Psychosis and Apathy in Parkinson's disease

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by

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Abstract

Increasingly recognized as a heterogenous syndromic condition with multi-neurotransmitter dysfunction involving complex endophenotypes, the modern management options for Parkinson's disease (PD) have evolved far beyond mere motor symptom control alone. Subtype-specific strategies for PD in the context of personalised medicine, with consideration of external influential factors such as age, personality, treatment preferences, cultural beliefs, lifestyle, socioeconomics, genetic framework, as well as comorbidities, are now regarded as the modern and holistic approach.

The focus of this thesis is on the two key non-motor symptoms of psychosis and apathy in PD, as well as their connections with each other. These are the two neuropsychiatric entities for which identification remains a challenge despite more than a decade of expanding research, and for which there is still much to be understood. For PD psychosis, the lack of a comprehensive and disease-specific instrument was the critical point of contention regarding the efficacy and safety of pimavanserin, the only medication licensed by the United States in 2016 for the treatment of psychosis in Parkinson's disease. For PD apathy, doubt remains on whether it is a clinically meaningful syndrome in PD, with its pervasive intersections with other established neuropsychiatric symptoms such as depression and anxiety.

As part of my efforts to investigate for potential risk factors for the phenotypic expression of neuropsychiatric symptoms in PD (specifically psychosis and apathy), I strove to determine if there are shared genetic risk factors between PD and psychiatric disorders, I conducted a large case-control genetic association study involving 1291 subjects. I found a borderline association between *CLCN*3 genetic variant (rs62333164) and PD in our Asian population, suggesting a potential overlap of genetic risk factors between the two disease groups. Further validation in independent cohorts and meta-analyses involving larger samples will be warranted, as identification

of shared genetic factors can help facilitate stratification of PD patients at risk of neuropsychiatric complications and selection for clinical drug trials.

Narrative reviews were conducted to establish a solid background on the phenomenology as well as kinetics of both psychosis and apathy (Chapters 1 and 2). A comprehensive review into the existing instruments that quantify psychosis severity in PD was completed, with an in-depth analysis of the strengths and limitations of each scale developed since 2008. All this information were then assimilated into the configuration of the Psychosis Severity Scale of Parkinson's disease, or Psy-PD. After going through cognitive pre-testing and standardised validation methods among a cohort of patients recruited at the King's College Hospital Parkinson's Foundation Centre of Excellence in the UK, the Psy-PD was demonstrated to be a feasible and acceptable scale, with appropriate basic clinimetric attributes to measure psychosis severity in PD.

Subsequently the results of two cohort studies conducted across two different locations (**London, Singapore**) looking at apathy among PwPs revealed that apathy exists independent of psychosis, depression, and anxiety in PD, and supports the prevailing notion of a complex non-dopaminergic circuit involvement in terms of pathogenesis. The prevalence of apathy is also ubiquitous in PD, regardless of ethnic boundaries or geographical disparities. Our research findings supported the growing recognition of non-motor endophenotypes of PD and suggested the existence of a specific clinical phenotype that is associated with a poor quality of life in PD. This proposed clinical phenotype of concurrent psychosis and apathy (without depression) in PD is significantly associated with a higher non-motor burden and reduced quality of life, compared to other phenotypes explored.

The research done for this academic work have increased our understanding about the range and nature of the two debilitating neuropsychiatric features of psychosis and apathy in PD. I hope that the findings will establish the groundwork for large-scale longitudinal research studies focusing on clinical and behavioural biomarkers towards refining a more holistic approach in terms of identification and management.

COVID-19 IMPACT STATEMENT

Singapore went on the alert in early January 2020 in response to the rising Coronavirus Disease 2019 (COVID-19) cases in Wuhan, China, and in the months thereafter imposed restrictions on overseas travel as well as cross-institutional movement for healthcare professionals, with border restrictions fully implemented from 23 March 2020. Subsequently I was re-deployed as part of the frontline COVID-19 team of healthcare professionals to the migrant worker dormitories and the pandemic wards in Singapore. All research unrelated to COVID-19 was curtailed. Although there was some interval loosening of restrictions later, Singapore re-entered partial lockdown from 16 May 2021, and again in early October 2021 due to an outbreak of the COVID-19 *Delta* and *Omicron* variants respectively. As a result, cross-campus movement was again severely restricted, with re-deployment of healthcare staff to the pandemic wards and emergency services of all hospitals in Singapore. Currently, Singapore is only just recovering from the recent Omicron COVID-19 surge, with cross-institutional movement allowed only from 15 March 2022.

My project was originally almost wholly based on clinical work amongst patients with Parkinson's disease (PD), with an overall theme comprising three different domains, specifically a diagnostic arm, an evaluation arm, and a therapeutic arm, all of which intersect with each other. The first two arms were planned to be done mainly in the UK which were supposed to be supplemented by relevant data collected from Singapore, whilst the therapeutic arm was originally arranged to be done primarily in Singapore, where we select a subpopulation of PD patients with apathy and psychosis, who will have the greatest potential to benefit from repetitive transcranial magnetic stimulation (rTMS).

Consequent to the emergent COVID-19 pandemic and subsequent lockdowns, clinical recruitment into all studies related to my PhD project was curtailed. I could not validate my newly developed scale amongst the patients with Parkinson's disease in Singapore as originally conceived. I had to utilize only the clinical data collected in the UK and Singapore in the period immediately prior to the pandemic. The rTMS idea needed to be adapted into a new laboratory-based project involving exploration of shared genetic loci across two major psychiatric disorders and PD.

Author Declaration

I, Yi Min Wan, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been specified as such in the thesis. I hereby declare that the contents of this dissertation have not been submitted in whole or in part for consideration for any other degree or qualification in this, or any other University.

This dissertation contains less than 100,000 words (exact word count : 51395) including tables, footnotes/endnotes, and table/figure legends and excluding abstract, tables of contents/of figures/of tables/ of acronyms, acknowledgements, Coronavirus disease 2019 statement, and references.

This is a thesis incorporating a publication, which is a variant of the traditional UK thesis, with the purpose to allow the candidate to include work they have published without having to rewrite it in the traditional thesis format. I hereby declare I have checked journal's requirements and the publication have been bound to the thesis as a pdf version without breaking publishers' copyright.

This is to certify that I have carried out the studies embodied in this thesis under the supervision of Professor K. Ray Chaudhuri, and Professor Eng-King Tan. The copyright of this thesis rests with the author and no quotation from it or information derived from it may be published without proper acknowledgement.

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Finally, I am extremely thankful to my dear husband Ryutaro, my parents, and siblings, as well as my friends for their ongoing love, support, and encouragement.

