Thesis

Non-motor Fluctuators:

Characterising non-motor and psychiatric fluctuations in advanced Parkinson's disease using clinicians' assessments and objective measures from a wearable device

submitted by

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Graz, 21.01.2026 *Tobias Sattler m.p.*

Abstract (German)

Hintergrund: Nicht-motorische Symptome, insbesondere Angst und Depression, tragen wesentlich zur allgemeinen Beeinträchtigung und zur verminderten Lebensqualität bei Morbus Parkinson (PD) bei. Angst kann als persistierendes Symptom auftreten oder in Abhängigkeit vom dopaminergen Status fluktuieren; etwa ein Drittel der Patient*innen berichtet über tägliche Angstzustände (1). Obwohl motorische und nicht-motorische Fluktuationen häufig gemeinsam auftreten, ist ihre Beziehung komplex und lässt sich nicht ausschließlich durch ein Levodopa-„wearing-off“ erklären (2). Die klinische Identifizierung und anschließende Behandlung können sich schwierig gestalten, da medizinisches Personal überwiegend auf subjektive Selbstauskünfte angewiesen ist und die Kommunikation über nicht-motorische Zustände in der Praxis herausfordernd sein kann.

Zielsetzung: Ziel dieser Studie war es, Unterschiede in der allgemeinen psychiatrischen Symptomlast, demografischen und klinischen Merkmalen, der Dauer objektiver motorischer Fluktuationen sowie der Lebensqualität (QoL) zwischen Fluktuierern und Nicht-Fluktuierern zu identifizieren. Definiert wurden diese Gruppen durch die „nicht-motorische“ Skala und die „psychiatrische“ Subgruppe des Wearing-Off Questionnaires (WOQ-19).

Methoden: Die Querschnittsstudie, durchgeführt in der Movement Disorder Clinic des St. George’s University Hospital in London, schloss 151 Patient*innen mit fortgeschrittenem PD, die für gerätegestützte Therapien evaluiert wurden, ein. Angst, Depression und Apathie wurden mit der Hamilton Anxiety Rating Scale (HARS), der Hamilton Depression Rating Scale (HDRS) und der Apathy Evaluation Scale (AES) erhoben. Die Lebensqualität wurde mittels Parkinson’s Disease Questionnaire (PDQ-39) bewertet, und objektive motorische Fluktuationen wurden mittels Parkinson’s KinetiGraph (PKG) quantifiziert. Psychiatrische und nicht-motorische Fluktuationen wurden mithilfe der WOQ-19-Subskalen identifiziert. Für beide Klassifikationen wurden Patient*innen als Fluktuierer (WOQ-19 ≥ 1 Punkt) oder Nicht-Fluktuierer (WOQ-19 = 0 Punkte) eingestuft. Gruppenvergleiche erfolgten mittels Mann-Whitney-U-Tests. Zusätzlich erfolgte zur Evaluierung der dopaminergen Responsivität eine klinische Untersuchung sowohl im on- als auch im off-Medikationszustand unter Verwendung der Movement Disorder Society–Unified Parkinson’s Disease Rating Scale (MDS-UPDRS).

Ergebnisse: Fluktuierer, unabhängig davon, ob sie über die nicht-motorische oder die psychiatrische Subskala des WOQ-19 definiert wurden, zeigten signifikant höhere Angst- (HARS) und Depressionswerte (HDRS) als Nicht- Fluktuierer ($p < .001$ für beide). Hinsichtlich Apathie ergaben sich keine signifikanten Gruppenunterschiede (non-motor: $p = .18$; psychiatric: $p = .061$). Unter den PDQ-39-Domänen war nach Bonferroni-Korrektur ausschließlich das emotionale Wohlbefinden (non-motor: $p = .004$; psychiatric: $p < .001$) bei Fluktuierern signifikant schlechter, was darauf hinweist, dass nicht-motorische/psychiatrische Fluktuationen einen besonders ausgeprägten Einfluss auf die subjektive Gesundheitswahrnehmung haben. In den PKG-Analysen verbrachten Fluktuierer deutlich mehr Zeit in Dyskinesie (non-motor: $p < .001$; psychiatric: $p = .002$) und weniger Zeit in Bradykinesie ($p < .001$ für beide) als Nicht-Fluktuierer, was auf eine größere motorische Variabilität hinweist. Es zeigten sich keine Gruppenunterschiede hinsichtlich Alter, Krankheitsdauer, Geschlecht oder MDS-UPDRS-Teil-III-Scores in beiden Medikationszuständen.

Schlussfolgerung: Patient*innen mit nicht-motorischen oder psychiatrischen Fluktuationen weisen ein charakteristisches klinisches Profil auf, das durch vermehrte Angst und Depression, vermindertes emotionales Wohlbefinden und ausgeprägtere objektive motorische Variabilität gekennzeichnet ist, trotz ähnlicher motorischer Beeinträchtigung in der klinischen Untersuchung (UPDRS III) wie nicht-Flutkuierer. Diese Ergebnisse unterstreichen die Bedeutung der Erfassung psychiatrischer und nicht-motorischer Fluktuationen bei fortgeschrittenem PD und sprechen für deren systematische Integration in die klinische Diagnostik und Therapieplanung.

Abstract

Background: Non-motor symptoms, particularly anxiety and depression, substantially contribute to disability and reduced quality of life in Parkinson's disease (PD). Anxiety may occur as a persistent symptom or fluctuate in relation to dopaminergic state, with approximately one third of PD patients experiencing it on a daily basis (1). Although motor and non-motor fluctuations often co-occur, their relationship is complex and cannot be attributed purely to levodopa-"wearing-off" (2). Clinical assessment and subsequent treatment remain challenging as clinicians must rely primarily on subjective self-report tools and communication about non-motor states can be challenging in clinical practice.

Objective: This study aimed to investigate differences in psychiatric symptom burden, demographic and clinical characteristics, objective motor fluctuations as well as quality of life (QoL) between fluctuators and non-fluctuators as identified by the Wearing-Off Questionnaire (WOQ-19) non-motor subscale and the psychiatric subgroup.

Methods: A cross-sectional study was conducted at the Movement Disorder Clinic, St. George's University Hospital, London, including 151 patients with advanced PD considered for device-aided therapies. Anxiety, depression and apathy were assessed through the Hamilton Anxiety Rating Scale (HARS), the Hamilton Depression Rating Scale (HDRS), and the Apathy Evaluation Scale (AES). Quality of life was evaluated with the Parkinson's Disease Questionnaire (PDQ-39). Objective motor fluctuations were quantified with the Parkinson's KinetiGraph (PKG). Psychiatric and non-motor fluctuations were defined using the WOQ-19 non-motor and psychiatric subscales. Patients were grouped as fluctuators (WOQ-19 $\geq$ 1) or non-fluctuators (WOQ-19 = 0) and between-group comparisons were conducted using Mann–Whitney U tests. In order to evaluate dopamine response, participants were additionally examined in both on and off medication states using the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS).

Results: Fluctuators, defined by either the WOQ-19 non-motor or psychiatric subscale, exhibited significantly higher anxiety (HARS) and depression (HDRS) scores than non-fluctuators ($p < .001$ for both). No significant group differences were found for apathy (non-motor: $p = .18$; psychiatric: $p = .061$). Among PDQ-39 domains, only emotional well-being (non-motor: $p = .004$; psychiatric: $p < .001$) was significantly worse in fluctuators,

suggesting that psychiatric fluctuations exert a more substantial influence on subjective health status than other non-motor or motor-related domains. PKG analyses demonstrated that fluctuators spent substantially more time in dyskinesia (non-motor: $p < .001$; psychiatric: $p = .002$) and less time in bradykinesia ($p < .001$ for both) than non-fluctuators, indicating greater motor variability. No group differences were observed for age, disease duration, gender, or MDS–UPDRS Part III motor scores in either medication state.

Conclusion: Patients with non-motor or psychiatric fluctuations exhibit a distinct clinical phenotype characterised by elevated anxiety and depression, poorer emotional well-being, and greater objective motor variability, despite comparable motor severity on clinical examination (UPDRS III). These findings highlight the importance of recognising psychiatric and non-motor fluctuations in advanced PD and integrating their assessment into routine clinical evaluation and treatment planning.

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List of abbreviations

ADL	Activities of daily living
AES	Apathy Evaluation Scale
DSM	Diagnostic and Statistical Manual of Mental Disorders
GBD	Global Burden of Disease
HARS	Hamilton anxiety scale
HDRS	Hamilton depression rating scale
HRQoL	Health-related quality of life
M	Mean value
MDS	Movement Disorder Society
NMS	Non-motor symptoms
PD	Parkinson’s disease
PDQ-39	Parkinson's Disease Questionnaire-39
PKG	Parkinson’s KinetiGraph
QoL	Quality of Life
RBD	REM sleep behaviour disorder
ROS	Reactive oxygen species
SD	Standard deviation
UPDRS	Unified Parkinson's Disease Rating Scale
WOQ-19	Wearing-Off Questionnaire
NMS	Non-motor symptoms

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1. Introduction

1.1. Overview

Parkinson's disease (PD) was first described in the early 19th century by the English physician James Parkinson, who provided a clinical characterisation of the disorder in his seminal essay on the "shaking palsy" (3). PD is a progressive neurodegenerative condition marked primarily by the degeneration of dopaminergic neurons in the substantia nigra pars compacta, resulting in a characteristic combination of motor symptoms, such as bradykinesia, rigidity, tremor, and postural instability, as well as a wide range of non-motor symptoms (4). PD is the second most common neurodegenerative disease after Alzheimer's disease (5,6) and currently the fastest-growing worldwide (7). The incidence of PD is 16,9 per 100.000 annually, but it is varying by geography, methodology and cohort characteristics (8,9). A consistent finding is that PD is more prevalent in males than in females. Potential explanations include sex-related endocrine differences, differential exposure to environmental toxins (e.g., pesticides), and the possibility of sex chromosome–linked protective mechanisms, although the underlying cause of this sex difference remains unclear (10,11). Ethnic differences have also been documented. For example, Van den Eeden and colleagues reported the highest incidence among individuals of Hispanic ethnicity, followed by non-Hispanic White, Asian, and Black populations (12).The most significant risk factor for PD is advancing age. Prevalence and incidence increase almost exponentially with age, with the highest rates observed in individuals older than 80 years (13,14) e.g., shown in four North American populations where the prevalence was below 1% for those aged 45-54 but increased to 2.4% respectively for women/men aged 85 and above (15). This age-related increase is attributed to cumulative neurodegenerative processes such as mitochondrial dysfunction, oxidative stress, and the aggregation of misfolded α-synuclein, which intensify with biological aging and progressively compromise dopaminergic neuronal integrity (16). Genetic factors also contribute to PD susceptibility. First-degree relatives of individuals with sporadic PD have a two- to threefold higher risk of developing the disease compared with relatives of unaffected individuals, underscoring the role of heritable mechanisms even in ostensibly non-familial cases (17).

In 2015 about 6 million people were affected by PD globally, which is twice as many as in 1991. By the year 2040 this number is predicted to double to over 12 million due to multiple factors including ageing with some estimations being even higher (18). The most important

driver is the global increase in life expectancy, as PD incidence rises sharply with age. Modelling studies from the Global Burden of Disease (GBD) 2021 project state that population aging accounts for nearly 90% of the expected increase in PD cases by 2050. Population growth itself contributes about 20%, while changes in age-standardized prevalence (reflecting factors such as improved diagnosis, increased disease duration, and possibly environmental exposures) play a lesser role (5,19).

1.1.1. Pathology

The pathological hallmark of PD is the progressive loss of dopaminergic neurons in the substantia nigra pars compacta in the midbrain. The neurodegeneration in this region leads to striatal dopamine deficiency and is understood to underlie the four cardinal motor symptoms of PD: bradykinesia, rigidity, tremor, and postural instability (20). Although nigral dopaminergic cell loss represents the most prominent pathological feature, PD is now recognized as a multisystem neurodegenerative disorder involving a broad range of additional neuronal populations. Affected structures include the hypothalamus, amygdala, dorsal motor nucleus of the vagus, locus coeruleus, pedunculopontine nucleus, nucleus basalis of Meynert, and raphe nuclei, among others (21,22).

