single support phase (%)	**BD** **PD** **HC**	36,34 ± 2,94 39,27 ± 1,78 39,85 ± 1,68	36,45 ± 2,84 38,67 ± 1,96 39,73 ± 1,96	34,73 ±3,28 37,70 ±2,18 38,48 ±1,68	**<0.001**	**< 0.001 (BD-PD;BD-HC)**	**<0.001**	BD: < 0.001 (GAIT-COG; MOT-COG) PD: 0.012 (GAIT-MOT); < 0.001 (GAIT-COG); 0.006 (MOT-COG) HC: <0.001 (GAIT-COG; MOT-COG)	0.528

Double support phase (%)	**BD** **PD** **HC**	13,61 ± 2,93 10,76 ± 1,99 10,26 ± 1,69	14,40 ± 3,27 11,34 ± 2,05 10,34 ± 1,98	15,19 ±2,96 12,29 ±2,10 12,23 ±3,17	**<0.001**	**< 0.001 (BD-PD)** **= 0.009 (BD-HC)**	**<0.001**	BD: 0.027 (GAIT-MOT); < 0.001 (GAIT-COG); 0.020 (MOT-COG) PD:0.022 (GAIT-MOT); 0.008 (GAIT-COG) HC: < 0.001 (GAIT-COG); < 0.001 (MOT-COG)	0.168
Velocity (m/s)	**BD** **PD** **HC**	0,72 ± 0,23 0,95 ± 0,19 1,08 ± 0,13	0,68 ± 0,22 0,93 ± 0,20 1,04 ± 0,14	0,60 ± 0,19 0,81 ± 0,23 1,00 ± 0.20	**< 0.001**	**< 0.001 (BD-PD;BD-HC)**	**< 0.001**	BD: 0.025 (GAIT-MOT); < 0.001 (GAIT-COG; MOT-COG) PD: 0.001(GAIT-COG); 0.003 (MOT-COG) HC:<0.001(GAIT-COG; MOT-COG)	0.388
Velocity (% height/s)	**BD** **PD** **HC**	43,91 ± 12,35 58,08 ± 11,37 64,75 ± 8,30	41,40 ± 12,07 56,16 ± 11,46 63,27 ± 7,83	36,55±10,95 49,08±13,75 62,65 ± 9,13	**<0.001**	**<0.001 (BD-PD;BD-HC)**	**<0.001**	BD: 0.003(GAIT-MOT); < 0.001 (GAIT-COG); 0.001 (MOT-COG) PD: 0.020 (GAIT-MOT); < 0.001(GAIT-COG); 0.002 (MOT-COG) HC: < 0.001 (GAIT-COG; MOT-COG)	0.314
Cadence (steps/min)	**BD** **PD** **HC**	98,17 ± 14,64 107,53 ± 12,98 109,77 ± 8,99	100,26±13,75 108,63±12,29 110,71 ± 8,48	90,02±15,04 101,03±14,82 104.54±11,73	**0.009**	**0.016 (BD-PD)** **0.015 (BD-HC)**	**<0.001**	BD: 0.012 (GAIT-MOT); < 0.001 (GAIT-COG; MOT-COG) PD: 0.009 (GAIT-MOT); 0.003(GAIT-COG); < 0.001 (MOT-COG) HC: < 0.001 (GAIT-COG)	0.889
Cycle length (m)	**BD** **PD** **HC**	0,88 ± 0,19 1,08 ± 0,15 1,18 ± 0,07	0,81 ± 0,19 1,03 ± 0,18 1,13 ± 0,10	0,79 ± 0,17 0,96 ± 0,21 1,08 ± 0,10	**0.035**	**0.022 (BD-PD)** **0.014 (BD-HC)**	**0.022**	BD: < 0.001 (GAIT-MOT; GAIT-COG) PD: < 0.001 (GAIT-MOT; GAIT-COG; MOT-COG) HC: < 0.001 (GAIT-MOT; GAIT-COG; MOT-COG)	0.403
Cycle length (% height)	**BD** **PD** **HC**	53,02 ± 10,13 65,48 ± 8,78 70,85 ± 4,44	49,08 ± 10,84 61,93 ± 10,11 68,50 ± 4,49	47,80 ± 9,77 58,01 ± 12,16 64,92 ± 4,74	**<0.001**	**<0.001 (BD-PD; BD-HC)** **0.018 (PD-HC)**	**0.001**	BD: < 0.001 (GAIT-MOT; GAIT-COG) PD: < 0.001 (GAIT-MOT; GAIT-COG; MOT-COG) HC: < 0.001 (GAIT-MOT; GAIT-COG; MOT-COG)	0.120
Step length variability	**BD** **PD** **HC**	0,17 ± 0,37 0,07 ± 0,19 0,08 ± 0,30	0,16 ± 0,27 0,06 ± 0,18 0,07 ± 0,02	0,18 ± 0,39 0,07 ± 0,11 0,06 ± 0,05	**<0.001**	**<0.001 (BD-PD)** **<0.001 (PD-HC)**	0.334	-	0.261
Step width (m)	**BD** **PD** **HC**	0,13 ± 0,08 0,08 ± 0,04 0,25 ± 0,14	0,13 ± 0,07 0,09 ± 0,08 0,20 ± 0,11	0,12 ± 0,06 0,08 ± 0,05 0,22 ± 0,11	**<0.001**	0.070 (BD-PD) **<0.001 (BD-HC)** **<0.001 (PD-HC)**	0.268	-	0.512