Table of Contents

Abbreviations

αSyn	α-Synuclein
AD	Alzheimer's Disease
AES	Apathy Evaluation Scale
AI	Apathy Inventory
ASBPD	Ardouin Scale of Behavior in Parkinson's Disease
Apo	Apomorphine
APP	Amyloid-β Precursor Protein
AS/SAS	Apathy Scale/ Starkstein's Apathy Scale
BDI-II	Beck's Depression Inventory-Second Revision
BEHAVE-AD	Behavioral pathology in Alzheimer's disease rating scale
BEHAVE-AD-FW	Behavioural pathology in Alzheimer's disease - Frequency-Weighted Severity Scale
BP-NPI	Brazilian Portuguese Neuropsychiatric Inventory
BPC	Behaviour Problem Checklist
BPRS	Brief Psychiatric Rating Scale
BP-NPI-12	Brazilian Portuguese Neuropsychiatric Inventory (12 items)
CBD	CorticoBasal Degeneration
CDR	Clinical Dementia Rating Scale
CGI-I	Clinical Global Impression (Improvement) Scale
CGI-S	Clinical Global Impression (Severity) Scale
CIRB	Centralised Institutional Review Board (Singapore)
CITI	Collaborative Institutional Training Initiative
*CLCN*3	Chloride voltage-gated channel 3
CNV	Copy Normal Variant
COMT	Catechol-O-MethylTransferase
CPMS	Central Portfolio Management System
CRISP	Community for Research Involvement and Support for people with Parkinson's
CRN	Clinical Research Network
CUP	Clinically Unclassifiable Parkinsonism
CSF	Cerebrospinal fluid

C-NPI-12	Chinese Neuropsychiatric Inventory (12 items)
DBRI	Dysfunctional Behaviour Rating Instrument
DBS	Deep Brain Stimulation
Df	Degrees of Freedom
DLB	Dementia of Lewy Bodies
DMV	Dorsal motor nucleus of the vagus nerve
E-BEHAVE-AD	Empirical Behavioural pathology in Alzheimer's disease rating scale
EBM	Evidence-Based Medicine
EDS	Excessive Daytime Sleepiness
ELEP	Longitudinal Study of Parkinson's disease
E-SAPS-PD	Enhanced Schedule for the Positive Symptoms in Parkinson's Disease
ESS	Epworth Sleepiness Scale
^{18}FDG-PET	18F-fluoro-2-deoxy-D-glucose-positron emission tomography
FrSBe	Frontal Symptoms Behavioural Scale
GBA	Glucocerebrosidase gene
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GWAS	Genome-Wide Association Studies
HADS	Hospital Anxiety and Depression Scale
H-BPRS	Hellenic translated Brief Psychiatric Rating Scale
HRA	Health Research Authority
HY	Hoehn and Yahr
H-NPI-10	Hellenic Neuropsychiatric Inventory (10 items)
ICC	Intraclass Coefficient
ICD	Impulse Control Disorders
IJLI	intrajejunal levodopa infusion
I-NEVHI	Informant-based North-East Visual Hallucinations Interview
IPMDS	International Parkinson and Movement Disorder Society
IQR	Interquartile Range
IRAS	Integrated Research Application System (UK)
KCH	King's College Hospital

KCL	King's College London
K-NPI-Q	Korean Neuropsychiatric Inventory Questionnaire
LARS	Lille Apathy Rating Scale
LB	Lewy Body
LBD	Lewy body Dementia
LCIG	Levodopa-carbidopa intestinal gel
L-Dopa	Levodopa
LEDD	Levodopa equivalent daily dose
MCAR	Missing Completely At Random
MCI	Mild Cognitive Impairment
MDRS	Mattis Dementia Rating Scale
MDS-UPDRS 1.2	United Parkinson's Disease Rating Scale Part I item 1.2 - Hallucinations and Psychosis (Movement Disorder Society sponsored revision)
MDS-UPDRS III	Movement Disorder Society-Unified Parkinson's Disease Rating Scale
MeSH	Medical Subjects Headings
MFs	Motor Fluctuations
MHs	Minor Hallucinations
MIBG	MetaIodoBenzylGuanidine
MMSE	Mini-Mental State Exam
MoCA	Montreal Cognitive Test
MRI	Magnetic Resonance Imaging
MSA	Multiple System Atrophy
NA	Not Applicable
NEVHI	North-East Visual Hallucinations Interview
NHS	National Health System
NIHR	National Institute for Health Research
NINDS-NIMH	National Institute of Neurological Diorders and Stroke-National Institute of Mental Health
NILS	Non-motor International Longitudinal Study
NMFs	Non-motor Fluctuations
NMS	Non-Motor Symptoms
NMSQuest	Non-Motor Symptoms Questionnaire

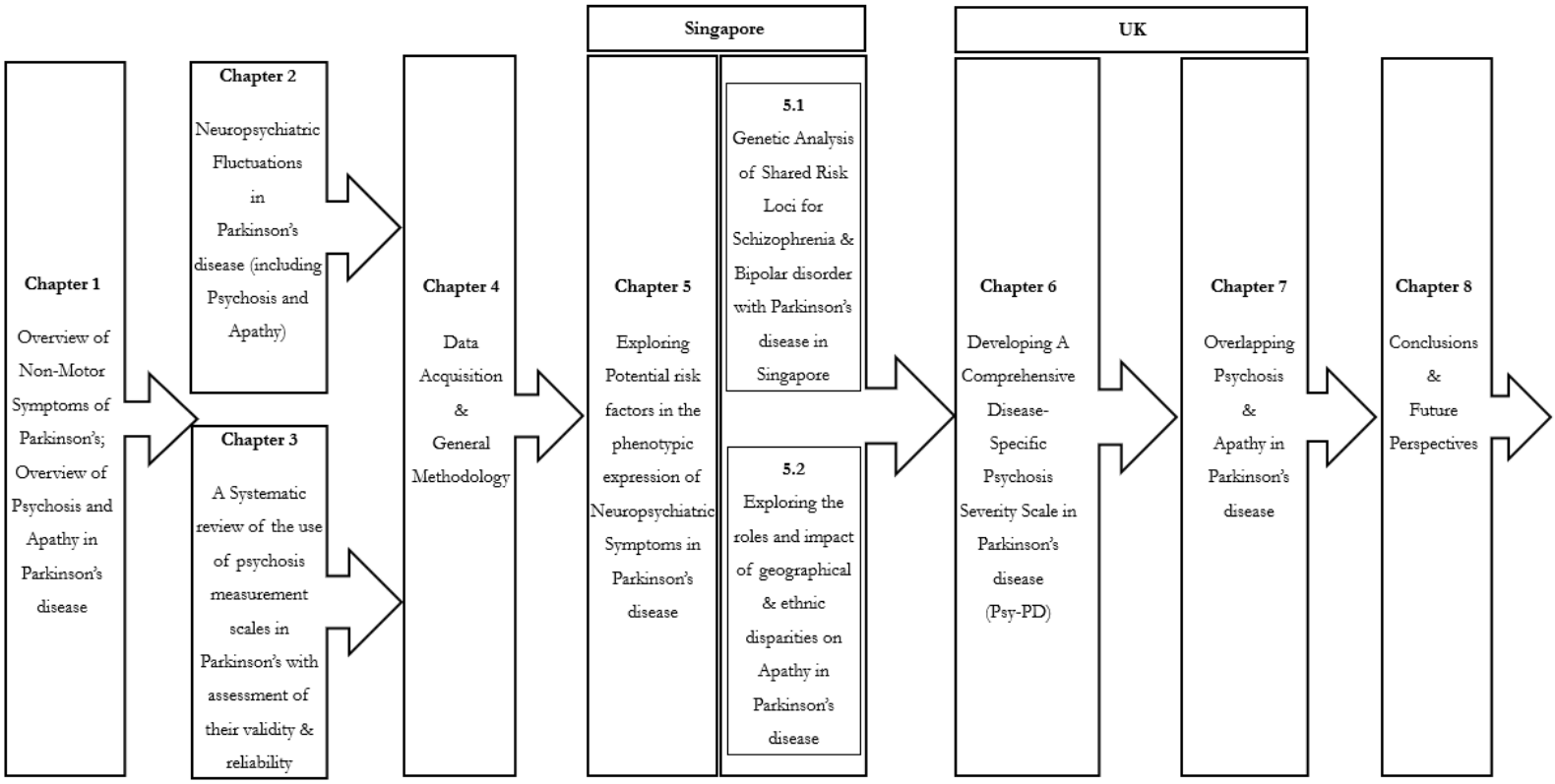
NMSS	Non-Motor Symptoms Scale
NoMoFA	Non-Motor Fluctuation Assessment
NPI	Neuropsychiatric Inventory
NPIa	Neuropsychiatry Inventory- Apathy subscale
NPI-10	Neuropsychiatric Inventory (10 items)
NPI-12	Neuropsychiatric Inventory (12 items)
NPI-4	Neuropsychiatric Inventory (4 items)
NPI-NH	Neuropsychiatric Inventory Nursing-Home
NPI-Q	Neuropsychiatric Inventory Questionnaire
OMIM	Online Mendelian Inheritance in Man
PANSS	Positive and Negative Syndrome Scale
PD	Parkinson's Disease
PD-CRS	Parkinson's Disease – Cognitive Rating Scale
PDP	Parkinson's Disease Psychosis
PDQ-8	Parkinson's disease Questionnaire-8
PDSS-2	Parkinson's Disease Sleep Scale-Revised
PET	Positron Emission Tomography
PIGD	Postural Instability/Gait difficulty Disorder dominant
PPI	Public and Patient Involvement
PPMI	Parkinson's Progression Markers Initiative
PPQ	Parkinson Psychosis Questionnaire
PPRS	Parkinson Psychosis Rating Scale
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSAS	Psycho-Sensory hallucinations Scale
PSP	Progressive Supranuclear Palsy
Psy-PD	Psychosis Severity Scale of Parkinson's Disease
PsycH-Q	Psychosis and Hallucinations Questionnaire
PwP	People with Parkinson's
QoL	Quality of Life
R&D	Research and Development
RBD	Rapid Eye Movement Sleep Behaviour Disorder