The histological characteristic of PD is the presence of intracellular inclusions, so-called Lewy bodies. Lewy bodies and neurites are built from insoluble abnormal folded protein aggregates. The specific protein, that leads to the Lewy pathology, has been identified as misfolded α-synuclein (23). Those accumulations of misfolded protein are not restricted to the substantia nigra pars compacta, but can be found in any part of the brain (24). The midbrain, the basal forebrain, the basal ganglia, the mesocortex and even the neocortex are structures that can be affected by the pathology at later stages of the disease (25). Furthermore the spinal cord and peripheral nervous system, including the vagus nerve, enteric nervous system, adrenal gland, cardiac plexus and salivary glands are also locations affected by the Lewy pathology (26–29). Braak and colleagues suggest, that the Lewy pathology follows a stereotyped caudal to rostral pattern across the nervous system starting in the medulla oblongata and olfactory structures during preclinical stadium (25). This widespread distribution of Lewy pathology offers a compelling explanation for the early and heterogeneous constellation of non-motor symptoms that often precede classical motor manifestations by years and may remain prominent throughout the disease course (30–32).

1.1.2. Pathogenesis

The pathogenesis of PD is multifactorial and involves a complex interplay of genetic susceptibility, environmental factors, and cellular vulnerabilities that converge to produce α-synuclein aggregation and neurodegeneration. A central mechanistic process is the misfolding and oligomerization of α-synuclein, which disrupts synaptic function and, when inadequately cleared, accumulates into insoluble aggregates that form Lewy bodies (see above). Impairments in key protein degradation pathways, particularly the ubiquitin-proteasome system and autophagy-lysosomal pathways, further promote α-synuclein accumulation and neuronal toxicity (33–35). Mitochondrial dysfunction represents an additional hallmark of PD pathogenesis, with deficits in mitochondrial complex I activity leading to impaired energy metabolism, increased production of reactive oxygen species, and heightened susceptibility of dopaminergic neurons to oxidative stress (35–37).

Neuroinflammation has more recently emerged as a key component of PD pathophysiology (38). Microglia and astrocytes become activated in regions of neurodegeneration and may exert both neuroprotective and neurotoxic effects. On the one hand, activated glial cells can clear extracellular debris and secrete trophic factors; on the other hand, they may release reactive oxygen and nitrogen species as well as pro-inflammatory cytokines, potentially exacerbating neuronal injury (39). The precise balance between these protective and detrimental mechanisms remains uncertain, but accumulating evidence suggests that chronic neuroinflammation interacts with α-synuclein aggregation, oxidative stress, and mitochondrial dysfunction in driving neurodegenerative processes in PD (7,40,41).

Environmental toxins such as pesticides and heavy metals may exacerbate these mitochondrial and oxidative mechanisms in genetically predisposed individuals (42,43). Neuroinflammation also contributes to disease progression: chronically activated microglia and astrocytes secrete pro-inflammatory cytokines and oxidative mediators that amplify neuronal injury and may facilitate the spread of misfolded α-synuclein between interconnected brain regions (38,39).

Genetic factors, including mutations or risk variants in genes such as SNCA, LRRK2, PARK2, PINK1, and GBA, further influence mitochondrial function, lysosomal activity, and α-synuclein homeostasis, linking inherited mechanisms with sporadic disease pathways (44–47). Together, these converging processes create a self-reinforcing cycle of protein

misfolding, impaired cellular clearance, oxidative damage, and inflammatory signalling that drives the progressive neurodegeneration characteristic of PD.

1.1.3. Dual Hit hypothesis

Early indicators of Lewy pathology manifest in the olfactory bulb and the enteric plexus of the stomach. A neurotropic agent, likely of viral origin, is thought to infiltrate the brain through two pathways: The first is the nasal route, progressing in a forward direction into the temporal lobe and the second is the gastric route, occurring potentially due to the ingestion of nasal secretions. These secretions may carry a neurotropic agent capable of transmitting across synapses, which enables retrograde transport into the medulla and subsequently into the pons and midbrain until the substantia nigra is reached, marking the onset of typical disease features. This point of view is clinically supported by the presence of olfactory and autonomic dysfunction (48,49). Olfactory dysfunction and autonomic dysfunction (such as constipation and orthostatic hypotension) are among the earliest clinical indicators of Lewy pathology, including PD and dementia with Lewy bodies. These non-motor symptoms often precede the onset of motor or cognitive manifestations by years to decades, reflecting early involvement of the olfactory bulb and peripheral autonomic nervous system by α-synuclein pathology (30–32). Taken together, the Dual-Hit Hypothesis provides a coherent framework for understanding the peripheral origins of PD pathology and offers a compelling explanation for the early emergence of non-motor symptoms long before classical motor features develop.

1.2. Motor symptoms

The four cardinal motor features: bradykinesia, rigidity, resting tremor, and postural instability, constitute the clinical hallmark of PD and reflect disruptions in the basal ganglia circuits responsible for movement initiation, scaling, and automaticity (50).

Resting tremor is one of the most recognizable motor features of PD. The classic “pill-rolling” tremor typically oscillates at a frequency of 4-6 Hz and is most prominent at rest. It usually begins unilaterally in the upper extremity and, with disease progression, may spread contralaterally or to other body regions such as the legs, jaw, or chin. Bradykinesia, defined as slowness and progressive reduction in amplitude and speed of voluntary movements, is also a very disabling motor feature and a required criterion for the diagnosis of PD. Patients

frequently describe bradykinesia as fatigue, heaviness, or perceived weakness, and it may manifest clinically as reduced facial expression (hypomimia), decreased arm swing, difficulty with fine motor tasks, or hesitancy in movement initiation. Rigidity refers to increased resistance to passive movement throughout the range of motion and can affect any body region. Rigidity contributes to musculoskeletal discomfort, reduced mobility, and difficulties with posture. Postural instability emerges in later disease stages and is characterized by impaired postural reflexes and diminished ability to maintain balance, substantially increasing the risk of falls (51).

Although motor symptoms are central to a PD diagnosis, their expression is heterogeneous, and individual patients may show varying combinations and severity over time. Moreover, as the disease progresses and dopaminergic responsiveness fluctuates, many patients experience motor fluctuations (periods of worsened motor symptoms- so called “off” states and episodes of dyskinesia (periods of involuntary movements) e.g., during peak dopaminergic stimulation). These complications become increasingly common in advanced disease and form an important clinical target for both oral and device-aided therapies, including continuous dopaminergic delivery systems (7,40,52,53). The presence and severity of such fluctuations were assessed in this study using clinical ratings and objective wearable sensor data.

1.3. Non-motor symptoms

Non-motor symptoms (NMS) have a substantial impact on quality of life in PD and require effective management at all disease stages, as they are frequently under-recognized and often more challenging to treat than motor symptoms (54). While motor manifestations arise predominantly from dopaminergic dysfunction, NMS reflect involvement of additional neurotransmitter systems, including serotonergic, cholinergic, and noradrenergic networks, which contribute to their diverse clinical presentation and challenges in the management thereof (55).

Notably, several non-motor characteristics, including REM sleep behaviour disorder (RBD) and hyposmia, may precede the onset of PD motor symptoms by several years, and occasionally even decades. The typical latency between the onset of RBD and the emergence of parkinsonian motor symptoms is estimated at 12 to 14 years (56).

Approximately 90% of individuals diagnosed with PD encounter NMS as the disease progresses and most patients experience multiple NMS during the disease course (57).
The spectrum of NMS encompasses cognitive impairment, behavioural and neuropsychiatric changes, sensory disturbances, autonomic dysfunction, and a variety of sleep disorders (58). Within the spectrum of NMS, fluctuating psychiatric symptoms, particularly anxiety, depression, and apathy, are of central importance, as they often parallel motor fluctuations and substantially affect daily functioning and will be further detailed in the following sections.

1.3.1. Anxiety

Anxiety is one of the most frequent psychiatric symptoms in PD, affecting up to 40% of patients, yet it is often underdiagnosed due to its substantial clinical overlap with depression (59,60). Anxiety and depression may also present concurrently, as demonstrated in a large cross-sectional PD cohort where 41% showed comorbid anxiety and depression, 15% had depression without anxiety, and 14% exhibited anxiety without depression (61). Anxiety contributes to diagnostic challenges, increased disability and suffering among those affected (62,63). A growing body of evidence highlights that anxiety symptoms may also fluctuate in parallel with, or independently from, motor fluctuations. Approximately 35% of patients with motor fluctuations report corresponding fluctuations in anxiety (64) and off-period anxiety has been documented in up to 81% of individuals with PD (65). Leentjens et al. further demonstrated that although many patients with motor fluctuations report anxiety symptoms, these are not always temporally linked to specific motor states. When a temporal relationship is present, anxiety most commonly intensifies during off periods, although a smaller proportion of patients report anxiety exclusively during on periods or on states with dyskinesia (66). Given the high prevalence, fluctuating nature, and strong association of anxiety with functional impairment, recognising anxiety fluctuations is important in clinical practice.

In the present study, anxiety was assessed using the WOQ-19 (non-motor and psychiatric subscales) to identify fluctuators and non-fluctuators and quantified using the Hamilton Anxiety Rating Scale (HARS). This approach enabled a systematic evaluation of both the occurrence and fluctuation of anxiety symptoms within the study cohort.

1.3.2. Depression

Depression is one of the most prevalent and burdensome neuropsychiatric symptoms in PD, although reported prevalence rates vary widely across studies. A meta-analysis by Reijnders et al. estimated weighted prevalence rates of 17% for major depression, 22% for minor depression, and 13% for dysthymia in PD, underscoring the high overall burden of depressive symptomatology (67). The identification of depression in PD is clinically challenging, as several depressive features, such as psychomotor slowing, anhedonia, sleep disturbance, and fatigue closely overlap with core motor and NMS of PD (68). Even screening for PD symptoms in individuals with depression has been suggested, as depressive symptoms may significantly precede the onset of motor symptoms in PD (69). The pathophysiology of depression in PD is multifactorial, involving not only dopaminergic dysfunction within mesolimbic pathways but also alterations in serotonergic, noradrenergic, and opioid neurotransmitter systems, as well as changes in limbic and prefrontal circuitry (70). These neurobiological disruptions may contribute to both persistent depressive symptoms and mood fluctuations observed in PD. Because depressive symptoms are strongly associated with reduced quality of life, increased disability, and caregiver burden, their systematic assessment is clinically essential (71–75).

In the context of the present study, depression was evaluated using the Hamilton Depression Rating Scale (HDRS) and fluctuations in depressive symptoms were identified by WOQ-19 non-motor and psychiatric subscales. This allowed for a structured comparison between fluctuators and non-fluctuators and provided a framework to examine how depressive symptom burden and fluctuation patterns relate to overall clinical status and quality of life.

1.3.3. Apathy

Apathy in PD is characterized by a reduction in goal-directed behaviour, diminished motivation, and blunted emotional responsiveness, often accompanied by cognitive disengagement (76–78). Reported prevalence rates vary widely, ranging from 17% to 70%, reflecting differences in assessment methods, disease stage, and sample characteristics. Apathy has significant clinical implications as it is associated with poorer treatment response to dopaminergic therapy, reduced functional independence, increased caregiver burden, and lower overall quality of life (79,80). Moreover, apathy has been linked to a heightened risk of developing dementia and greater difficulty with daily decision-making and initiation of actions (81). Unlike anxiety and depression, apathy in PD is often conceptualized as a more

stable, trait-like phenomenon rather than a fluctuating state. This distinction is clinically relevant, as it may influence how apathy responds to dopaminergic medication cycles and how its progression relates to disease duration and cognitive decline (80,82).

In the present study, apathy was measured using the Apathy Evaluation Scale (AES), and its fluctuation was assessed via the WOQ-19 non-motor and psychiatric subscales. This allowed for a systematic evaluation of whether apathy differentiated fluctuators from non-fluctuators in the same manner as anxiety and depression, and provided insight into the stability of motivational deficits within the clinical profile of PD.