Table 3.7. Comparison on spatio-temporal characteristics among patients with BD, PD, and HC. Data are expressed as mean ± standard deviation. Statistical significance was set at 0.05, and significant results are shown in bold. Abbreviation: BD: Bipolar Disorder; PD: Parkinson's Disease; HC: Healthy Control; GAIT: Single Walking Task; MOT: Motor Dual-Task; COG: Cognitive Dual- Task.

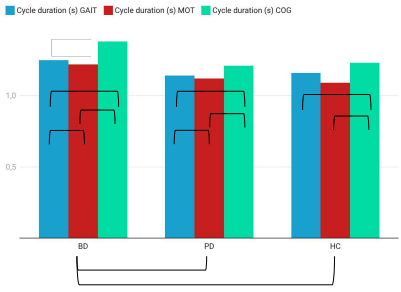
Spatio-temporal Parameters	Group	Task			Group		Task	Group * Task
		1 GAIT	2 MOT	3 COG		Post -hoc		
Cycle duration (s)	**1.BD +** **2.BD -** **3.PD**	1,34 ± 0,27 1,21 ± 0,19 1,12 ± 0,17	1,29 ± 0,23 1,18 ± 0,19 1,09 ± 0,11	1,48 ± 0,29 1,31 ± 0,23 1,16 ± 0,27	**0.042**	**< 0.001 (1-3)**	0.221	0.281
Stance duration (s)	**1.BD +** **2.BD -** **3.PD**	0,87 ± 0,19 0,78 ± 0,17 0,69 ± 0,12	0,84 ± 0,17 0,76 ± 0,13 0,67 ± 0,07	1,00 ± 0,25 0,86 ± 0,20 0,74 ± 0,18	**0.003**	**< 0.001 (1-3)**	0.156	0.913
Swing duration (s)	**1.BD +** **2.BD -** **3.PD**	0,47 ± 0,07 0,43 ± 0,03 0,44 ± 0,06	0,46 ± 0,07 0,42 ± 0,03 0,42 ± 0,16	0,48 ± 0,07 0,45 ± 0,03 0,44 ± 0,15	0.095	-	0.842	0.740
Swing variability	**1.BD +** **2.BD -** **3.PD**	0,06 ± 0,10 0,04 ± 0,01 0,04 ± 0,01	0,04 ± 0,02 0,04 ± 0,01 0,09 ± 0,16	0,03 ± 0,01 0,04 ± 0,02 0,03 ± 0,05	0.369	-	0.550	0.352
Stance phase (%)	**1.BD +** **2.BD -** **3.PD**	64,71 ± 1,81 63,40 ± 4,24 61,24 ± 2,46	64,36 ± 2,34 63,64 ± 3,98 61,40 ± 2,35	66,68 ± 3,91 65,71 ± 3,59 62,61 ± 2,05	**0.004**	**< 0.001 (1-3)**	0.849	0.872
Swing phase (%)	**1.BD +** **2.BD -** **3.PD**	35,28 ± 1,81 36,60 ± 4,25 38,76 ± 2,46	35,64 ± 2,33 36,35 ± 3,98 38,59 ± 2,34	33,32 ± 3,91 35,09 ± 3,60 37,90 ± 3,07	**0.040**	**< 0.001 (1-3)**	0.184	0.989
Single support phase (%)	**1.BD +** **2.BD -** **3.PD**	35,29 ± 1,82 36,60 ± 4,26 38,76 ± 2,47	35,64 ± 2,33 36,35 ± 3,99 38,59 ± 2,32	33,32 ± 3,92 35,10 ± 3,92 37,90 ± 3,94	**0.042**	**< 0.001 (1-3)**	0.115	0.868
Double support phase (%)	**1.BD +** **2.BD -** **3.PD**	14,77 ± 1,92 13,37 ± 4,22 11,58 ± 2,40	15,94 ± 2,69 13,61 ± 4,00 11,62 ± 3,37	16,54 ± 3,25 14,91 ± 3,42 12,07 ± 5,18	**0.028**	**0.025 (1-3)**	0.428	0.867