RBD-HK	Rapid Eye Movement Sleep Behaviour Disorder Questionnaire - Hong Kong
REC	Research Ethics Committee
RERE	arginine-glutamic acid dipeptide repeats
RHEBL1	Ras Homolog Enriched in Brain-Like Protein 1
RTG	Rotigotine
RTMS	Repetitive Transcranial Magnetic Stimulation
SCZ	Schizophrenia
SAPS	Schedule for the Assessment of Positive Symptoms
SAPS-PD	Schedule for the Assessment of Positive Symptoms for Parkinson's Disease
SCOPA-AUT	Scales for Outcomes in Parkinson's Disease-Autonomic
SCOPA-PC	Scales for Outcomes in Parkinson's Disease – Psychiatric Complications
SD	Standard deviation
SEADL	Schwab and England Activities of Daily Living Scale
SENS-PD	SEverity of predominantly Nondopaminergic Symptoms in PD
SGH	Singapore General Hospital
SNP	Single Nucleotide Polymorphism
SNpc	Substantia nigra pars compacta
SPECT	Single Photon Emission Computed Tomography
STN-DBS	Deep Brain Stimulation of the Subthalamic Nucleus
TUHARS	Tottori University Hallucination Rating Scale
UM-PDHQ	University of Miami Parkinson's disease Hallucinations Questionnaire
UPDRS	United Parkinson's Disease Rating Scale
UPDRS III	United Parkinson's Disease Rating Scale (Part III)
Vs	Versus
VRK2	Vaccinia-Related Kinase 2
WHO	World Health Organization
ZBI	Zarit Burden Interview

Table List

Figure list

Outline of Thesis Plan



Peer-reviewed publications associated with this thesis

1. Lazcano-Ocampo C [#], **Wan YM** [#], van Wamelen DJ, Batzu L, Boura I, Titova N, Leta V, Qamar M, Martinez-Martin P, Ray Chaudhuri K. Identifying and responding to fatigue and apathy in Parkinson's disease: a review of current practice. *Expert Rev Neurother.* 2020 May;20(5):477-495. **([#] - joint first authors) –** incorporated into Chapter 1.

2. Martinez-Martin P, **Wan YM**, Ray Chaudhuri K, Schrag AE, Weintraub D. Impulse control and related behaviors in Parkinson's disease with dementia. *Eur J Neurol.* 2020;27(6):944-950. doi:10.1111/ene.14169.

3. Sauerbier, A, Sivakumar, C, Klingelhoefer, L, Martinez-Martin, P, Perkins, L, Inniss, R, Rizos, A, Trivedi, D, Leta, V, **Wan YM**, Parry, M, van Wamelen, D, Reichmann, H & Chaudhuri, KR. Restless legs syndrome - the under-recognised non-motor burden: a questionnaire-based cohort study. *Postgraduate Medicine.* 2019 vol. 131, no. 7, pp. 473-478.

4. Leta V, van Wamelen DJ, Rukavina K, Jaakkola E, Sportelli C, **Wan YM**, Podlewska AM, Parry M, Metta V, Chaudhuri KR. Sweating and other thermoregulatory abnormalities in Parkinson's disease: A Review. *Annals of Movement Disorders: Official Journal of the Movement Disorders Society of India.* 2019, 2(2):39-47.

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7. Creese B, Albertyn CP, Dworkin S, Thomas RS, **Wan YM**, Ballard C. Executive function but not episodic memory decline associated with visual hallucinations in Parkinson's disease. *J Neuropsychol.* 2018 Jul 23.

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Chapter 1

Introduction

1.1 Parkinson's: Non-motor symptoms

Globally, Parkinson's disease (PD) is one of the fastest and most widespread neurodegenerative disorder in terms of prevalence, disability-adjusted life years, and deaths; the number of PD cases is expected to expand to over 12 million by 2040 (Dorsey et al., 2018; G. B. D. Neurology Collaborators, 2019). First characterized by James Parkinson more than 200 years ago in his 1817 seminal text "*Essay on the Shaking Palsy*" as a progressively debilitating malady comprising a conjunction of tremor, rigidity, and gait disturbances (Hurwitz, 2014), the symptomatology was later supplemented with the description of bradykinesia, and the condition itself named as Parkinson's disease by Jean-Martin Charcot over 50 years later (Charcot, 1872). An account of heterogenous "non-motor" symptoms (NMS) in PD were also observed and detailed, including that of constipation, depression, and swallowing difficulties (Goetz, 2011; Hurwitz, 2014).

Although the cardinal motor symptoms of PD (bradykinesia, muscular rigidity, resting tremor, loss of postural reflexes) (Jankovic, 2008) are still considered its primary features, NMS has been increasingly recognized as a crucial and integral part of the disease (Chaudhuri & Schapira, 2009; Todorova et al., 2014).

Now widely acknowledged to be a heterogenous syndrome with etiologies involving an interplay between genetics and environmental factors, PD is characterized by complex biomarker-driven phenotypes (Di Battista et al., 2018; Marras & Chaudhuri, 2016; Sauerbier et al., 2016; Sauerbier, Rosa-Grilo, et al., 2017), comprising dysfunction of cholinergic, noradrenergic, serotonergic, and mixed neurotransmitter networks underpinned by dopamine deficits (Sauerbier et al., 2016; Titova & Chaudhuri, 2018; Zis, Martinez-Martin, et al., 2015). NMS in PD, frequently termed as "the hidden

face" (Titova & Chaudhuri, 2017a), are often undeclared to (Chaudhuri et al., 2010), and poorly recognized by (Gallagher et al., 2010), attending physicians, despite the devastating impact on health-related quality-of-life (Duncan et al., 2014; Martinez-Martin, 2014; Schrag, 2006; Schrag et al., 2000), caregiver burden (Schrag et al., 2006), and mortality (Bugalho et al., 2019; Lo et al., 2009; Louis et al., 1997).