Apathy, depression, and anxiety frequently co-occur in Parkinson's disease and are understood to represent partially overlapping but neurobiologically distinct syndromes. While depression and anxiety share a high degree of symptom and temporal overlap, apathy is more often conceptualized as an independent motivational deficit (80,83,84). Empirical studies consistently demonstrate associations between these three domains. Meta-analytic data show that up to 40–60% of patients with apathy also meet criteria for depression, and approximately 30–40% exhibit clinically relevant anxiety symptoms (85,86). Importantly, the co-occurrence of apathy with affective symptoms is associated with poorer functional outcomes, increased caregiver burden, and lower quality of life compared to their isolated occurrence (87–89). Although apathy tends to be more trait-like and less responsive to dopaminergic states, its overlap with depression and anxiety complicates diagnostic classification and underscores the importance for multidimensional assessment tools such as the WOQ-19 and disease-specific mood scales (90).

1.4. Progression of the disease

As PD advances, symptom expression becomes increasingly heterogeneous, with many patients developing not only motor complications but also fluctuations in non-motor domains. While early motor symptoms usually respond well to dopaminergic therapy, long-term treatment and disease progression lead to a pattern of variability in both motor and NMS. In the later stages, treatment-resistant motor and NMS become particularly prominent. Axial motor issues, including freezing of gait, postural instability, falls, speech impairments and dysphagia, often occur at later stages. It has been reported that up to 80% of patients may experience freezing of gait and falls, with as many as 50% reporting incidents of

choking approximately 17 years following the onset of the disease (91,92). Importantly, neuropsychiatric and autonomic disturbances, such as anxiety, depression, apathy, and cardiovascular or gastrointestinal symptoms, often fluctuate in parallel with, or independently from, motor states (93,94). These symptoms do not respond well to levodopa treatment, significantly contributing to disability, and serving as strong predictors for the need for institutional care and mortality (95).

These points provide the clinical rationale for examining non-motor fluctuations in the present study involving patients with advanced PD and to further characterise patient profiles who tend (not) to present with non-motor fluctuation and to explore how these fluctuations relate to mood burden, motor function, and quality of life.

1.5. Treatment and motor fluctuations

Levodopa is the golden standard of symptomatic treatment. Recorded levodopa response even aids diagnosis of PD (96). Challenges associated with levodopa therapy may occur during the course of the disease and may present clinically as motor fluctuations and/or dyskinesias (97). These complications are amongst others the result of a narrowing of the therapeutic window, the pulsatile character of oral therapies as well the progressive nature of the neurodegeneration (98). For those who develop the condition at a younger age, motor fluctuations and dyskinesias may occur earlier in the disease course (99,100). Elderly patients may also struggle with cognitive and psychiatric challenges, along with issues related to balance and speech (98). During extended periods of levodopa treatment, only about a quarter of patients maintain a satisfactory and consistent response (97,101). Bothersome dyskinesias and motor fluctuations, or a substantial or complete loss of therapeutic effectiveness are often seen in advanced PD. Motor fluctuations typically become evident within five years of initiating levodopa therapy. Initially, these fluctuations manifest as "wearing-off", characterized by changes in motor disability linked to the timing of levodopa intake. These motor fluctuations become increasingly abrupt and unpredictable, as the disease progresses. This process eventually culminates in the so-called "on-off effect", which is characterised by sudden and unpredictable shifts in motor disability that are unrelated to the timing of levodopa consumption (98). It has been demonstrated that the primary risk factors associated with the development of motor fluctuations appear to be the duration of treatment and the dosage thereof (102–104). A number of additional risk factors

have been identified, including younger age, female sex, genetic predisposition, lower initial body weight and weight loss during the course of the disease (105). In the fully established "on-off" state, the swings in motor function and other symptoms may become highly erratic and rapid, occasionally resulting in "sudden offs". Some doses of levodopa may no longer have any effect, or there may be a significant delay before the patient experiences a remission of motor function (98).

Motor fluctuations often coexist with, precipitate, or parallel fluctuations in non-motor and psychiatric domains, again highlighting the clinical importance of further characterising patients at risk.

1.6. Non motor fluctuations

While motor fluctuations primarily arise from variations in dopamine levels in the blood, the pathomechanisms of how dopamine contributes to non-motor fluctuations or if these fluctuations result from interactions between multiple neurotransmitters remains unclear (55,106,107). Although motor fluctuations in PD have been extensively studied in both on and off periods, there has been relatively limited research into fluctuations associated with NMS. It may be plausible to classify these NMS fluctuations into two separate categories. Some NMS persist throughout "on" periods and worsen during motor "off" periods, while others solely emerge during "off" periods. (108). This correlation carries important implications for addressing NMS in individuals whose symptoms are solely linked to "off" periods, like depression. In such instances, the treatment strategy should prioritize the elimination of "off" periods rather than resorting to the use of antidepressant medications (11). Given this limited understanding and the potential clinical relevance of distinct fluctuation patterns, the present study aims to characterise non-motor and psychiatric fluctuators more precisely by comparing their demographic, clinical, motor, and quality-of-life profiles within an advanced PD cohort.

1.7. Impact of motor and non-motor symptoms on quality-of-life

The primary objective of PD treatment is to minimize the impact of symptoms on daily functioning and quality of life (QoL). Consequently, evaluating treatment effectiveness requires systematic assessment of both functional outcomes and health-related quality of life (HRQoL). While the World Health Organization defines global QoL as an individual’s

perception of their position in life within the context of cultural and personal expectations (85), clinical research typically focuses on HRQoL, a more specific construct referring to the patient's appraisal of how a disease and its consequences affect physical, psychological, and social well-being (109–111). PD encompasses a broad spectrum of motor and non-motor manifestations that contribute to reduced HRQoL. Early motor symptoms such as tremor, rigidity, and bradykinesia may be compounded over time by treatment-related complications, including dyskinesias, dystonia, and motor fluctuations (111). As the disease advances, patients frequently experience additional cognitive, behavioural, autonomic, and sleep disturbances as well as emotional instability and symptoms such as fatigue, balance impairment, pain, and speech difficulties, all of which further diminish HRQoL (112). Motor and neuropsychiatric symptoms often interact, with several studies suggesting that off-related worsening of motor symptoms coincides with heightened neuropsychiatric burden (65,113). Importantly, neuropsychiatric symptoms exert a profound independent effect on HRQoL and are overall stronger predictors of HRQoL than motor features alone (108,114). Anxiety contributes to functional disability, diagnostic complexity, and reduced HRQoL, and patients with anxiety consistently report poorer HRQoL than those without (62,63,115). Depression is one of the most robust predictors of HRQoL across all stages of PD, strongly associated with impaired functioning and diminished well-being (67,116–120). Apathy, which often co-occurs with depression and cognitive slowing, is likewise linked to lower HRQoL, particularly when executive apathy is pronounced (121).

In summary, PD is a progressive neurodegenerative disorder in which non-motor and more specifically psychiatric symptoms play a central role in determining HRQoL. Although motor fluctuations and dyskinesias are well recognized complications of long-term dopaminergic therapy, much less attention has been given to the fluctuating nature of NMS, particularly anxiety, depression, and apathy. These neuropsychiatric symptoms are common in PD, may co-occur with motor fluctuations, and exert a strong and independent influence on HRQoL. However, current evidence provides limited insight into how patients with non-motor or psychiatric fluctuations differ from those without fluctuations in demographic characteristics, clinical symptom burden, motor function, or QoL. To address this gap, the present study groups patients with advanced PD into fluctuators and non-fluctuators using the WOQ-19 non-motor and psychiatric subscales, and systematically compares these groups across demographic variables, clinical measures (anxiety, depression, apathy, motor scores, motor complications), and HRQoL. Additionally, objective motor data obtained from

a wearable device (PKG) are analysed to quantify differences in time spent in bradykinesia and dyskinesia between groups. This integrated approach aims to characterize “fluctuator-profiles” in advanced PD and to clarify their association with psychiatric symptom burden, motor function, and QoL.

2. Methods

2.1. Subjects

A cross-sectional study was carried out at St. George's University Hospital's Movement Disorder Clinic in London, UK involving consecutive PD patients under regular follow-ups. These patients had been referred to the clinic for device-aided therapies aimed at managing their motor complications at an advanced stage of their disease. The recruitment was conducted from 2016 to 2022, during which patients provided written, informed consent. The study adhered to institutional ethics guidelines and was conducted in accordance with the principles outlined in the Declaration of Helsinki.

Three inclusion criteria were defined: 1) a confirmed diagnosis of PD as per MDS Criteria (122); 2) the absence of clinically significant dementia following DSM-IV criteria; 3) maintenance of stable dopaminergic treatment for a minimum of 3 months prior to the assessment.

2.2. Outcome measures

Mood and psychiatric symptoms were the primary outcome measures in this study and were assessed through the Hamilton Depression Rating Scale (HDRS) (123), the Hamilton Anxiety Rating Scale (HARS) (124) and the Apathy Evalutation Scale (AES) (125). In addition to these measures, dichotomous self-reports were collected for anxiety and depression. Patients were asked whether they subjectively felt anxiety or depression. They were asked to answer with “yes” or “no.” Additionally, for assessment of QoL the Parkinson's Disease Questionnaire (PDQ-39) (126) was completed. These questionnaires were completed once and reflect (depending on the questionnaire) the patients’ symptom burden and perceived QoL in the past 1-4 weeks (further details see chapter 2.2.1). Demographic data collected included gender, age and disease duration.

The Wearing-Off Questionnaire-19 (WOQ-19) served as a measure to assess the presence of wearing-off phenomena and was used to group the cohort into fluctuators and non-fluctuators. To differentiate general non-motor fluctuations from those primarily driven by psychiatric symptoms, groupings were created using both the WOQ-19 *non-motor subscale* and its *psychiatric item subset*. Recommended by the Movement Disorders Society Task Force, the WOQ-19 is a disease-specific self-administered scale for sensitive screening of both motor and non-motor wearing-off phenomena in clinical contexts (127,128). Patients indicate the presence or absence of symptoms and record any improvement after their subsequent medication dose. Wearing-off is present, when symptoms improve following the subsequent medication dose (129). A score of ≥1 on either the WOQ-19 non-motor subscale or psychiatric subset indicates the presence of fluctuations (130). All mentioned questionnaires will be discussed in more detail in chapter 2.2.1.

Additionally, patients included in the study underwent clinical assessment in both the "off-medication" (off) state, following a withdrawal from medication for a minimum of 12 hours (including night hours and the morning dose), and in their "on-medication" (on) condition, approximately 60 minutes after intake of a supramaximal dose of levodopa, equivalent to their regular morning dose increased by 50%. Using the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS; Part II, III) (131) symptoms in both states were evaluated. This was done in order to compare on and off scores as an indicator of dopaminergic responsiveness and motor fluctuation severity. UPDRS IV was completed once assessing the degree of therapy related motor complications in this cohort.

Finally, motor activity was objectively recorded using the Parkinson's KinetiGraph (PKG; Global Kinetics Corporation, Australia), a wrist-worn medical device containing a tri-axial accelerometer that continuously captures movement data. The PKG algorithm automatically derives summary scores for bradykinesia and dyskinesia for each 2-minute epoch throughout the recording period. For analysis, data were aggregated across all valid recording days, where patients were instructed to wear the device on the wrist of their most affected side continuously for five consecutive days, 24 hours a day. Any intervals during which the device was not worn or when the patient remained immobile were excluded from the analysis. For the analyses performed in this thesis, the percentage of time spent in bradykinesia and dyskinesia across the recording period was subsequently derived based on standard PKG thresholds (132). These quantitative indices provide objective measures of the

duration of daily motor fluctuation and were compared to subjective reports of patients and between fluctuators and non-fluctuators as defined by the WOQ-19.

2.2.1 Questionnaires and Scales

Hamilton anxiety rating scale (HARS)

The HARS was used to evaluate the severity of anxiety symptoms. It distinguishes between psychic anxiety (e.g., mental agitation and emotional distress) and somatic anxiety (e.g., physical symptoms related to anxiety). The scale consists of 14 items, each rated from 0 (no symptoms) to 4 (very severe symptoms), yielding a total score between 0 and 56. Scores below 17 suggest mild anxiety, scores from 18 to 24 indicate mild to moderate anxiety, and scores from 25 to 30 reflect moderate to severe anxiety (133).