Velocity (m/s)	**1.BD +** **2.BD -** **3.PD**	0,58 ± 0,20 0,77 ± 0,25 0,93 ± 0,17	0,55 ± 0,17 0,73 ± 0,27 0,93 ± 0,13	0,50 ± 0,16 0,65 ± 0,22 0,86 ± 0,22	**0.003**	**0.007 (1-3)**	0.548	0.746
Velocity (% height/s)	**1.BD +** **2.BD -** **3.PD**	35,64 ± 8,95 48,70 ± 15,83 58,07 ± 9,88	32,76 ± 9,07 46,62 ± 15,41 57,72 ± 9,60	30,23 ± 9,00 40,72 ± 13,45 53,61 ± 27,90	**0.009**	**0.002 (1-3)**	0.506	0.998
Cadence (steps/min)	**1.BD +** **2.BD -** **3.PD**	92,38 ± 17,29 102,04 ± 15,45 107,93 ± 14,42	95,04 ± 14,96 103,40 ± 15,30 110,64 ± 10,36	84,62 ± 16,15 95,04 ± 14,74 104,40 ± 38,44	0.090	-	0.074	0.961
Cycle length (m)	**1.BD +** **2.BD -** **3.PD**	0,77 ± 0,12 0,88 ± 0,21 1,04 ± 0,13	0,68 ± 0,15 0,84 ± 0,20 1,01± 0,14	0,70 ± 0,16 0,80 ± 0,17 0,99 ± 0,17	**0.014**	**0.012 (1-3)**	0.260	0.726
Cycle length (% height)	**1.BD +** **2.BD -** **3.PD**	46,01 ± 5,88 56,07 ± 12,70 64,31 ± 8,70	41,09 ± 8,60 53,13 ± 12,55 62,31 ± 9,27	41,85 ± 8,81 50,65 ± 9,74 61,14 ± 11,53	**0.012**	**< 0.001 (1-3)**	0.103	0.524
Step length (m)	**1.BD +** **2.BD -** **3.PD**	0,36 ± 0,08 0,44 ± 0,10 0,52 ± 0,13	0,32 ± 0,08 0,41 ± 0,09 0,50 ± 0,12	0,31 ± 0,13 0,40 ± 0,08 0,38 ± 0,17	**0.023**	**< 0.001 (1-3)**	0.291	0.816
Step length variability	**1.BD +** **2.BD -** **3.PD**	0,16 ± 0,33 0,04 ± 0,18 0,03 ± 0,35	0,18 ± 0,32 0,04 ± 0,19 0,03 ± 0,34	0,27 ± 0,62 0,06 ± 0,02 0,07 ± 0,04	0.491	-	0.982	0.896
Step width (m)	**1.BD +** **2.BD -** **3.PD**	0,10 ± 0,06 0,10 ± 0,04 0,07 ± 0,07	0,10 ± 0,06 0,10 ± 0,06 0,07 ± 0,06	0,12 ± 0,08 0,09 ± 0,04 0,10 ± 0,08	0.521	-	0.959	0.938