1.2 Parkinson's : Neuropathophysiology

Widespread aggregation of misfolded α-synuclein (αSyn), the basic pathological protein and precursor of inclusion bodies or Lewy bodies (LB) formation, across different regions of the brain, remains the hallmark of disease in PD and related synucleinopathies (Dickson et al., 2009). The main distinctive morphological change in PD is observed to be progressive depletion of neuromelanin-containing neurons in the substantia nigra pars compacta (SNpc), extending to the noradrenergic neurons of the locus coeruleus, as well as the dorsal motor nucleus of the vagus nerve. Robust evidence from experimental (animal studies) and clinical cohort studies have shown that this progressive multiorgan disorder affects multiple overlapping neural pathways, including the four key neurotransmitter networks: dopaminergic, cholinergic, noradrenergic, and serotonergic (Halliday et al., 2011; Jellinger, 2001, 2015; Kingsbury et al., 2010).

1.2.1 Braak Staging Hypothesis

Originally posited in 2003 by Braak and colleagues and derived from postmortem studies, the main staging system of LB distribution in PD was divided into six stages (Table 1.1) (Braak, Rub, et al., 2003). The process of caustal-to-rostral spread of LB pathology has been suggested to start simultaneously in the enteric nervous system (ENS)- dorsal motor nucleus of the vagus nerve (DMV) axis, and the olfactory bulb; in other words "in the gut and nose simultaneously", subsequently

propagating to the pontine tegmentum via the nuclei of the lower brainstem, which is said to be stages one and two of the prodromal period. Correspondingly, clinical manifestations include olfactory impairment, autonomic dysfunction (particularly gastrointestinal issues)(Bhattacharyya et al., 2019; Metta et al., 2022), REM sleep behaviour disorder (RBD), and affective disorders commonly seen during the prodromal and early stages of PD.

Once the substantia nigra and other nuclei of the midbrain and forebrain are affected, representing stages three and four respectively, this will usually coincide with the onset of clinical motor signs and thereby formal diagnosis of PD. Stages five and six signify more advanced disease, with diffuse deposition of LB in the cortical regions of the brain, which are usually reflected in the prominent cognitive and neuropsychiatric symptoms occurring particularly during this period.

***Table* 1.1: Braak stages**

Stage 1	Appearance of Lewy pathology in the olfactory bulb, the anterior olfactory nucleus, and the lower brainstem with involvement of the vagus nerve.
Stage 2	Appearance of Lewy pathology in affecting the lower brainstem with involvement of the raphe nuclei (serotonin) and migrating up the brainstem affecting the locus coeruleus in the pontine tegmentum (noradrenaline).
Stage 3	Appearance of Lewy pathology in the substantia nigra, and the basal nucleus of Meynert (acetylcholine).
Stage 4	Appearance of Lewy pathology in the SNpc further advance; the mesocortex and the allocortex are affected as well.
Stage 5-6	Appearance of Lewy pathology in the temporal, parietal, and frontal lobes of the neocortex

(Braak, Del Tredici, et al., 2003)

1.2.1.1 Critique of Braak's Hypothesis

Despite the clinical support for this hypothesis however, there has been criticism that it is based on the abnormal propagation of LB and not on neuronal cell loss. It is still contentious as to the extent LB pathology represented pathogencitiy and the role they play in neuronal dysfunction and degeneration.

A small number of PwP (7-17%) have been shown not to have pathological αSyn in the DMV even when regions of the neocortex was affected (Jellinger, 2003; Rietdijk et al., 2017). Additionally, presence of LB in the enteric system can occur independent of olfactory dysfunction (Lebouvier et al., 2011).

Braak's hypothesis also did not explain abnormal cardiac metaiodobenzylguanidine (MIBG) scintography results amongst PwP (Orimo et al., 2012; Orimo et al., 2007), nor the presence of prodromal cognitive symptoms recently described from the Parkinson's Progression Markers Initiative (PPMI), that can occur in early stages of the disease (Weintraub et al., 2015). Cortical symptoms such as psychosis and apathy that may be present in the *de novo* stage of PD as part of an early cholinergic subtype of PD (Titova & Chaudhuri, 2017c; Zis, Erro, et al., 2015) , supported by neuroimaging evidence (LaBelle et al., 2017; Pavese et al., 2010; Sawamoto et al., 2008) , contradict the suggested concept of Braak theory. Another study also stipulated that in 8.3% of the PwP, there was no LB pathology found in the DMV despite higher brainstem and cortical involvement, while 18.3% did not conform to the Braak distribution (Attems & Jellinger, 2008).

An alternative theory (Borghammer, 2021, 2023) therefore is the "*body-first*" and "*brain-first*" hypothesis, which postulates that the first pathology appears in either the gut/DMV/sympathetic systems or in the amygdala/olfactory bulb, but rarely simultaneously in both regions. An olfactory/amygdala start leads to the clinical "*brain-first*" phenotype where parkinsonism is one of the first symptoms to appear, i.e. before RBD and autonomic symptoms appear – and before mild cognitive impairment and neuropsychiatric symptoms appear in most patients. In contrast, a gut/DMV/sympathetic origin leads to the "*body-first*" clinical phenotype, where RBD and dysautonomia appears before parkinsonism. The "*body-first*" clinical phenotype progresses faster to dementia and presents with more neuropsychiatric symptoms. Most patients with dementia with Lewy bodies (DLB) (approximately 75%) seem to be of the "*body-first*" phenotype, whereas many PD patients (an estimated 66%) seem to be "*brain-first*" in phenotypic presentation. (Boeve et al., 1998; Borghammer, 2023; van de Beek et al., 2020).

Nevertheless, all these studies support an intricate and extensive spread of PD pathology, beyond the striatum and dopaminergic network, which may have been the basis for the heterogenous non-motor endophenotypic manifestations of PD (Chaudhuri & Odin, 2010; Sauerbier et al., 2016; Sauerbier, Rosa-Grilo, et al., 2017; Titova, Qamar, & Chaudhuri, 2017), highlighting the complexity of the disease. As such, clinical presentation for each patient can be distinct and diverse, leading to unpredictable response to medications, and with important implications on prognosis; therefore, driving the key concept of personalized medicine ("*One size does not fit all*") as being particularly relevant for PD (Titova & Chaudhuri, 2017b).

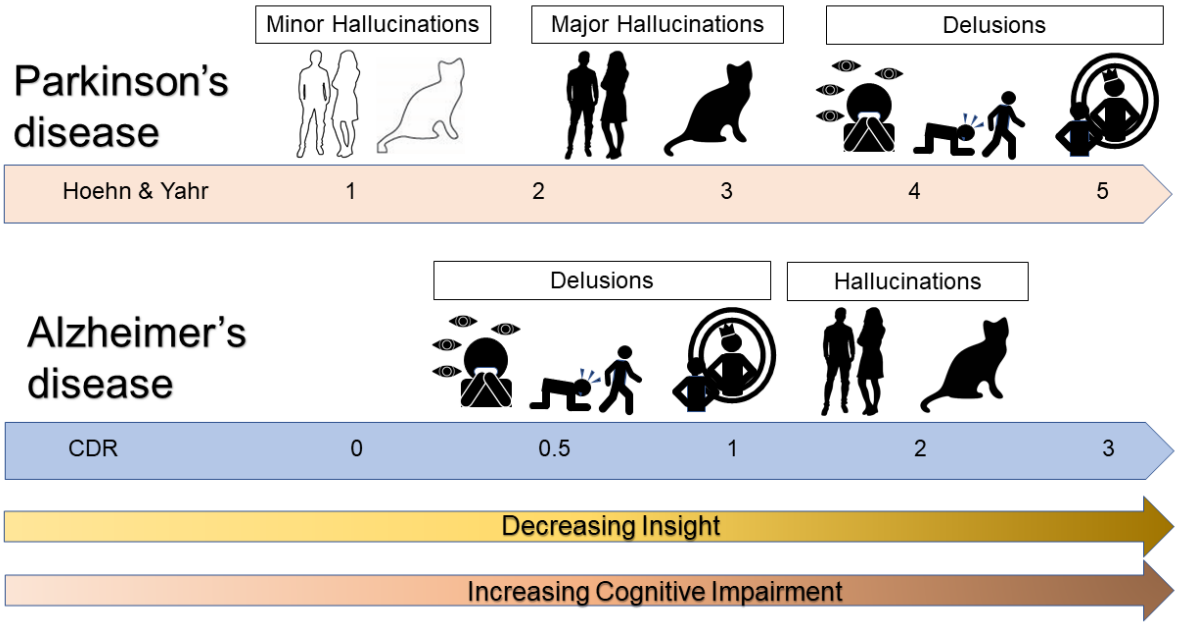
1.3. Parkinson's disease: Psychosis and Apathy