Hamilton Depression rating scale (HDRS)

The HDRS was initially developed to measure the severity of depressive symptoms and to track treatment response in adults already diagnosed with depression. As an interviewer-administered tool, it is not designed for diagnostic purposes. To ensure consistency in its use, a structured guide for administering the HDRS was introduced in 1988. The scale is most commonly used in two versions: a 17-item and a 21-item format. Scores from 0-9 indicate no depression, 10-20 mild, 21-30 moderate and > 30 points a severe depression. The 17-item version assesses depressive symptoms experienced over the past week, while the 21-item version includes four additional items (18–21) aimed at identifying specific subtypes of depression; these extra items do not contribute to the overall score. In this thesis the 17-item version of the HDRS was used.

Apathy Evaluation Scale (AES)

The AES is designed for screening apathy and assessing its severity within the past 4 weeks. It includes 14 items and each is rated from 0 to 3, contributing to a total score ranging from 0 to 42. Items 1 to 8 are scored inversely on a scale from 3 ("not at all") to 0 ("a lot"), while items 9 to 14 are scored directly from 0 ("not at all") to 3 ("a lot"). The presence of apathy in a patient is suggested at a score of 14 and above (125).

Wearing-Off Questionnaire (WOQ-19)

The WOQ-19 is a self-administered tool used to identify fluctuations in PD patients encompassing a range of motor symptoms (n=9), including tremor, overall stiffness, challenges in rising from a seated position, balance issues, slowness, weakness, speech difficulties, reduced hand coordination, and muscle cramps. Furthermore, the assessment of non-motor fluctuations consists of a total of ten items, namely, anxiety, mood fluctuations, cognitive impairment or dulled thinking, numbness, panic attacks, pain and general body aches, abdominal discomfort, and heightened sensitivity to temperature changes and sweating. Patients were asked to report whether a symptom was present and if it improved under medication (134). There are three sub-categories into which NMS are divided by the questionnaire: psychiatric, sensory and autonomic. The psychiatric category includes questions on anxiety, panic attacks, mood changes, and cognitive impairment characterised by a sense of mental cloudiness or dullness. The sensory category includes pain, numbness and aching. The autonomic category consists of symptoms such as abdominal discomfort, sweating, and experiencing hot and cold sensations (129). For the purpose of this analysis, we used the total non-motor score to identify non-motor fluctuators as well as the sub-score psychiatric to identify what we label as psychiatric fluctuators. This was done in order to in distinguish broader non-motor fluctuation profiles from those driven by affective symptomatology.

Parkinson's Disease Questionnaires-39 (PDQ-39)

The PDQ-39 is the most widely used disease-specific instrument for assessing HRQoL in individuals diagnosed with PD. It consists of 39 items grouped into eight domains: mobility, activities of daily living (ADL), emotional well-being, stigma, social support, cognition, communication, and bodily discomfort. The mobility domain assesses walking, balance, falls, and difficulties moving outside the home. ADL encompass self-care and routine tasks such as dressing, eating, housework, and using transportation. Emotional well-being captures mood-related aspects including depression, anxiety, hopelessness, and irritability. Stigma reflects feelings of embarrassment, being stared at, or social rejection. Social support measures perceived support from family and friends as well as feelings of being ignored. Cognition includes concentration, memory, and logical thinking difficulties. Communication evaluates problems with speaking, understanding, and other aspects of verbal interaction. Finally, bodily discomfort assesses pain, unpleasant sensations, and muscle cramps. Patients rate how often they have experienced each problem related to PD

during the past month using a five-point Likert scale: never, occasionally, sometimes, often, or always. Scores for each domain are calculated using the method of summated ratings described by Likert in 1932, where item responses are summed without weighting or standardization. The resulting domain scores are transformed to a scale ranging from 0 to 100, with higher scores indicating greater impairment (135,136).

Unified PD Rating Scale (UPDRS II-IV)

Parts II, III, and IV of the UPDRS were used to evaluate ADL, motor function and treatment-related complications. UPDRS Part II assesses motor experiences of daily living, including speech, swallowing, dressing, hygiene, handwriting, and mobility, based on patient-reported difficulties during the preceding week. UPDRS Part III was used to quantify examiner-rated motor impairment and responsiveness to dopaminergic medication. This section includes 18 items evaluating tremor, rigidity, bradykinesia, posture, and gait. Assessments were conducted in both the on and off medication states to determine dopaminergic responsiveness. UPDRS Part IV evaluates motor complications, including dyskinesias, motor fluctuations, and painful dystonia, over the preceding week. Higher scores on Parts II–IV indicate greater impairment or complication burden (137).

2.3. Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics, Version 28. Descriptive statistics were calculated for all variables, including mean (M) and standard deviation (SD). To allow for a more nuanced characterization of the examined cohorts, the analyses were conducted separately for the Wearing-Off Questionnaire–19 (WOQ-19) non-motor subscale and its psychiatric subgroup. The non-motor subscale encompasses a broad range of fluctuation phenomena, including autonomic, sensory, cognitive, and emotional domains, thereby providing an overall measure of non-motor wearing-off. In contrast, the psychiatric subgroup isolates mood- and anxiety-related symptoms, offering a more specific assessment of affective fluctuations. Examining these dimensions separately enables differentiation between general non-motor fluctuations and those primarily driven by psychiatric symptomatology and their potentially distinct impact on HRQol. Patients were classified as non-motor fluctuators if they reported ≥1 non-motor symptom that improved with dopaminergic medication on the WOQ-19 non-motor scale, and as psychiatric fluctuators if ≥1 psychiatric item improved with medication on the WOQ-19 psychiatric subset.

Participants with a score of 0 on the respective scales were classified as non-fluctuators. Group comparisons between fluctuators and non-fluctuators were performed using the Mann–Whitney U test for independent, nonparametric samples. This test was chosen because several continuous variables (e.g., HARS, HDRS, PDQ-39, and PKG measures) did not follow a normal distribution according to the Shapiro–Wilk test (see suppl. Table 1). Differences between UPDRS part III scores in the ON and OFF conditions were analyzed using the Wilcoxon signed-rank test. This non-parametric test was applied due to the non-normal distribution of the data and the paired nature of the measurements.

The primary objective was to investigate group differences between fluctuators and non-fluctuators in affective symptoms, specifically anxiety, depression, and apathy. In addition, demographic variables (sex, age, and disease duration), motor severity and complications (UPDRS parts III and IV), and QoL (assessed using the PDQ-39 index) were compared between the two groups. Furthermore, objective motor outcomes derived from the portable PKG (percentage of time spent in bradykinesia and dyskinesia) were analysed and matched to patients' subjective symptom reports. Differences in the percentage of time spent in bradykinesia and dyskinesia between fluctuators and non-fluctuators, as classified by both WOQ-19 scales, were evaluated.

The significance level was set at $\alpha = .05$. Accordingly, *p*-values below .05 were considered statistically significant, indicating rejection of the null hypothesis (no difference) in favour of the alternative hypothesis (a difference exists), acknowledging a potential Type I error. To control the familywise error rate, Bonferroni correction was applied to each family of multiple comparisons (e.g., psychiatric outcomes or motor outcomes).

3. Results

3.1 Description of the cohort

The studied sample comprised 151 patients, 88 of whom were female and 63 male, who had a diagnosis of advanced PD (for demographics see Table 1). The age ranged from 47 to 82 years with a mean value of 62.93 ± 7.03 years (*SD*). Disease duration was collected in 147 individuals of the sample and spans from 2 to 28 years (*M*=10.31 ± 4.23). Motor severity and motor complications were assessed using the MDS-UPDRS Parts II, III, and IV. UPDRS II scores were available for 147 participants and indicated mild functional impairment in the on state (*M* = 8.20, *SD* = 6.71), which increased to moderate impairment during the off state (*M* = 17.65*, SD* = 7.72). UPDRS III motor examination scores showed a similar pattern: among the 133 patients assessed in the on state, mean motor severity was moderate (*M* = 23.73*, SD* = 12.00), while off state assessment available for 137 participants demonstrated substantially greater impairment (*M* = 43.34*, SD* = 14.77). Motor complications, captured by UPDRS Part IV, were reported for 142 individuals and revealed a mean score of 6.15 (*SD* = 3.27), consistent with a cohort in the advanced stages of PD and typical for patients being evaluated for device-aided therapies. In the total cohort, PDQ-39 Summary Index scores (summary index: *M* = 35.74, *SD* = 17.59) indicated markedly reduced HRQoL consistent with advanced PD, demonstrating substantial impairment across multiple domains (see Table 1).

	n	*M* ± *SD*
gender	151	(m:f) 63:88
age (years)	151	62.93 ± 7.03
disease duration (years)	147	10.31 ± 4.23
UPDRS II on total score (points)	147	8.20 ± 6.71
UPDRS II off total score (points)	147	17.65 ± 7.72
UPDRS III on total score (points)	133	23.73 ± 12.00
UPDRS III off total score (points)	137	43.34 ± 14.77
UPDRS IV total score (points)	142	6.15 ± 3.27
PDQ-39 Summary Index	143	35.74 ± 17.59

Table 1: Demographics and UPDRS scores; Note: Unified Parkinson disease Rating Scale=UPDRS

Mood and neuropsychiatric symptoms were assessed using the HDRS, the HARS, and the AES (see Table 2). HDRS scores were available for 146 patients and indicated mild to moderate depressive symptom severity (*M* = 8.52*, SD* = 6.02) across participants. Anxiety severity, measured in 150 participants, showed a comparable range (*M* = 9.97*, SD* = 7.59). Apathy scores, collected from 141 individuals, reflected moderate apathy levels (*M* = 29.55*,*

SD = 7.96). In addition to continuous measures, dichotomous self-reports were collected for anxiety and depression. Among the 150 patients who provided anxiety yes/no data, 41% reported anxiety, and among the 146 individuals with available depression yes/no data, 49% reported depressive symptoms. These descriptive findings reflect a cohort with a high prevalence of mood symptoms also consistent with advanced Parkinson's disease.

	n	*M* ± *SD*
HDRS (points)	146	8.52 ± 6.02
HARS (points)	150	9.97 ± 7.59
AES (points)	141	29.55 ± 7.96

Table 2:Neuropsychiatric data of cohort; Note: Hamilton anxiety rating scale =HARS, Hamilton depression rating scale=HDRS, Apathy Evaluation Scale= AES

3.2. Comparing anxiety, depression and apathy scores in fluctuators vs. non-fluctuators grouped by the WOQ-19 *non-motor subscale*

After dividing the sample into two subgroups using the WOQ-19 non-motor subscale, 119 patients were classified as fluctuators and 32 as non-fluctuators. Due to missing data, not all patients could be included in every analysis, resulting in varying group sizes across measures. For the analysis of anxiety, the fluctuators group comprised 119 participants and the non-fluctuators group 31 participants. For depression, the fluctuators group included 115 participants and the non-fluctuators group 31 participants. To examine apathy, 115 fluctuators and 26 non-fluctuators were included (see Table 3).

Fluctuators showed numerically higher mean scores on the HARS (*M* = 10.92*, SD* = 7.55) and HDRS (*M* = 9.30*, SD* = 5.98) compared with non-fluctuators (*M* = 6.32*, SD* = 6.66, *M* = 5.61*, SD* = 5.30, respectively). The mean scores on the AES were similar between groups, with non-fluctuators scoring *M* = 28.15 *(SD* = 8.50) and fluctuators scoring *M* = 29.86 *(SD* = 7.83). A Mann–Whitney U test was conducted to determine whether there were significant differences in anxiety, depression, and apathy scores between groups. Statistically significant differences were found between fluctuators and non-fluctuators for both anxiety and depression. Specifically, for anxiety (HARS), $U = 1126$, $Z = -3.34$, $p < .001$, and for depression (HDRS), $U = 1091$, $Z = -3.32$, $p < .001$. This increase crosses a validated clinical

threshold and corresponds to a clinically noticeable increase in symptom burden. No significant difference was observed for apathy, $U = 1243$, $Z = -1.34$, $p = .18$. After Bonferroni correction for the three psychiatric outcomes (adjusted $\alpha = .017$) the results discussed above remained unchanged.