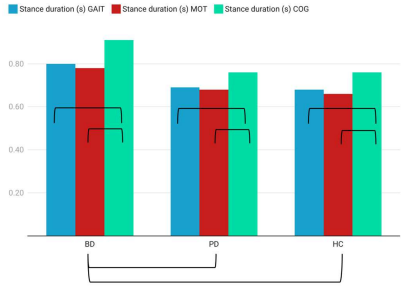
Table 3.8. Comparison on spatio-temporal parameters among patients with BD +, BD -, and PD. Data are expressed as mean ± SD. Statistical significance was set at 0,05, and significant results are shown in bold. Abbreviation: Bipolar Disorder (BD) patients with evidence of striatal dopaminergic denervation (BD+) and without it (BD−); PD: Parkinson's Disease; HC: Healthy Control; GAIT: Single Walking Task; MOT: Motor Dual-Task; COG: Cognitive Dual- Task.

Results

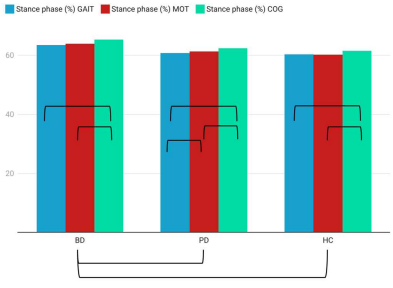
[CYCLE DURATION (S)]



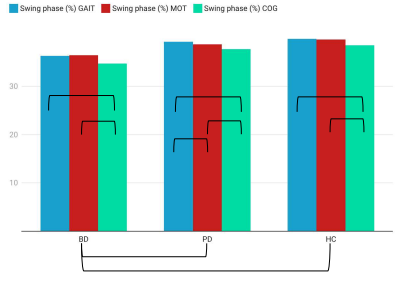
[STANCE DURATION (S)]



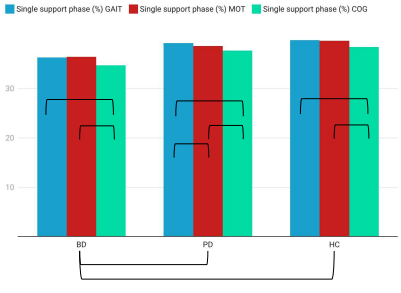
[STANCE PHASE %]



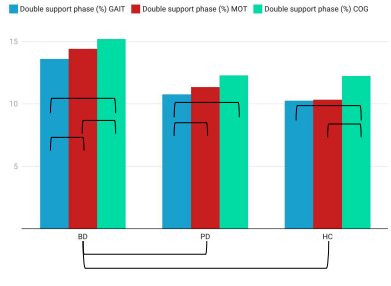
[SWING PHASE %)]



[SINGLE SUPPORT PHASE %)]



[DOUBLE SUPPORT PHASE %)]