1.3.1 Psychosis in Parkinson's disease

Psychosis, consisting of the cornerstone features of hallucinations and delusions, represent a complex yet fundamental concept in Psychiatry. Prevalent across a wide range of neurodegenerative diseases including Alzheimer's disease (AD), and α-synucleinopathies that include PD, DLB (Jellinger, 2012a), and multiple system atrophy (Papapetropoulos & Mash, 2005) psychosis is frequently associated with advanced disease stages, and progressive cognitive impairment (Ballard et al., 2004; Fenelon & Alves, 2010; Ropacki & Jeste, 2005). A key predictor of poor outcomes, psychosis aggravates patients' global well-being, and increases caregiver burden across several neurodegenerative conditions(Murray et al., 2014). Despite this, it is often undeclared by patients and unrecognized by clinicians (Chaudhuri et al., 2010), with effective treatment remaining elusive.

The array of psychotic manifestations is also heterogenous across AD, PD, and other related degenerative diseases (*Figure* 1.1), presenting exceptional challenges and mandating a scrupulous approach to its identification, monitoring, and treatment.

***Figure* 1.1: Comparisons of the clinical presentation of psychosis and associations across PD &AD, the top two commonest neurodegenerative disorders**



CDR: Clinical Dementia Rating Scale

Figure 1.1 compared between the clinical continuums of psychosis between the two commonest degenerative diseases (AD and PD) according to literature to date.

In AD, the prevalence of psychosis occurred up to 74.1%, depending on clinical setting. Psychotic symptoms can occur two to six times per week, persist for 12 weeks among 32%, and recur in 50% within 12 months, according to the review by Lanctot et al 2017 and an exploratory analysis study by Ballard et. al in 1995 (Ballard et al., 1995; Lanctot et al., 2017). Delusions can occur at all stages of AD (Rao & Lyketsos, 1998) and has been associated with early disease (Goodman, 1953). Delusions occur at a rate of 12.2% to 74.1% with persecutory delusions experienced earlier than that of misidentification delusions, although the frequencies of both increase with dementia severity (Ropacki & Jeste, 2005). Hallucinations were less prevalent, ranging from 4 to 41%, with visual hallucinations being more frequent than that of other modalities (Leroi et al., 2003), and rarely occur independently.

In PD, the prevalence of psychosis ranged from 16-74%, with the point prevalence increasing over time to a peak of 74% in 20 years (Hely et al., 2008). A 2011 longitudinal study by Goetz et al (Goetz et al., 2011) showed that visual hallucinations dominated the early forms of hallucinations (approximately 88%) at 6 months, with a progressive decrease thereafter.

In general, a fifth of PD patient experienced psychotic symptoms, with the pooled frequency of 20.7% across 15 studies (Chendo et al., 2022). Delusions, on the other hand, occur in a PD clinical setting at 16%, rising to 47% in a subgroup of patients with PD psychosis(Factor et al., 2014), and are generally associated with later stages of disease (Ffytche et al., 2017; Kashihara et al., 2005). Earlier studies on psychosis among PD patients indicated an even higher prevalence of delusions (53%-76%) (Chou et al., 2005; Kashihara et al., 2005). Known to fluctuate throughout the course of a day (elaborated in Chapter 2), PD psychosis (specifically the minor hallucinations – as elaborated further below) has been described to occur even in the premotor phases of disease (Pagonabarraga et al., 2016).

1.3.1.1 Classification of PD Psychosis (PDP)

Rapidly accumulative data from recent years have shown that the constellation of psychotic symptoms in PD differ in temporality and clinical profile from those observed in primary psychiatric conditions and other neurological conditions.

In 2007, an international workgroup redefined PD psychosis in a consensus, recognizing it as a spectrum of "positive" or "excessive function" symptoms comprising illusions, hallucination, and delusions, in contrast with "negative" symptoms of deficit (Ffytche et al., 2017; Ravina et al., 2007). The formal diagnostic criteria for PD psychosis have been proposed (Ravina et al., 2007)to include :

(1) presence of at least one characteristic symptom, including that of visual illusions, sense of presence, hallucinations, or delusions;

(2) primary diagnosis of PD according to the UK Brain Bank criteria (Hughes et al., 1992);

(3) symptoms occurring after the onset of PD;

(4) symptoms that are recurrent or continuous for more than one month; and

(5) exclusions of other causes such as acute confusional states (delirium), other neurodegenerative conditions (e.g. AD, DLB) or psychiatric disorders (e.g. schizophrenia, bipolar disorders).

This reclassification of PD psychosis from independent symptomatology to a progressive continuum, resulted in landmark implications in the subsequent arsenal of related research. Initially reported as almost wholly drug-induced (Chou et al., 2005), the PD psychosis spectrum has been consolidated as such: "minor" phenomena with initially preserved insight in early PD, evolving into well-formed hallucinations (typically of people or animals), with insight lost in later phases (Ffytche et al., 2017), along with the development of delusions as well as non-visual hallucinations. Non-visual hallucination modalities may co-occur either separately, or as part of a multimodal hallucination. False beliefs (delusions) were either associated with the hallucinations (secondary delusions) or have unrelated themes such as persecution, misidentification, and infidelity (Mueller et al., 2018). PD psychosis has been shown to occur independent of dopaminergic treatment, with the risk not equal for all dopamine agonists, and continuous apomorphine infusion appearing to have a lower risk than most (Dafsari et al., 2019; Weintraub et al., 2022).

The majority of early studies used unspecified questionnaires or unvalidated interviews to capture the data on PDP, and focused mainly on visual hallucinations(Table 1.1a). Several cross-sectional studies have suggested psychotic symptoms to predominantly occur in environments of low ambient stimulation (Barnes & David, 2001; Fenelon, 2008; Fernandez et al., 1992; Haeske-Dewick, 1995; Sanchez-Ramos et al., 1996) , but one study had observed no relation to the light cycle (Papapetropoulos et al., 2008). However, the study by Papapetropoulos et al was a pilot study using a

single item question to assess for conditions under which the hallucinations occurred, in the then newly-developed but not-yet formally validated 20-item scale - The University of Miami Parkinson's disease Hallucinations Questionnaire (UM-PDHQ) - to quantify type and presence of hallucinations in a clinic population of 70 PD patients, which may account for the inconsistent findings.

A 2010 longitudinal study over 12 years by Forsaa et. al (Forsaa et al., 2010) found a 5-fold increased prevalence of PDP over time in demented compared non-demented patients. However, both this and another 4-year longitudinal study by Goetz et. al(Goetz et al., 2001), agreed that lower MMSE scores per se were neither associated with nor predicted future development of PDP in multivariate models. The 2010 study also showed that dementia did not predict future development of PDP in their sample cohort, with the authors suggesting that psychotic symptoms in PD tend to develop either prior to or in parallel with severe cognitive impairment.