Finally, no statistically significant difference between the groups was found regarding age, disease duration or gender as well as UPDRS III. Fluctuators scored significantly higher on the UPDRS Part IV ($M = 6.83$, $SD = 3.12$) compared with non-fluctuators ($M = 3.30$, $SD = 2.20$), $U = 563.5$, $Z = -5.17$, $p < .001$, indicating a greater burden of motor fluctuations in this group ($\Delta M \approx 3.53$ points). Table 3 and Figure 1 illustrate these results.

	non-fluctuators $M \pm SD$	*fluctuators* $M \pm SD$	*p-value*
age (years)	64.22±7.89	62.58±6.77	.24
disease duration (years)	9.91±4.65	10.43±4.13	.45
gender (f/m)	22/10	66/53	.18
UPDRS III off med total score (points)	39.88±13.29	44.11±15.03	.19
UPDRS III on med total score (points)	24.75±13.18	23.50±11.78	.70
UPDRS IV (points)	3.30±2.20	6.83±3.12	**<.001**
HARS (points)	6.32±6.66	10.92±7.55	**<.001**
HDRS (points)	5.61±5.30	9.30±5.98	**<.001**
AES (points)	28.15±8.50	29.86±7.83	.18

Table 3: Comparison of fluctuators and non-fluctuators using the WOQ-19 non-motor scale; Note: Hamilton anxiety rating scale =HARS, Hamilton depression rating scale=HDRS, Unified PD Rating Scale=UPDRS, Apathy Evaluation Scale= AES

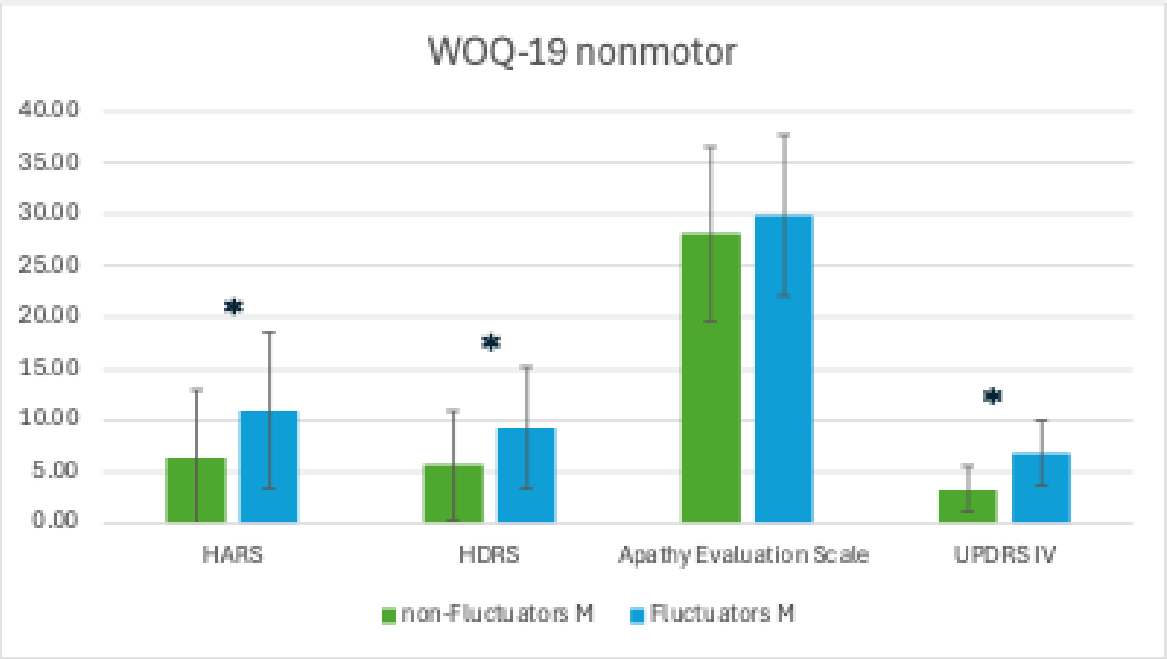

*Figure 1: Comparison of non-motor fluctuators vs. non-fluctuators using HDRS (p<.001), HARS (p<.001), AES (p=.18) and the UPDRS IV (p<.001); Note: Hamilton anxiety rating scale=HARS, Hamilton depression rating scale=HDRS, Unified Parkinson Disease Rating Scale=UPDRS, units: points, * indicates statistically significant results.*

3.3. Comparing anxiety, depression and apathy scores in fluctuators vs. non-fluctuators using the WOQ-19 *psychiatric subgroup*

After dividing the sample into two subgroups, 102 patients were classified as fluctuators and 49 as non-fluctuators based on the WOQ-psychiatric subgroup. Due to missing data, not all participants could be included in every analysis, resulting in varying group sizes across measures. For the analysis of anxiety, the fluctuators group comprised 102 participants, and the non-Fluctuators group comprised 48 participants. For depression, the fluctuators group included 98 participants and the non-Fluctuators group 48 participants. To examine apathy, 99 fluctuators and 42 non-fluctuators were included. For summary see Table 4.

Fluctuators showed numerically higher mean scores on the HARS (M = 11.88, SD = 7.56) and the HDRS (M = 9.84, SD = 5.97) compared to non-fluctuators (M = 8.92, SD = 5.90; M = 5.83, SD = 5.20) indicating greater symptom severity. The mean scores on the AES were similar between groups, with non-fluctuators scoring M = 27.86 (SD = 7.61) and fluctuators scoring M = 30.26 (SD = 8.03). Similar to the results of the previous section, there was a statistically significant difference between fluctuators and non-fluctuators in anxiety and

depression scores on Mann–Whitney U test. Specifically, for anxiety (HARS), a significant difference was found (U = 1252, Z = −4.82, p < .001). The difference in HARS scores between fluctuators and non-fluctuators ($\Delta M \approx 6$ points) represents a clinically meaningful increase in anxiety severity, shifting the group mean from the minimal to mild range. This finding suggests that psychiatric fluctuators experience a higher anxiety burden. Fluctuators also showed significantly higher scores on the HDRS, (U = 1370, Z = −4.10, p < .001) indicating increased depressive symptom burden. Although mean HDRS scores in both groups remained within the non-clinical to mild range, fluctuators showed significantly higher depression scores ($\Delta M \approx 4$ points), representing a clinically relevant difference. This was not the case for apathy scores, where no statistically significant difference was found between the two groups (U = 1665, Z = −1.97, p = .061). After Bonferroni correction for the three psychiatric outcomes (adjusted α = .017) the results discussed above remained unchanged. Table 4 and Figure 2 illustrate these findings.

Again, the groups did not differ in age, gender UPDRS III score and disease duration, however, fluctuators (M = 6.96, SD = 3.02) compared with non-fluctuators (M = 4.36, SD = 3.11) showed a higher degree of motor complications reflected by higher UDPRS IV scores (U = 1167.5, Z = −4.38, p < .001, $\Delta M \approx 2.6$ points), indicating a clinically relevant increased burden of motor complications in the psychiatric fluctuation subgroup.

	non-fluctuators $M \pm SD$	*fluctuators* $M \pm SD$	*p-value*
age (years)	64.35 ± 7.70	62.25 ± 6.61	.11
disease duration (years)	9.89 ± 4.37	10.5 ± 4.18	.36
gender (f/m)	32/17	56/46	.23
UPDRS III off med (points)	41.35 ± 13.73	44.15 ± 15.17	.31
UPDRS III on med (points)	25.34 ± 12.29	23.08 ± 11.90	.27
UPDRS IV (points)	4.36 ± 3.11	6.96 ± 3.02	**<.001**
HARS (points)	5.92 ± 5.90	11.88 ± 7.56	**<.001**
HDRS (points)	5.83 ± 5.20	9.84 ± 5.97	**<.001**
AES (points)	27.86 ± 7.61	30.26 ± 8.03	.061

Table 4: Comparison of fluctuators and non-fluctuators using the WOQ-19 psychiatric scale; Note: Hamilton anxiety rating scale=HARS, Hamilton depression rating scale=HDRS, Unified Parkinson Disease Rating Scale=UPDRS, Apathy Evaluation Scale= AES

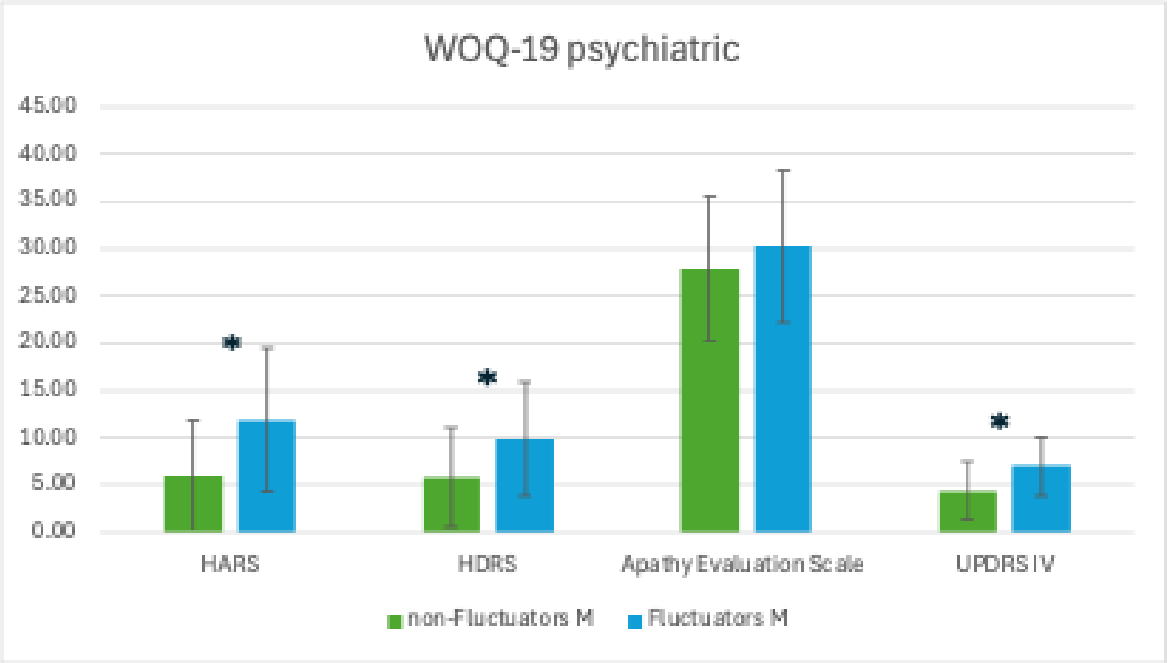

*Figure 2: Comparison of psychiatric fluctuators vs. non-fluctuators using HDRS (p<.001), HARS (p<.001), Apathy Evaluation Scale (p=.18) and the UPDRS IV (p<.001); Note: Hamilton anxiety rating scale=HARS, Hamilton depression rating scale=HDRS, Unified Parkinson Disease Rating Scale=UPDRS, units: points, * indicates statistically significant results.*

3.4. Comparing quality of life scores in fluctuators vs. non-fluctuators grouped by the WOQ-19 *non-motor subscale*

To examine whether the presence of non-motor fluctuations were associated with worse quality-of-life outcomes, PDQ-39 summary index and subdomain scores were compared between fluctuators and non-fluctuators as defined by the WOQ-19 non-motor subscale (see Table 5 and Figure 3). Across all PDQ-39 domains, fluctuators reported numerically higher mean scores, indicating poorer QoL.

A Mann–Whitney U test revealed that group differences approached significance for the PDQ-39 summary index ($U = 1156$, $Z = -1.91$, $p = .056$). Statistically significant differences were found for several PDQ-39 subscales, including emotional well-being ($U = 965.5$, $Z = -2.87$, $p = .004$), cognition ($U = 1068$, $Z = -2.33$, $p = .020$), communication ($U = 1099$, $Z = -2.22$, $p = .027$), and bodily discomfort ($U = 830$, $Z = -3.62$, $p < .001$). No significant group differences were found for mobility ($U = 1208$, $Z = -1.53$, $p = .125$), ADL ($U = 1132$, $Z = -1.15$, $p = .249$), stigma ($U = 1297$, $Z = -1.12$, $p = .264$), or social support ($U = 1349$, $Z = -0.87$, $p = .385$). After Bonferroni correction for multiple comparisons (adjusted $\alpha = .006$), differences in ***emotional well-being*** **and** ***bodily discomfort*** remained statistically significant.

These findings indicate that non-motor fluctuations are particularly associated with poorer emotional and impaired internal physical experience impacting QoL, whereas physical/motor, functional and social domains appeared less affected.