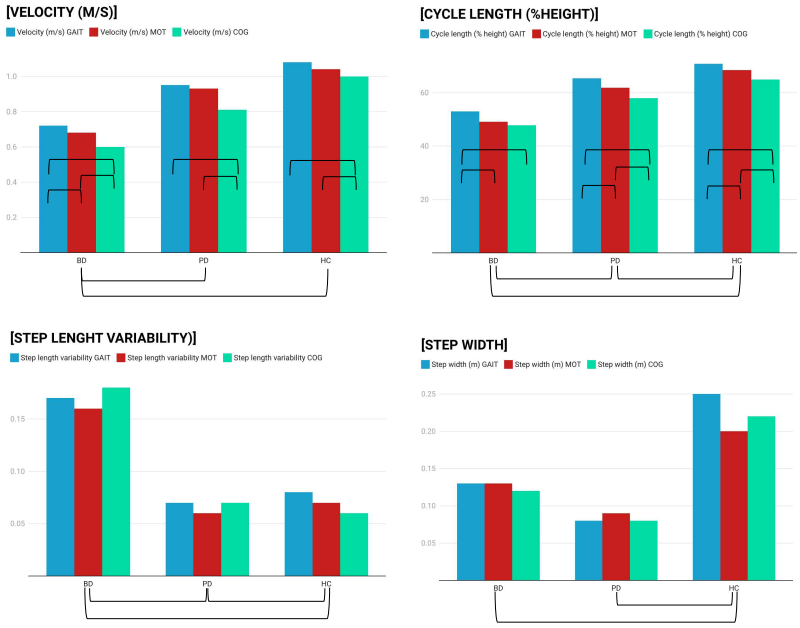


Fig. 12. Histograms showing mean values of the main gait differences (cycle and stance duration in seconds, percentage of stance, swing, single and double support phases, velocity in meters per second, cycle length normalized to height, step length variability, step width in meters) emerged in BD vs. PD vs. HC comparison. Bars represent statistically significant differences between groups and/or between tasks for each group.