Table 1.1a ***Summary of studies of visual hallucinations/psychosis in Parkinson's patients with disease***											
Study	**No. of patients (hallucinators)**	**Control/ comparison group (non-hallucinators)**	**Sample**	**Mean age (years) (SD or %)**	**Disease duration (years)(SD or %)**	**Levodopa equivalent daily dose (mg)(SD or %)**	**Cognitive impairment**	**Hoehn& Yahr stage, (SD)**	**Sleep disturbance**	**Screening /rating instrument for hallucinations**	**Comments**
(Fenelon et al., 2000)	86	109	Consecutive clinical (M:F	73.9 (7.0) (hallucinators) vs 67.5 (9.6) (non-hallucinators)	12.9 (7.5) (hallucinators) vs 8.5 (5.6) (non-hallucinators)	766 (365) (hallucinators) vs 711 (452) (non-hallucinators)	64.6 % diagnosed w dementia (DSM) (hallucinators) vs 6.1% (non-hallucinators)	2.5 (0.6) (hallucinators) vs 1.8 (0.8) (non-hallucinators)	Assessed – daytime somnolence predicts VH	Unspecified semi-structured questionnaire in French	21 had auditory hallucinations. Formed VH occurred in 48 (22% of whole sample). Minor hallucinations occurred in 25.5% of the sample. Hallucinations occurred predominantly at night.
(Papapetropoulos et al., 2008)	31	39	Consecutive clinical	64.3 (10.5) (hallucinators) vs 53.9 (10) (non-hallucinators)	8.5 (5.3) (hallucinators) vs 9.5 (5.6) (non-hallucinators)	Not assessed	MMSE (SD): 26.1(4.2) (hallucinators) vs 25 (4.7) (non-hallucinators)	2.3 (0.9) (hallucinators) vs 2.6 (0.7) (non-hallucinators)	Not assessed	UM-PDHQ (not validated at the time of this study)	10% has non-visual hallucinations. Majority of patients said that 58% hallucinations occurred at any time, with only 29% stating that it mostly occurred at night.
(Barnes & David, 2001)	21	23	Clinical survey	67.6 (6.52) (hallucinators) vs 63.23 (10.82) (non-hallucinators)	11.76 (5.42) (hallucinators) vs 8.30(4.38) (non-hallucinators)	578 (163) (hallucinators) vs 670(159) (non-hallucinators)	MMSE (SD): 26.7(1.4) (hallucinators) vs 27.6(1.1) (non-hallucinators)	3.47(0.63) (hallucinators) vs 2.95(0.57) (non-hallucinators)	Not assessed	Unspecified questionnaire described as a typed A4 booklet investigating general visual changes in PD.	52.4% had visual hallucinations only in dim lighting.

(Sanchez-Ramos et al., 1996)	55	159	Consecutive clinical(cross-sectional)	70 (10.3) (hallucinators) vs 66 (9.18) (non-hallucinators)	8.6 (5.6) (hallucinators) vs 6.3 (5.4) (non-hallucinators)	426 (216) (hallucinators) vs 443 (310) (non-hallucinators)	MMSE (SD): 21.8 (6.6) (hallucinators) vs 27.3 (2.4) (non-hallucinators)	3.2 (0.9) (hallucinators) vs 2.3 (0.8) (non-hallucinators)	40% has sleep disturbance (hallucinators) vs 18.3% (non-hallucinators)	Unspecified questionnaire	62% of patients stated they experienced visual hallucinations in the "on" state. Hallucinations were more common at night. Higher anticholinergic and bromocriptine in non-hallucinator group.
(Haeske-Dewick, 1995)	16	20	Clinic survey; initial mailing(cross-sectional)	72.1(7.34) (hallucinators) vs 67.3 (10.34) (non-hallucinators)	10.5 (8) (hallucinators) vs 5.5 (6) (non-hallucinators)	400 (300) (hallucinators) vs 400 (300) (non-hallucinators)	MMSE (SD): 26 (6.5) (hallucinators) vs 29 (2.5) (non-hallucinators)	3 (1) (hallucinators) vs 2 (1) (non-hallucinators)	Not assessed	Unspecified self-report questionnaire	Hallucinations usually occurred at night
(Fernandez et al., 1992)	30	20	Random clinical(cross-sectional)	65 (8.8) (hallucinators) vs 54 (11.5) (non-hallucinators)	12.5 (5.7) (hallucinators) vs 11.2 (4.9) (non-hallucinators)	695 (495) (hallucinators) vs 731 (539) (non-hallucinators)	MMSE (SD): 23.9 (6.3) (hallucinators) vs 29.2 (1.3) (non-hallucinators)	3.6 (0.5) (hallucinators) vs 3.2 (0.6) (non-hallucinators)	Not assessed	Personal interview from patients with help from caregivers and relatives.	37% hallucinators experienced mainly in the evening and at night. 8 patients' VH associated with "off" periods. No association with medication dose or duration.

SD: standard deviation; VH: Visual hallucinations; MMSE: Mini-mental state examination; UM-PDHQ: University of Miami Parkinson's disease Hallucination Questionnaire; PDSS: Parkinson's Disease Sleep Scale

It is possible that cognitive deficits (e.g attentional-executive and visuospatial impairments) which are not adequately measured by the MMSE, may precede the onset of PDP. For instance, in a community-based cohort of non-demented patients with newly diagnosed PD, 20% of participants were classified with mild cognitive impairment , but only 1.5% reported PDP using the Neuropsychiatric Inventory (NPI) (Aarsland, Bronnick, Alves, et al., 2009; Aarsland, Bronnick, Larsen, et al., 2009). In another cross-sectional study where a more comprehensive neuropsychological battery was used and which also includes assessment of minor hallucinations using the NINDS-NIMH criteria, those with PDP was worse in terms of frontal executive function (focused attention and set-shifting ability), working memory, and visuospatial function. (Lenka et al., 2021)

Longitudinal studies suggest that psychosis in Parkinson's disease has strong associations with disease duration (parallel in progression over time), excessive daytime sleepiness, rapid eye movement behaviour sleep disorder, depression, and dyskinesias (Marinus et al., 2018; Weintraub et al., 2022). Cross-sectional evidence also reported an association of psychosis with autonomic dysfunction and visual disturbances (Barrett et al., 2017; Ffytche et al., 2017). Therefore, definitions of psychosis applied to other psychiatric or neurodegenerative illnesses have limited utility in characterizing the scope of psychotic phenomena in PD. For these reasons, it is an immense challenge for any single tool to capture the variable timing and nature of psychotic symptoms that occur across the different disorders. Few studies considered the full spectrum of PD psychosis in the cascade of research regarding its phenomenology, prevalence, clinical prognosis, mechanisms, and management.

1.3.1.2 Pathophysiology

The exact aetiology of PDP is unknown but is reported to be complex and multi-factorial in origin, based on clinical, polysomnographic, functional imaging and histopathological studies. Traditional theories on the pathophysiology of PDP focused on dopaminergic medications implicated in its causality.

A prominent hypothesis is that of selective neuronal vulnerability to stress (van Wamelen et al., 2020) in PD involving chronic hyperstimulation and hypersensitization of the mesocorticolimbic D_2 and D_3 receptors, leading to limbic dysfunction (Zahodne & Fernandez, 2008). PDP is associated with neurodegeneration of the cholinergic nucleus Ch4) of the basal forebrain, which includes the nucleus basalis of Meynert (Barrett et al., 2018). There is also widespread neurodegeneration in the cytoarchitecture of the occipital, parietal, temporal, frontal, and limbic lobes, with relative sparing of the left ventral occipito-temporal cortex in visual hallucinators (Vignando et al., 2022). One of the earliest cortical regions to be affected in PDP was the cuneus, when only minor hallucinations occur (Pagonabarraga et al., 2014; Vignando et al., 2022) . In the context of visual hallucinations, another proposed hypothesis is based on an imbalance of external and internal inputs as well as impairment in reality tracking (Diederich et al., 2009; Diederich et al., 1998).