PDQ39 domain	*non-fluctuators* $M \pm SD$	*fluctuators* $M \pm SD$	*U*	*Z*	*p*
Mobility score	36.35 ± 29.43	44.78 ± 26.52	1208	-1.53	.13
Adl score	34.54 ± 26.81	40.98 ± 24.43	1132	-1.15	.25
Emotional well-being	22.57 ± 20.95	35.17 ± 21.55	965.5	-2.87	**.004**
Stigma score	31.97 ± 27.86	36.91 ± 25.05	1297	-1.12	.26
Social score	16.66 ± 25.72	17.88 ± 20.49	1348.5	-0.87	.39
Cognition score	23.31 ± 19.74	33.37 ± 21.77	1068	-2.33	.02
Communication score	20.98 ± 21.03	32.84 ± 25.41	1098.5	-2.22	.027
Discomfort score	27.55 ± 22.96	49.12 ± 26.20	830	-3.62	**<.001**
Summary index	30.37 ± 20.09	36.94 ± 16.84	1155.5	-1.91	.056

Table 5: Comparison of fluctuators and non-fluctuators on PDQ39 domains using WOQ-19 non-motor scale; Note: activities of the daily living=adl, all units: points, adjusted α = .006.

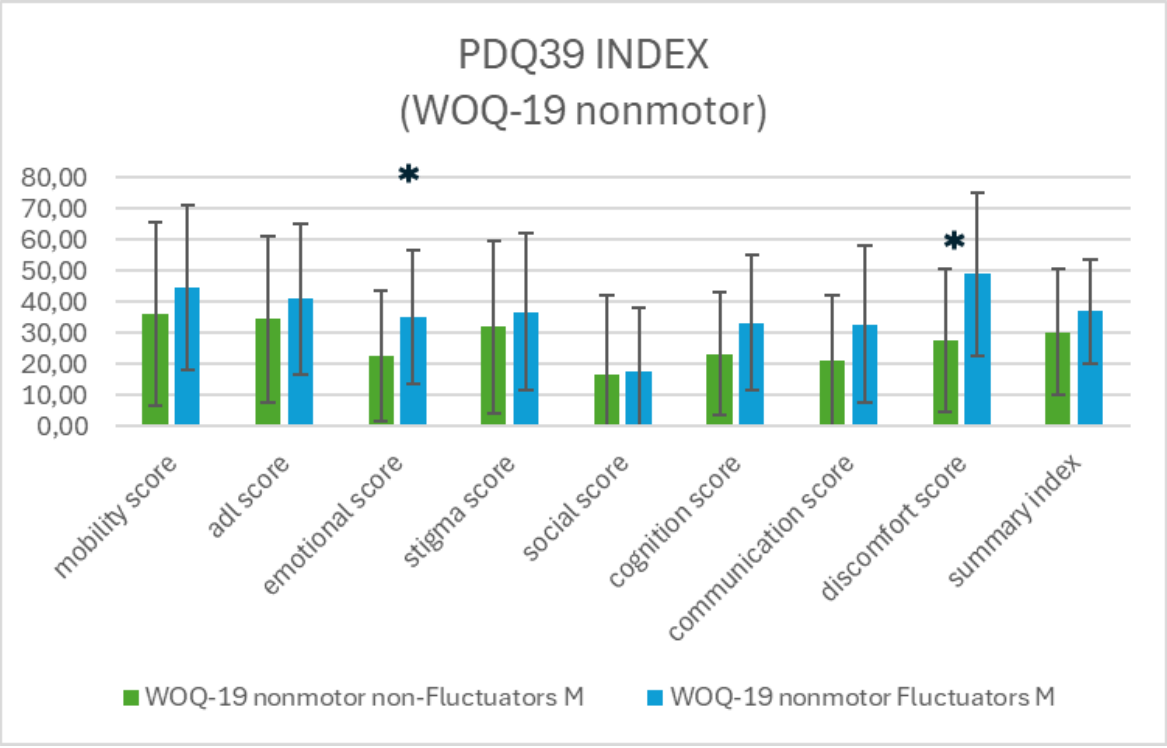

Figure 3: Comparison of fluctuators and non-fluctuators on the PDQ39 index and subitems using the WOQ19 non-motor scale. Significant results are indicated with "". PDQ-39 index (p=.056), PDQ-39 "mobility" (p=.13), PDQ-39 "ADL" (p=.25), PDQ-39 "emotional well-being" (p=.004), PDQ-39 "stigma" (p=.26), PDQ-39 "social support" (p=.39), PDQ-39 "cognition" (p=.02), PDQ-39 "communication" (p=.027) and PDQ-39 "bodily discomfort" (p<.001). note; activities of the daily living=adl, units: points, * indicates statistically significant results after Bonferroni correction*

3.5. Comparing quality of life scores in fluctuators vs. non-fluctuators grouped by the WOQ-19 *psychiatric subscale*

Across all domains, fluctuators reported numerically higher impairment scores than non-fluctuators, indicating poorer QoL. A Mann–Whitney U test revealed a statistically significant group difference for the overall PDQ-39 summary index, $U = 1601$, $Z = -2.31$, $p = .021$. Significant group differences were also found for several PDQ-39 subscales: emotional well-being ($U = 1167.5$, $Z = -4.38$, $p < .001$), stigma ($U = 1643$, $Z = -2.05$, $p = .040$), social support ($U = 1625$, $Z = -2.19$, $p = .028$), cognition ($U = 1376$, $Z = -3.25$, $p = .001$), communication ($U = 1527$, $Z = -2.64$, $p = .008$), and bodily discomfort ($U = 1528$, $Z = -2.64$, $p = .008$). No significant differences were observed for mobility ($U = 1823$, $Z = -1.32$, $p = .186$) or ADL ($U = 1837$, $Z = -0.31$, p = .759). After Bonferroni correction for multiple comparisons (adjusted $\alpha = .006$), the differences in **emotional well-being and cognition** remained statistically significant. Table 6 and Figure 4 illustrate these findings. Overall, these findings indicate that patients experiencing psychiatric fluctuations report a significantly poorer QoL, particularly in the emotional and cognitive domains of the PDQ-39.

PDQ39 domain	*non-fluctuators* $M \pm SD$	*fluctuators* $M \pm SD$	*U*	*Z*	*p*
Mobility score	38.89 ± 28.61	45.06 ± 26.47	1823	-1.32	.19
Adl score	38.74 ± 26.08	40.30 ± 24.50	1836.5	-0.31	.76
Emotional well-being	22.11 ± 19.20	37.38 ± 21.50	1167.5	-4.38	**<.001**
Stigma score	29.91 ± 25.81	38.57 ± 25.14	1642.5	-2.05	.04
Social score	13.89 ± 22.96	19.24 ± 20.68	1625	-2.19	.028
Cognition score	23.36 ± 19.77	34.96 ± 21.64	1376	-3.25	**.001**
Communication score	23.90 ± 26.72	33.51 ± 23.85	1527	-2.64	.008
Discomfort score	35.90 ± 24.94	49.07 ± 26.85	1527.5	-2.64	.008
Summary index	30.56 ± 17.52	37.90 ± 17.24	1600.5	-2.31	.021

Table 6: Comparison of fluctuators and non-fluctuators on PDQ39 and subitems using WOQ-19 psychiatric subscale for differentiation Note: activities of the daily living=adl, units: points, adjusted α = .006

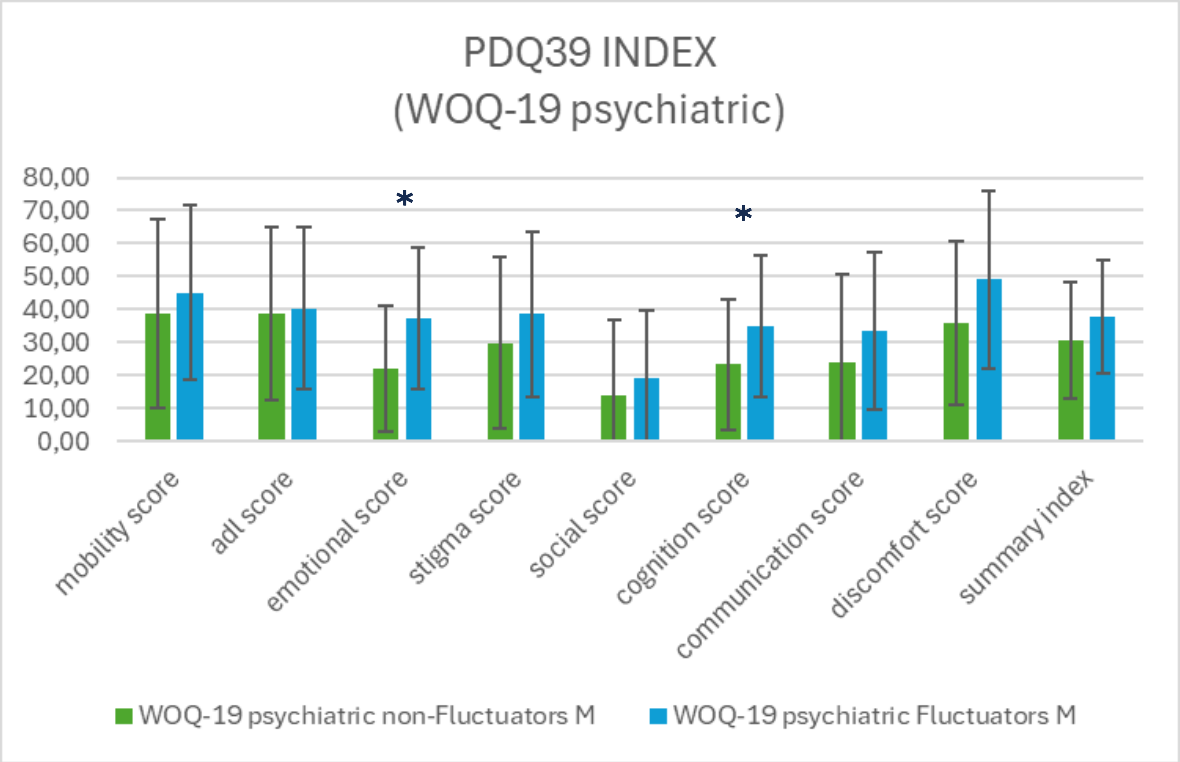

Figure 4: Comparison of fluctuators and non-fluctuators on the PDQ39 index and subitems using the WOQ19 psychiatric scale. Significant results indicated with a "". PDQ-39 index (p=.021), PDQ-39 "mobility" (p=.19), PDQ-39 "ADL" (p=.76), PDQ-39 "emotional well-being" (p<.001), PDQ-39 "stigma" (p=.04), PDQ-39 "social support" (p=.028), PDQ-39 "cognition" (p=.001), PDQ-39 "communication" (p=.008) and PDQ-39 "bodily discomfort" (p=.008). Note: activities of the daily living=adl, units: points, * indicates statistically significant results after Bonferroni correction*

3.6. Comparing UPDRS III Motor Scores (on vs. off medication)

Motor performance was assessed using the UPDRS Part III in both the on and off medication states to quantify dopaminergic responsiveness. Across the total cohort, UPDRS III scores improved significantly following dopaminergic medication, indicating a robust treatment response. Before Differentiation (see Table 1 und 7) in fluctuators and non-fluctuators, participants had a mean UPDRS Part III score in the on-medication state of 23.73 (SD = 12.00; n = 133). In contrast, the off medication UPDRS Part III total score was substantially higher, with a mean of 43.34 (SD = 14.77; n = 137). In fact, there was a significant difference in UPDRS-III values between the on and off (Z = −9.99, p <.001) indicating preserved levodopa response/improved motor performance on vs. off medication.

	n	$M \pm SD$
UPDRS3 on total score	133	23.73 ± 12.00
UPDRS3 off total score	137	43.34 ± 14.77

Table 7: Descriptive statistic before differentiation in fluctuators and non-fluctuators

For the WOQ-19 non-motor subgroup, no statistically significant group differences emerged between on and off examination (see Table 8). Off-state motor scores did not differ significantly between non-fluctuators and fluctuators, $U = 1166$, $Z = -1.30$, $p = .19$, and on-state scores likewise showed no significant difference, $U = 1241$, $Z = -0.39$, $p = .70$. Similarly, for the WOQ-19 psychiatric subgroup, Mann–Whitney U tests showed no significant differences between non-fluctuators and fluctuators in either the off or on medication state. Off-state motor severity did not differ significantly between groups, $U = 1727.5$, $Z = -1.00$, $p = .31$, likewise on-state scores were comparable, $U = 1581.5$, $Z = -1.11$, $p = .27$. Overall, neither non-motor nor psychiatric fluctuation status corresponded to differences in UPDRS III on and off motor performance.

	state	*non-fluctuators* $M \pm SD$	*fluctuators* $M \pm SD$	*U*	*Z*	*p*
WOQ-19 non-motor	**off**	39.88 ± 13.29	44.11 ± 15.03	1166	-1.30	.19
	on	24.75 ± 13.18	23.50 ± 11.78	1241	-0.39	.7
WOQ-19 psychiatric	**off**	41.35 ± 13.73	44.15 ± 15.17	1727.5	-1.00	.31
	on	25.34 ± 12.29	23.08 ± 11.90	1581.5	-1.11	.27

Table 8: Comparison of UPDRS III on/off differentiating in fluctuators and non-fluctuators, units: points

3.7. Objective data on motor symptoms: Comparing time spent in bradykinesia and dyskinesia in fluctuators vs. non-fluctuators using a wearable device

Objective motor data obtained from the PKG were analysed to examine whether fluctuators differed from non-fluctuators in the percentage of time spent in bradykinesia and dyskinesia. Both groups (non-motor/psychiatric fluctuators) were again analysed separately.