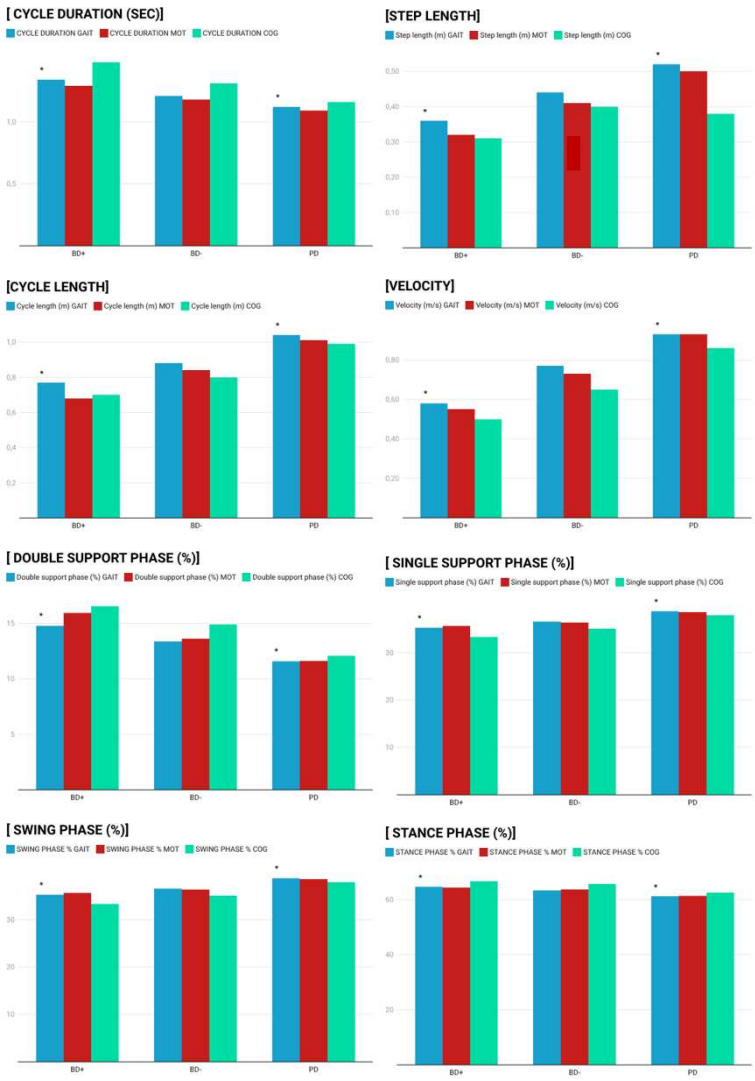


Fig. 13. Histograms showing mean values of the main gait differences (cycle duration in seconds, step and cycle length in meters, velocity in meters per second, percentage of double support, single support, swing and stance phase) emerged in the subanalysis involving BD+, BD- and PD patients, and across the three tasks (see colour legend for reference). * represents statistically significant between group differences.

4. Discussion

In our cohort, about 20% of BD patients with clinical parkinsonism have an underlying dopaminergic deficit, as measured by DaTSCAN.

This confirms previous results obtained in a pilot study conducted on a smaller cohort (Erro et al. 2021).

The two populations (BD+ vs BD-) differ in terms of age (the BD+ population being older than the BD- populations) as well as for trends in referred hyposmia (more frequent in the BD+ population), RBD score (slightly higher in the BD+ population), distribution of the “gait” item of the MDS-UPDRSIII scale (with a higher score in the BD+ populations). Conversely, the BD- population showed a trend in higher number of episodes and higher current neuroleptic exposure.

As a whole, the BD+ population is older than the BD- population: however, appropriate age-matching has been conducted in all sub analyses (see previous sections) in order to eliminate this possible confounding factor as

much as possible. Moreover, SPECT results are calculated in contrast to a database of age-matched healthy subjects (Brogley 2019), which indicates that the DaT binding values we measured in the BD+ group can be considered pathological.

The detected trends of sex distribution in our subclasses actually reflect the fact that our BD sample is mainly composed of men subjects. Since PD is more common in men (Balestrino and Schapira 2020), we cannot exclude that gender might also play a role in the development of degenerative or persistent parkinsonism in BD, and deserves future ad hoc investigations, further considering possible different clinical profiles of BD between men and women (Diflorio and Jones 2010). Compared to women, men with a diagnosis of BD tend to have earlier onset and a more frequently manic onset (Kennedy et al. 2005).

Some reports also suggest that BD type 1 may be more frequent in men and BD type II more frequent in women (Gogos et al. 2019).

Thus, it cannot be ruled out that males may be more prone than females to develop degenerative or at least persistent parkinsonism by virtue of the higher baseline susceptibility to neurodegeneration and possible sex related biological differences influencing the underlying disease course.

In our pilot study (Erro et al. 2021) we compared BD+ patients SPECT results to a population of age-matched PD patients with a homogeneous motor burden. In brief, BD+ patients had higher striatal binding ratio in both the most affected and least affected putamina as well as higher putamen-to-caudate ratios in both hemispheres than had PD patients.

The observed different patterns of striatal denervation in the comparison between BD+ and PD patients would suggest that the two groups might have a different pattern of dopaminergic deficit. Indeed, the higher striatal binding ratios observed in the most affected putamen when compared with PD patients means that motor symptoms in our sample of BD+ patients do not linearly reflect the underlying putaminal denervation, as instead is observed in PD. This discrepancy between the clinical and functional imaging data might be due to a possible role of pharmacological therapy in explaining at least part of the symptoms.

Coherently, the detected trends (see fig.9) in higher number of episodes, probably reflecting a more serious disease and, consequently, requesting higher exposure to antipsychotics (as documented by a trend in higher CED) in our BD- population, could explain the similar clinical burden (MDS-UPDRSIII score) in the two subpopulations, being mostly attributable in the BD- population to the pharmacological exposure.