Greater ophthalmological disease (Fenelon et al., 2000; Holroyd et al., 2001) has also been found amongst PD visual hallucinators, which may be linked to the dopamine deficit found at the level of the retina (Onofrj et al., 2006). Functional MRI studies found that PD hallucinators catalogued more frontal and subcortical (caudate nucleus) and less visual cortical activation than non-hallucinators (Stebbins et al., 2004). A positron emission tomography study in PD visual hallucinators revealed higher 5-HT_{2A} receptor levels in the inferolateral temporal cortex, as well as in the prefrontal cortex and the ventral visual pathway (Ballanger et al., 2010). Other noted dysfunctions involved models of deafferentation hyperexcitability (impaired excitability in the visual associative cortices due to deafferentation), perception and attention deficits (co-occurring visuoperceptual and attentional cognitive deviations), and attentional control (reduced involvement of the dorsal attention network, increased activation of the ventral attention network, and disruption of the default mode network)(Vignando et al., 2022; Weintraub et al., 2022).

1.3.1.3 Minor Hallucinations

Early studies by Fenelon et. al. showed minor hallucinations (MHs) to be the commonest initial type of psychotic feature in PD (Fenelon et al., 2000; Fenelon et al., 2011; Fenelon et al., 2010). MHs can occur up to 8 years preceding the motor phase of PD (Pagonabarraga et al., 2016) in drug-naïve patients, further demonstrating the role of psychotic symptoms being an intrinsic part of the disease. In 2021, Zhang et. al (Zhang et al., 2021) identified frontal dysfunction and advanced HY stages to be independent predictors of MHs, consistent with the results of other recent studies (Lenka et al., 2021; Lenka et al., 2019; Omoto et al., 2021).

Minor hallucinations (MHs) are considered to consist of the following (Ffytche et al., 2017):

(i) Presence hallucinations (or the feeling of presence), referring to the sensation of someone as present nearby, independent from self, in the absence of suggestive external sensory stimuli;

(ii) Passage hallucinations, referring to the fleeting image of a person/animal/object passing within the peripheries of the visual field;

(iii) Visual illusions, referring to the brief misperceptions of object/person/animal that differ from objective reality.

MH can occur independently from other psychotic symptoms, or concurrent with well-formed hallucinations, typically of the visual modality (Lenka et al., 2021).It can occur up to 8 years preceding the onset of PD motor symptoms, and are considered a possible forme fruste of major hallucinations (Pagonabarraga et al., 2016). The distribution of MHs was also shown to vary across different PD severity stages (Zhang et al., 2021). In early PD (HY stages 1-2.5), 24.1% had MHs, with over 80% isolated MHs, which gradually increased to 59.5% with advanced phases of PD (HY stages 3-5), and 32.4% concurrent with major hallucinations(Zhang et al., 2021).

1.3.1.3.1 Presence Hallucinations

Sensed presence(s) is a sensory domain that have been described to be overrepresented in bereavement (Grimby, 1993; Rees, 1972) and has been generally erroneously described as a form of illusion despite the subtle differences existing between these two concepts in psychiatric literature. Sensed presence or presence hallucinations (an arguably more accurate term) had been shown to be a predictor of well-structured hallucinations, even if not the most common (Zhang et al., 2021). PwPs who had more than one type of MHs all experienced presence hallucinations (Zhang et al., 2021).

1.3.1.3.2 Passage Hallucinations

Very few studies have studied passage hallucinations in depth, with most categorizing it together with visual hallucinations. Passage hallucinations have been most commonly described as the fleeting and poorly defined vision of a shadow passing through the periphery of the visual field, or as a walking person or running animals (cats, rats, dogs), or as undefined moving objects, moving forward from behind and close to patients' shoulders (Lenka et al., 2019; Pagonabarraga et al., 2016). Patients usually have an irrepressible urge to look towards the illusory moving perception, turning their head behind them (Pagonabarraga et al., 2016).

Table 1.3 summarizes the key data from reviewed studies on minor hallucinations (MHs) across the world. Most studies are cross-sectional, and few utilized validated scales in determining the characteristics of psychotic symptoms from PwP, although in recent years, the eSAPS-PD (discussed in Chapter 6) - which has also not been validated amongst PwP - have been increasingly used. Only one so far examined for MHs in patients with *de novo* PD (Pagonabarraga et al., 2016). Not many studies assessed insight, and those which did found it generally preserved. Consistent with other studies (Barrett et al., 2017; Goetz et al., 2010), a significant association between PDP and REM sleep behaviour disorder (RBD) has been demonstrated, with a point prevalence above 25%.

***Table* 1.3: Demographic data and clinical correlates of minor hallucinations of all papers captured**

City, Country	**Paris, France**	**Pavia, Italy**	**London, England**	**Paris, France**	**Spain**	**USA**	**Online**	**Barcelona, Spain**	**USA**	**New York, USA**	**Japan**	**Shanghai, China**
Authors, Year	Fenelon et. al, 2000	Pacchetti et. al, 2005	Williams et. al, 2008	Fenelon et al, 2010	Fenelon et. al, 2011	Mack et. al, 2012**	Wood et. al, 2015	Pagonabarraga et. al, 2016	Barrett et. al, 2017	Kulick et. al, 2018 ♀	Omoto et al., 2020	Zhang et al, 2021
Sample size	216	289 PD	115 PD	116 PD	52 PD (78 control)	250 PD (65 with psychosis)	414 (208 with MHs)	50 PD (100 control)	101 PD	199 PD (30 with isolated MHs)	100 PD	149 PD (non-demented)
Sample Population	Multi-center (two specialist clinics) outpatients	Single center outpatients	Single center outpatients with parkinsonism	Single center outpatients	Single center: 38 outpatients, 14 inpatients with "*presence*" phenomena	Multi-center community-based outpatients	Online PD patient network	Single-center outpatients - "*de novo*" PD	Single-center outpatients	Single-center outpatients	Single-center outpatients	Single-center outpatients
Instrument	• A semi-structured questionnaire	• Structured questionnaire that included DSM-IV criteria for hallucinations and delusional disorders	• Queen's Square Visual Hallucination Inventory	• A semi-structured questionnaire	• A semi-structured questionnaire	• Personal checklist • Retrospectively applied NINDS-NIMH criteria for PD Psychosis	• Web-based questionnaire	• MDS-UPDRS Part I • A semi-structured interview	• SAPS • A structured interview to assess for illusions and sense of presence.	• eSAPS-PD • UPDRS • NMSS	• MDS-UPDRS Part I • A semi-structured interview of patients & caregivers	• eSAPS-PD
Study design	Cross-Sectional	Cross-sectional	Cross-sectional validation study	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional	Prospective longitudinal	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional
Mean age, years (SD)	69 (9.7)	68.3	66.8	67 (9.9)	67 (8.8)	64.2 (10)	61.9(8.2)	68.8 (10)	61.2 (11.1)	66 (9)	68.6 (9.9)	68.41(7.46)
Mean education, years	Unknown	Unknown	Unknown	NA	NA	15.6 ±3		9.1 ± 4	[Median 16 (14-18)]	[28 (93%) college or higher]	16	Unknown
Gender, male (%)	56.9	53.6	70	64.7	62	61.5	51.8	57.1	59.4	67	65	52.2
Mean HY (SD)	2 (0.8)	NA	2.5	2.1 (0.8)	2.7 (0.8)	2.1 (0.1)	2.1 (0.9)	1.9 (0.2)	NA	NA	NA	NA
Median HY	NA	<3 (128 patients)/ ≥3 (149 patients)	NA	NA	NA	NA	NA	NA	NA	2	3	2.5
Mean UPDRS III	*On* 15.4 (8.8)	*On* 21.6 (11.9) *Off* 46.1 (15.4)	28.8	NA	NA	16.2 ±1.3, n=64	Unknown	18.3 ± 9	[Median UPDRS III 24 (17-36)]	[Median UPDRS III 23 (16-31)]	24	PD-control: 18.81 (8.71) PD-MHs: 26.51(12.53)