3.7.1. WOQ-non-motor-subscale & percentage of time spent in bradykinesia/dyskinesia

The group of non-motor fluctuators comprised 118 patients, whereas the non-fluctuators group included 32 patients. Due to missing data, one participant had to be excluded from the analysis. The percentage of time spent in bradykinesia ranged from 1% to 100% ($M = 46.85$), and the percentage of time spent in dyskinesia ranged from 0% to 84.9% ($M = 15.14$). Table 9 shows the mean and standard deviation of percentage of time spent in bradykinesia and dyskinesia for fluctuators and non-fluctuators. Non-fluctuators exhibited a greater mean

bradykinesia time (*M* = 65.03%, *SD* = 30.52%) than fluctuators (*M* = 41.92 %, *SD* = 30.44%). Conversely, fluctuators showed a greater mean dyskinesia time (*M* = 17.43%, *SD* = 20.71%) compared with non-Fluctuators (*M* = 6.6%, *SD* = 11.12%).

A significant difference was found on Mann-Whitney U test between groups for percentage of time spent in bradykinesia, $U = 1090$, $Z = -3.66$, $p < .001$, and for percentage of time spent in dyskinesia, $U = 1159$, $Z = -3.36$, $p < .001$. These remain significant after Bonferroni correction.

	non-fluctuators *M ± SD*	*fluctuators* *M ± SD*	*U*	*Z*	*p*
Time in bradykinesia (%)	65.03 ± 30.52	41.92 ± 30.44	1090	-3.66	**<.001**
Time in dyskinesia (%)	6.69 ± 11.12	17.43 ± 20.71	1159	-3.36	**<.001**

Table 9: PKG data: Comparison of percentage time spent in bradykinesia and dyskinesia between fluctuators and non-fluctuators (WOQ-19 non-motor)

Figure 5 illustrates these findings. Both groups spent more time in bradykinesia than in dyskinesia. However, the fluctuators group spent a greater proportion of time in dyskinesia than the non-fluctuators, whereas the non-fluctuators group spent more time in bradykinesia than the fluctuators.

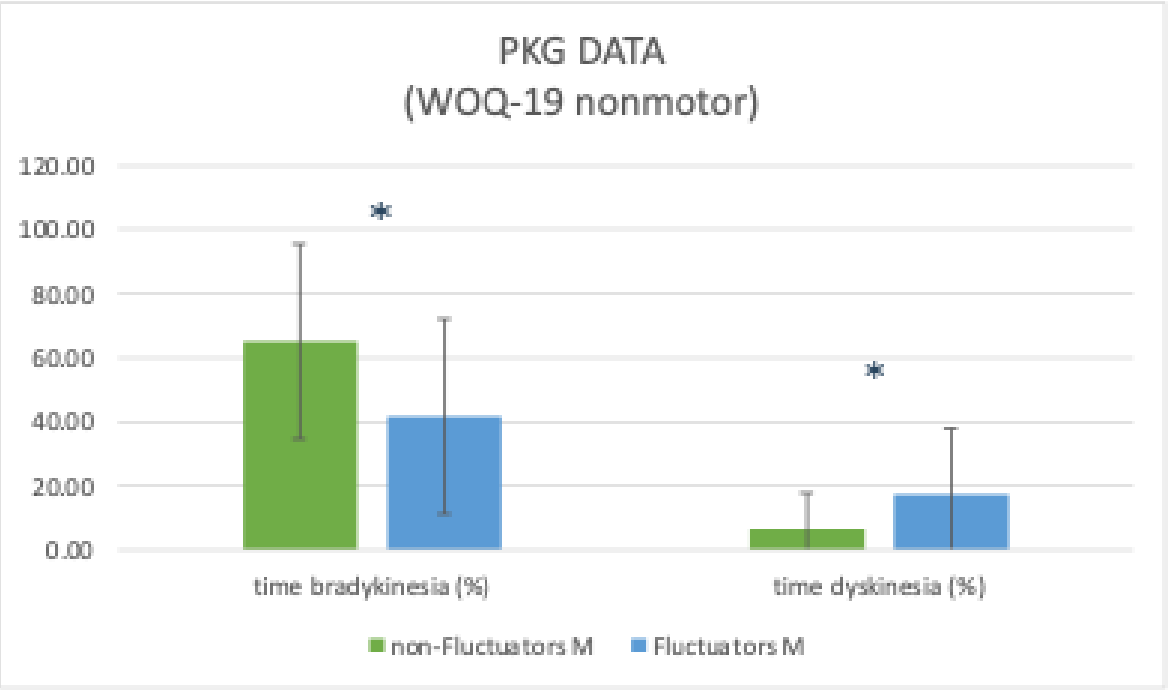

*Figure 5: PKG data Comparison between fluctuators and non-fluctuators in "time spent in bradykinesia" (p <.001) and "time spent in dyskinesia" (p <.001) using the WOQ-19-non motor scale; units: %, * indicates statistically significant results after Bonferroni correction*

3.7.2. WOQ-psychiatric-subgroup & time spent in bradykinesia/dyskinesia

Psychiatric fluctuators (n =101) spent significantly more time in dyskinesia (M = 18.01%, SD = 21.15%) and less time in bradykinesia (M = 39.98%, SD = 30.15%) compared to non-fluctuators (n = 49), who spent a larger proportion of time in bradykinesia (M = 61.00%, SD = 30.71%) and less time in dyskinesia (M = 9.22%, SD = 14.17%). Mann–Whitney U tests confirmed these differences: fluctuators spent significantly less time in bradykinesia, U = 1522, Z = −3.82, p < .001, and significantly more time in dyskinesia, U = 1701.5, Z = −3.11, p = .002. Both differences remained statistically significant after Bonferroni correction for multiple comparisons (adjusted α = .025). Table 10 and Figure 6 illustrate these findings.

	non-fluctuators $M \pm SD$	*fluctuators M* $\pm SD$	*U*	*Z*	*p*
Time in bradykinesia (%)	61.00 ± 30.71	39.98 ± 30.15	1522	-3.82	**<.001**
Time in dyskinesia (%)	9.22 ± 14.17	18.01 ± 21.15	1701.5	-3.11	**.002**

Table 10: PKG data: Comparison of percentage time spent in bradykinesia and dyskinesia between fluctuators and non-fluctuators (WOQ-19 psychiatric)

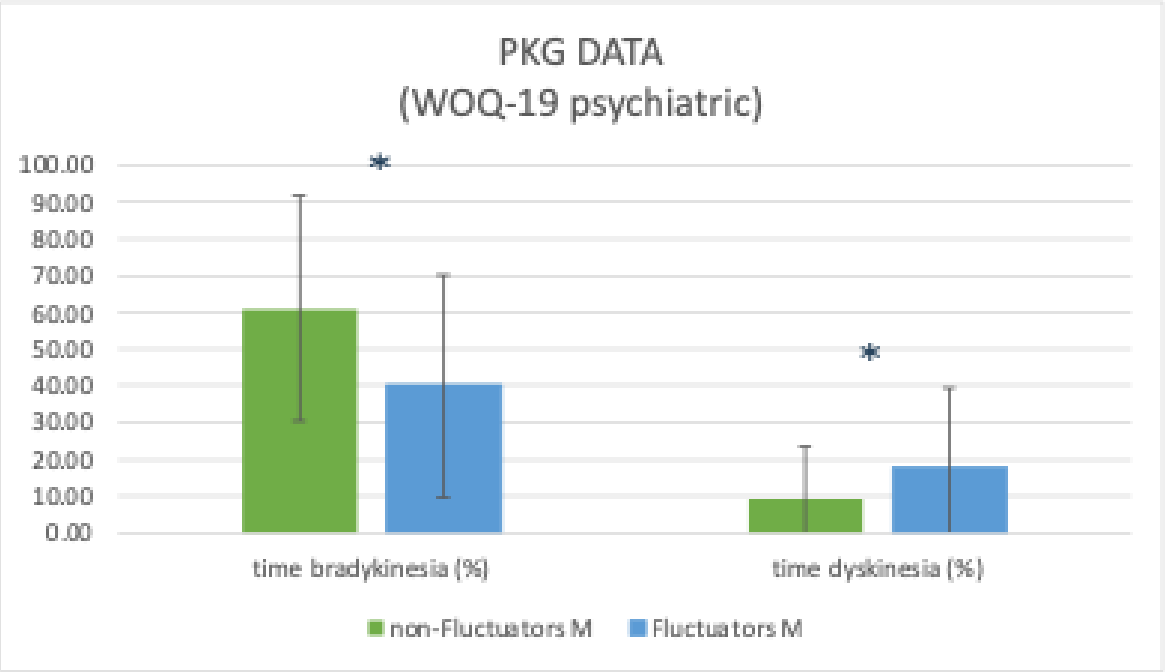

*Figure 6: PKG data Comparison between fluctuators and non-fluctuators in "time spent in bradykinesia" (p>0001) and "time of dyskinesia" (p=.002) using the WOQ-19-psychiatric scale. units: %, * indicates statistically significant results after Bonferroni correction*

These findings indicate that PD patients experiencing non-motor fluctuations generally but also psychiatric fluctuations more specifically, as defined by the WOQ-19 non-motor/psychiatric subscale, exhibit more pronounced motor fluctuations on objective PKG measures, characterized by increased dyskinesia and reduced bradykinesia time.

4. Discussion

The present study investigated the clinical, affective, and motor characteristics associated with non-motor and psychiatric fluctuations in PD, using both subjective and objective assessments to characterize fluctuation phenotypes. Two complementary definitions of fluctuation status were applied, based on the WOQ-19 non-motor subscale and the psychiatric subset, enabling distinct subgrouping into a broad non-motor fluctuation phenotype and a more affectively focused psychiatric fluctuation subgroup. Affective symptom load as reported by HARS, HDRS and AES served as primary outcome measures and were compared between the groups (fluctuators vs. non fluctuators). In addition, data on QoL, data from continuous objective motor monitoring with the Parkinson's KinetiGraph (PKG) and dopaminergic responsiveness derived from MDS-UPDRS III on vs. off levodopa provided mechanistic insight into the motor correlates of these fluctuation states.

Across both classification approaches (non-motor and psychiatric), fluctuators demonstrated a markedly higher burden of psychiatric symptoms, specifically anxiety ($p < .001$ for both) and depression ($p < .001$ for both), than non-fluctuators, whereas apathy did not differ between groups (non-motor: $p = .18$; psychiatric: $p = .061$). Additionally, quality-of-life impairments, especially in the area of emotional well-being (both subscales), bodily discomfort (non-motor subscale) and cognition (psychiatric subscale), were markedly worse in both fluctuator groups. Objective PKG measurements indicated that fluctuators spent more of the day in dyskinesia (non-motor: $p < .001$; psychiatric: $p = .002$). and less in bradykinesia ($p < .001$ for both), paralleled by significantly higher UPDRS IV scores ($p < .001$ for both). Interestingly, no group differences in UPDRS III on and off scores were found.