Furthermore, the BD+ scintigraphic pattern, formerly compared to PD, might further suggest a higher caudate involvement in BD+. This aspect has already been reported by (Anand et al. 2011) (see Introduction). Caudate dysfunction in the neuropsychiatric features of BD+ is in line to the evidence linking caudate dysfunction and mood disorders also in PD (Erro et al. 2012).

The available longitudinal assessments (see fig.10) for patients who were dopaminergic drug – naïve at baseline and started a dopaminergic therapy, confirms that both SPECT status and psychiatric pharmacological modifications have a certain impact on MDS-UPDRSIII changes. These data represent a further confirmation of the hybrid nature of motor disability in these patients.

Non motor symptoms, such as hyposmia and RBD, are core features in PD (Kalia and Lang 2015). Thus, the observed trends in the BD population may be considered as possible predictive factors of neurodegeneration. However, RBD have been described as being a possible additional feature in many psychiatric diseases, including Bipolar Disorder, with comparable clinical features as those of idiopathic RBD (Lam et al. 2013).

Moreover, as far as hyposmia is concerned, our UPSIT study shows that the BD population as a whole presents low UPSIT scores (in the range of severe hyposmia according to the latest normative values published by (Brumm et al. 2023)), but with no differences in the two (BD+ vs. BD-) classes. Studies about odor identification ability in BD patients have reported conflicting results. Indeed, an impairment in odor identification, as measured by the UPSIT, has been described in Bipolar Disorder I patients, especially when psychotic features are present (Kamath et al. 2018). Another study (Lahera et al. 2016) reports olfactory deficits in BD even in the euthymic state. A study by (Krüger et al. 2006) reported more sensitive acuity in a subset of bipolar disorder patients who experienced event-related affective episodes compared to BD patients who did not. Hedonic responses to olfactory stimuli have also provided conflicting results: a study by (Swiecicki et al. 2009) found that BD patients tended to rate more olfactory stimuli as pleasant compared to depressed patients. On the contrary, (Kazour et al. 2022) found that patients in manic episodes show deficits in identifying positive odours. They evaluate these smells as less pleasant and less emotional compared to remitted bipolar subjects and healthy controls.

In sum, despite some authors have pointed out that non-motor symptom profile may distinguish drug-induced parkinsonism from PD (Morley and

Duda 2014), this aspect must be carefully taken into account because these symptoms may be rather part of the underlying psychiatric disease. In addition, conventional methods for assessing olfactory function (through the expression of a judgment about an odorous stimulus) may have limited reliability and, consequently, limited informative value in patients with BD.

Overall, the BD population shows poorer gait features compared to PD patients. Differences mainly concern spatio-temporal parameters related to worse dynamic unbalance.

Studies investigating gait and posture in BD patients using automated approaches have revealed that swing time variability is significantly larger in patients with either BD or major depression compared to healthy controls (Hausdorff et al. 2004). Moreover, in euthymic BD patients, postural abnormalities have been correlated to illness burden, higher illness burden (especially a higher number of depressive episodes) being associated with lower postural variability during daytime (Halabi et al. 2024). Furthermore, balance control and movement speed have also been correlated to mood state in BD, being more impaired in depressed episodes (Kang et al. 2019, 2018).

Our BD and PD patients have both MoCA average scores lower than the optimal cut-off (<22/30) for the diagnosis of mild cognitive impairment in

PD (Fiorenzato et al. 2024). However, our BD cohort presents significantly lower MoCA scores compared to the reference PD population. Cognitive impairment has been commonly associated to BD even in the euthymic states (Delaloye et al. 2009). In a recent metanalysis, euthymic BD showed significant impairment in general cognitive functioning, verbal memory, executive function, visuo-spatial memory, attention/processing speed, working memory, and premorbid IQ (Swidzinski et al. 2025). In addition, earlier occurrence of dementia has been described in patients with PD and pre-existing BD (Onofrj et al. 2021).