4.1. Affective symptom burden in fluctuators

A principal finding of this study is that patients identified as fluctuators, whether by the broader WOQ-19 non-motor subscale or the more specific psychiatric subscale, showed significantly higher levels of anxiety and depression. These results are consistent with the growing body of evidence indicating that psychiatric symptoms in PD are not static comorbidities but often fluctuate in close temporal association with dopaminergic state changes (138–140). Anxiety is particularly sensitive to acute off states and may escalate

rapidly, whereas depressive symptoms also tend to worsen with insufficient dopaminergic stimulation but typically exhibit a more gradual fluctuation pattern (141,142). Shared neurochemical mechanisms, particularly within mesolimbic dopaminergic and serotonergic pathways, are thought to underlie the parallel expression of motor and affective fluctuations (74,143,144). Importantly, the magnitude of the group differences observed in this study was not only statistically significant but clinically meaningful. Fluctuators scored within the mild range on both the HARS and the HDRS, while non-fluctuators remained in the minimal to non-clinical range. These differences may translate into impaired social functioning, reduced engagement in physical activity, and increased sensitivity to motor symptom fluctuations. Even when fluctuators are defined solely by affective symptoms (psychiatric fluctuators), the clinical profile closely mirrors that of the broader non-motor fluctuation group. The similar pattern of results obtained across the two WOQ-19 classifications suggests that psychiatric fluctuations represent a central feature of non-motor wearing-off.

In contrast, apathy levels did not differ between fluctuators and non-fluctuators using either WOQ-19 definition. Although apathy is typically more prevalent in advanced PD, the mean AES scores in this cohort remained in the low-to-moderate range (145). This may reflect a selection bias inherent to candidates for device-aided therapies, who may exhibit relatively preserved motivation and cognitive capacity. Consequently, baseline apathy levels in this sample were lower than might be expected in unselected advanced PD populations. Our findings align with the conceptualization of apathy as a trait-like, motivational deficit linked primarily to structural and functional disruptions within frontostriatal and limbic circuits. Unlike anxiety and depression, apathy appears relatively insensitive to acute dopaminergic fluctuations and has been reported to be more strongly associated with cognitive decline, executive dysfunction, and disease progression (90). The present findings therefore reinforce the distinction between state-like affective symptoms that fluctuate with dopaminergic tone and trait-like motivational deficits that remain stable across both fluctuator-subgroups.

Regarding the dichotomous self-reports that were collected for anxiety and depression, our results are in line with current literature, supporting the conclusion that anxiety and depression are highly prevalent in advanced Parkinson's disease. For example, Weintraub et al. state that in advanced disease, approximately 60% experience depressive symptoms, and anxiety is frequently comorbid, often affecting a substantial proportion of patients (74). Broen et al. found a pooled prevalence of anxiety disorders of 31%, with clinically

significant anxiety symptoms present in about 26%, but individual studies report rates up to 55% (146). Yamanishi et al. found anxiety in 55% and depression in 56% of a Japanese PD cohort, with substantial overlap (147).

4.2. Distinction between non-motor and psychiatric fluctuation phenotypes

Examining both WOQ-19-based fluctuation categories allowed for differentiation of broader NMS from more targeted affective fluctuations. The strong overlap in psychiatric symptom burden and HRQoL impairment between the two groups suggests shared underlying mechanisms. However, the psychiatric subgroup represents a more refined phenotype characterized by disproportionate affective reactivity to dopaminergic state changes. This distinction is clinically relevant, especially in the context of treatment. Patients with predominant psychiatric fluctuations may benefit from tailored treatment strategies that specifically address emotional lability, off-related anxiety, and mood dysregulation. Conversely, those identified as general non-motor fluctuators may also require interventions targeting sensory, autonomic, and cognitive variability in addition to or instead of affective symptoms (148,149).

4.3. Quality of life impacts and domain-specific differences

QoL measured by the PDQ-39 Summary Index was significantly impaired in this cohort, reflecting a level of HRQoL impairment characteristic of advanced PD populations. The observation that emotional well-being is consistently worse in fluctuators, regardless of whether they are defined by the WOQ-19 non-motor or psychiatric subscale, indicates that affective dysregulation is a shared and central component of the both fluctuation phenotypes. This may indicate that both types of fluctuations may have a greater impact on subjective physical experiences compared to motor functional capacity. The described findings are consistent with current clinical knowledge: non-motor fluctuations in PD have a greater and more pervasive impact on QoL than motor fluctuations, particularly with regard to emotional well-being, bodily discomfort and cognition. Studies using the PDQ-39 and WOQ-19 have shown that patients experiencing both motor and non-motor fluctuations report significantly poorer QoL, particularly with regards to emotional well-being, bodily discomfort and in the cognitive domains. Non-motor fluctuations, such as anxiety, depression, pain, fatigue, and cognitive impairment, are frequently reported to be more disabling than motor symptoms

and are closely linked to subjective physical experiences and overall HRQoL. These symptoms often fluctuate independently of motor state and can be more difficult to manage, as highlighted in recent reviews and cohort studies (108,150–153). For example, emotional well-being and cognition are disproportionately affected in patients with non-motor fluctuations, and bodily discomfort is more strongly associated with non-motor than motor fluctuations (150,151,153). Together, these findings contribute to a growing recognition that non-motor fluctuations are among the most disabling aspects of PD, often exerting greater influence on QoL than motor symptoms themselves (154).

4.4. Objective Motor Fluctuation Patterns: PKG Findings

Objective PKG measurements corroborated subjective reports of fluctuation status. Across both WOQ-19 classifications, fluctuators spent significantly less time in bradykinesia ($p <$ .001 for both) and more time in dyskinesia (non-motor: $p <$ .001; psychiatric: $p =$ .002), indicating more pronounced motor fluctuations throughout the day. These results align with established associations between wearing-off phenomena, increased dyskinesia, and reduced time spent in optimal motor states (155). Our PKG findings offer an important external validation of the WOQ-19 subscales in this cohort. While the WOQ-19 relies on patient-reported symptom variability, PKG provides continuous and objective measurement of motor states throughout the day. The convergence of subjective and objective data supports the use of patient-reported outcomes to identify clinically meaningful motor and non-motor fluctuations. Moreover, the PKG profiles of psychiatric fluctuators suggest that affective instability does not occur in isolation but is embedded within broader physiological dysregulation of dopaminergic signalling.

Taken together, our PKG findings and the higher UPDRS IV scores but the absence of group differences in UPDRS III on/off scores are consistent with recent evidence that non-motor and psychiatric fluctuations in PD represent a distinct clinical dimension, not merely a marker of advanced motor disease. Objective measurements using the PKG have demonstrated that motor fluctuations can be quantified and are associated with higher motor complication scores, but do not necessarily correlate with the severity of motor impairment as measured by UPDRS III (156,157). These findings highlight the multidimensional and clinically meaningful impact of non-motor and psychiatric fluctuations in PD and underscore their relevance for patient well-being and disease management.

4.5. Methodological considerations and limitations

Several limitations warrant consideration. First, the cross-sectional design precludes conclusions regarding causality or temporal sequencing between dopaminergic fluctuations and psychiatric symptom variability. Longitudinal studies are required to determine whether affective fluctuations precede the development of motor fluctuations, reflect parallel processes, or emerge secondarily. Group sizes in our cohort were unequal, with fluctuators substantially outnumbering non-fluctuators due to the advanced state of the disease in this cohort. Although the use of nonparametric tests mitigates concerns related to unequal variances and non-normal distributions, statistical power may differ across comparisons. Additionally, missing data resulted in varying sample sizes for different analyses (e.g., HARS, HDRS, AES, PKG), which may introduce bias and limit comparability across domains. Furthermore, our analysis did not differentiate by motor phenotype (tremor-dominant vs. akinetic-rigid vs. mixed). Motor phenotype is known to influence non-motor profiles, progression rates, and psychiatric symptom burden, and future studies should stratify analyses accordingly (158–161). Regarding the differentiation between non-motor and psychiatric fluctuators clear statements on the importance of psychiatric symptoms in the context of overall NMS burden would also warrant further analyses of sensory and autonomic subsets of NMS, which were not part of this work. Finally, another limitation of this study is that analyses were not adjusted for disease duration, which is known to influence the severity of both motor and NMS in PD. However, as compared groups did not differ significantly in disease duration, the likelihood that duration acted as a confounding factor in the observed between-group differences is reduced.

4.6. Future directions

Building upon the present findings, future investigations should adopt longitudinal and multimodal designs to map the trajectory of psychiatric and non-motor fluctuations across disease stages. Combining continuous PKG monitoring (or similar) with ecological momentary assessment of mood could clarify temporal associations between motor and affective states. Functional neuroimaging may elucidate the neural correlates of psychiatric fluctuation patterns, particularly in limbic and frontostriatal circuits. In addition, future trials should evaluate whether interventions that stabilize dopaminergic stimulation also attenuate

psychiatric fluctuation severity. Continuous infusion therapies, deep-brain stimulation, or adjunct serotonergic agents are reported to reduce affective variability and improve overall QoL (158,162,163). Finally, incorporating caregiver variables into fluctuation research could enhance understanding of the broader impact of these symptoms on family systems and social functioning.

4.7. Conclusion

In summary, this study demonstrates that non-motor and psychiatric fluctuations in PD are common in advanced disease stages and strongly associated with increased anxiety and depression, greater motor complication burden, and reduced emotional well-being. Objective PKG findings confirm that non-motor/psychiatric fluctuators as defined by WOQ-19, also experience more pronounced motor instability, indicating that motor and affective fluctuations may share overlapping physiological mechanisms. Apathy appears relatively stable across fluctuation states, supporting its characterization as a trait-like symptom less influenced by acute dopaminergic variability. By integrating subjective and objective measures, this study contributes to a more comprehensive understanding of fluctuation phenomena in PD. The findings also underscore the importance of routinely assessing psychiatric and non-motor fluctuations in clinical practice and highlight the need for personalized therapeutic approaches aimed at stabilizing both motor and emotional functioning.

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6. Supplemental Material

Tests auf Normalverteilung

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistik	df	Signifikanz	Statistik	df	Signifikanz
hars_total_score	,097	107	,015	,941	107	<,001
hdrs_total_score	,121	107	<,001	,929	107	<,001
apathy_evaluation_scale_total_score	,131	107	<,001	,939	107	<,001
age	,078	107	,104	,981	107	,126
gender	,372	107	<,001	,631	107	<,001
disease_duration	,164	107	<,001	,908	107	<,001
updrs3_total_offmed	,049	107	,200*	,989	107	,531
updrs3_total_onmed	,078	107	,105	,976	107	,046
pdq39_mobility_score	,116	107	,001	,955	107	,001
pdq39_adl_score	,124	107	<,001	,957	107	,002
pdq39_emotional_score	,148	107	<,001	,878	107	<,001
pdq39_stigma_score	,149	107	<,001	,929	107	<,001
pdq39_social_score	,210	107	<,001	,800	107	<,001
pdq39_cognition_score	,129	107	<,001	,936	107	<,001
pdq39_communication_score	,150	107	<,001	,923	107	<,001
pdq39_discomfort_score	,102	107	,008	,967	107	,009
pdq39_summary_index	,088	107	,042	,957	107	,001
pkg_time_bradykinesia	,111	107	,002	,920	107	<,001
pkg_time_dyskinesia	,213	107	<,001	,789	107	<,001
woq19_psychiatric_domain	,237	107	<,001	,874	107	<,001
woq19_nonmotor_domain	,131	107	<,001	,933	107	<,001

*. Dies ist eine untere Grenze der echten Signifikanz.

a. Signifikanzkorrektur nach Lilliefors

Suppl. Table 1 Shapiro Wilk test for scores included in the analyses;

The following tools were used for linguistic optimization in all parts of this thesis: ChatGPT (GPT-4o); OpenAI, L.L.C. [https://chat.openai.com]; 18.12.2025; DeepL Write; DeepL SE [https://www.deepl.com/write]; 21.01.2026