Cognition and gait seem to be closely related in a complex fashion. Gait is no longer considered just an automated motor task but an activity requiring integration of several cognitive skills to ensure safe walking (Amboni et al. 2013), thus gait dysfunctions being considered surrogate biomarker of cognitive decline (Mollenhauer et al. 2014). Deterioration of gait performance during dual task conditions have been interpreted as a possible marker of cognitive decline in PD and in other conditions, with a direct relationship between the magnitude of dual-task-related gait interference and the severity of cognitive impairment (Russo et al. 2023; Amboni, Ricciardi, Adamo, et al. 2022) (Amboni, Ricciardi, Cuoco, et al. 2022; Amboni et al. 2013; Di Filippo et al. 2025). Moreover, dual task conditions, especially those requiring a substantial cognitive effort, may

exert a detrimental effect on gait patterns even in healthy, elderly people (Amboni et al. 2013). These data are coherent to what observed in our cohort: worsening of gait parameters under dual task conditions affects both the BD and PD group, and, to a lesser extent and mainly for the COG dual task, the HS group.

Overall, worsening of gait parameters under COG dual-task conditions, associated to what observed during single-task walking, may partly reflect the poorer cognitive performance of the BD group compared with the PD group. Indeed, DTE observed for cycle and stance duration can be read as a greater impact of COG dual task on these parameters for BD patients. On the other hand, the lower DTE observed for the same parameters in PD class, can be explained as a less effcient postural adjustement during complex tasks (Bloem et al. 2006).

In the PD class, a different and higher impact of the MOT dual task on a number of gait parameters (such as stance phase, swing phase and single support phase) can be observed in the comparison with the BD class. Gait worsening under motor dual task has been described in PD and associated to reduced movement automaticity due to basal ganglia dysfunction (Kelly et al. 2012).

Sub-analysis comparing BD+ and BD- patients shows that the worst performances have been obtained by the BD+ class in comparison with PD, with BD- class showing intermediate parameters. This is coherent to the trend detected using machine learning approaches, regarding the distribution of the “gait” subitem of the MDSUPDRSIII scale across the two classes of BD patients (see violin plots in the previous section).

A recent study found impaired performance in the instrumented Timed Up and Go Test in patients with drug-induced parkinsonism associated to SPECT evidence of neurodegeneration compared to patients with “pure” drug-induced parkinsonism (Aamodt et al. 2022). In this perspective, we may speculate that, also in our cohort, the additional nigrostriatal degeneration as revealed by SPECT imaging may contribute to the worse gait patterns in BD+ patients within the whole BD class. As regards dual-task-related gait interference, the sub-analysis fails to find any significance, very likely due the small sample size of the subgroups.

Conclusion

Despite the limitations arising from the small sample size, our results confirm that the risk of developing a parkinsonism sustained by a nigrostriatal degeneration is higher in patients with BD compared to the general population (Ben-Shlomo et al. 2024; de Rijk et al. 1997). The demographic characteristics of the BD+ population in our cohort are consistent with the increasing prevalence of degenerative parkinsonism with age (Ou et al. 2021).

The analysis of possible predictive factors of neurodegeneration in BD patients suggest that, despite a comparable motor burden as revealed by routine motor screening test, BD patients with parkinsonian syndrome show a greater functional impairment as revealed by gait analysis, than PD patients, and that gait features could be predictive of concomitant neurodegeneration in BD patients.

In the BD cohort, the scintigraphic uptake pattern, as well as the longitudinal course of symptoms in response to dopaminergic therapy, are not in line with the typical course of PD. The non-motor symptom profile is unable to fully differentiate patients presenting with a scintigraphic picture of neurodegeneration from all the others.

Probably, we cannot rely on the classic diagnostic and supportive criteria (such as the response to dopaminergic drugs and the non-motor profile)(Postuma et al. 2015), since BD is a complex disorder with some features that may resemble those observed in PD.

For these reasons, a biological characterization of a degenerative parkinsonism (i.e. α-synuclein detection in biological specimens) may be, in the next future, of crucial importance to add a contribution to disease definition (Höglinger et al. 2024).

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