Mean disease duration, years (SD)	9.5 (6.2)	8.4 (5.4)	10.0	9.1 (5.8)	11.5 (6.5)	10.2 (7.8)	7.3 (5.0)	1.6 (1.3)	6.1 (3.8)	[Median disease duration 7.1 (4.7-9.1)]	6	7.62(4.27)
Mean LEDD,mg (SD)	705 (414)	Unclear		758 (429)	959 (472)	606.3 (51.4)	Unknown	Unknown	[Median LEDD 598.5 (400-750)]	[Median LEDD 400(300-788)]	450	PD-control: 451.28 (267.72) PD-MHs: 558.04 (302.14)
Mean cognitive score (SD)	MMP 25.2(5.9)	MMSE 26.3 (3.54)	MMSE 27.7	NA	MMSE 25.4(4)	28.3 (0.2)	Unknown	MDRS 135(5) PD-CRS 95.1 (16)	All recruited had MoCA ≥21/30	[Median MoCA: 25(24-27)]	[Median MoCA 26.5 (24-28)] [Median MMSE 28 (26.3-30)]	All recruited had MMSE>24
%MHs in total study sample	25.5	22.6	75	45	NA	20.4	50.4	42	24.8%	23	38	32.9
Presence hallucinations	35 (64%)	Unknown	46%	33%	52 (100%)	9 (3.6%)	102 (24.6%)	14.3%*	5%	6%	Unclear	13.4%
Passage hallucinations	18 (33%)	Unknown	52%	16%	15 (29%)	45 (18%)	190 (45.9%)	28.6%*	Unknown	18%	Unclear	17.4%
Visual	48 (22.2%)	86 (29.8%)	78 (68%)	16%	20 (38%)	17 (6.8%)	64 (32.8%)	2 (9.5%) *	6.9%	3%	Unclear	12.1%
Auditory	21 (9.7%)	Unknown	16%	18%	14 (27%)	9 (3.6%)	Unknown	1 (4.8%) *	7.9%	2%	Unclear	9.4%
Olfactory	0	Unknown	NA	11%	9 (17%)	5 (2%)	Unknown	2 (9.5%) *	4%	6%	Unclear	8.1%
Tactile/ Somatic	0	Unknown	NA	12%/1%	14 (27%)	3 (1.2%)	Unknown	Unknown	2%	4%	Unclear	4.7%
Gustatory	0	Unknown	NA	3%	5 (10%)	Unknown	Unknown	Unknown	Unknown	1%	Unclear	Unknown
Delusions	0	19 (6.6%)	NA	4%	7 (13%)	8 (3.2%)	Unknown	Unknown	5%	6%	Unclear	3.4%
Insight	96.8% Preserved	Unknown	Unknown	NA	77% Preserved	-	Unknown	Preserved	Unknown	-	Unknown	Unknown
Description	**Presence:** presence of a person, and occasionally a rat	**Delusions**: Mostly persecutory and jealous subtype	-	-	**Presence:** persistent or recurrent presence of a person who had just left the scene	-	-	**Presence:** known person (partner, siblings, caregiver, deceased spouse)	-	**Passage:** people or animals passing in the peripheral vision; non-specific	-	**Presence:** Feeling of a known person behind the shoulder

					"*palinparousia*"; unformed visual hallucinations; 44% identified as a relative			**Passage:** Shadow (10/21, 47.6%), anonymous people (38.1%), animals (6/21, 28%), undefined objects (6/21, 18%)		shadows or flashing lights		**Passage:** vision of a shadow, a person, or animals (running cats, rats, or dogs) passing sideways in the periphery of the visual field, and moving forward from behind the shoulder **Delusions:** Mainly persecution, abandonment, religion.
RBD, %	NA	26.6%	NA	NA	NA	NA	NA	37.8% (p = 0.03) *	54.3% (p=0.012)	37%	34%	Unclear, although the complex MHs group had higher RBDQ-HK scores.

MHs=Minor Hallucinations; HY=Hoehn and Yahr; RBD=REM Sleep Behaviour Disorder; MDRS: Mattis Dementia Rating Scale; PD-CRS: Parkinson's Disease-Cognitive Rating Scale; eSAPS-PD: enhanced Scale for the Assessment of Positive Symptoms in PD; RBDQ-HK, rapid eye movement sleep behavior disorder questionnaire Hong Kong; Data displayed as mean (%) or Median (Range) unless otherwise specified; SD=standard deviation; NA=Not Applicable

*Results reported at baseline. ** Data displayed are for patients with PD psychosis only. ♀ Data only of the participants with minor hallucinations

1.3.1.4 Delusions

Although reported to be far less common than hallucinations in PD, with an estimated prevalence between 5% and 16% (Factor et al., 2014; Kiziltan et al., 2007; Lee & Weintraub, 2012), delusions are associated with a considerable impact on quality of life and increased caregiver burden, increased risk of nursing-home placement(Goetz & Stebbins, 1993), as well as increased risk of hospitalisation rates (Aarsland, Larsen, Cummins, & Laake, 1999). Isolated delusions, without concurrent hallucinations, are considered rare (Kiziltan et al., 2007; Stefanis et al., 2010).

The pathogenesis of delusions in PD patients implicated dopamine, through observations that dopaminergic medications may be precipitative of these symptoms (Graff-Radford et al., 2010; Nagy et al., 2012), and also because atypical antipsychotic medications have been reported to reduce the frequency and intensity of the delusions (Mohr et al., 2000), possibly through a dopamine mediated action at D2 receptors in limbic and striatal locations. In particular, the mesolimbic dopamine system is seen as a crucial feature of the "attribution of salience," a process whereby events and thoughts come to grab attention, drive action, and influence behaviour, because of their association with reward or punishment, possibly explaining why patients tend to look for further confirmatory evidence for previous delusional experiences, especially in the context of cognitive distortions present in PD patients (Djamshidian et al., 2012). Poletti et. al (Poletti & Bonuccelli, 2013) postulated that at least two conditions could be necessary for the development of delusions: (1) a state of aberrant salience attribution, associated with a dysregulated striatal dopamine signalling system; and (2) abnormal top-down cognitive explanations attributed to subjective experiences of aberrant salience.

A 2017 systematic review (Warren et al., 2018) reported that delusions in PD (n=184) of mainly early-onset PD cases, were primarily persecutory (63.6%) in nature, with the themes of

others ranging across delusional jealousy (23.9%), misidentification syndromes (11.4%) such as Capgras (9.2%), reduplication paramnesia (1.6%) and Fregoli (0.5%), grandiosity (3.8%), reference (3.8%), infestation (3.3%), nihilism (1.63%), guilt (1.1%), somatic concerns (1.1%), to religion (0.5%). Many experience more than one delusional subtype, while approximately half reported concurrent hallucinations. The onset of delusions was said to be related to a change in dopaminergic treatment in 53(28.8%) of cases, and secondary to deep brain stimulation in 10 (5.4%). With increasing age, the frequency of misidentification syndromes increased, delusional jealousy decreased, and persecutory delusions remained stable (Warren et al., 2018), although there was one report of misidentification syndrome occurring in early-onset PD (Islam et al., 2015). The presence of delusional jealousy in PD has been linked to dopamine agonist use (Poletti et al., 2012).

Delusional misidentification syndromes, such as Capgras (CS; the belief that someone familiar has been replaced by a stranger), Fregoli (the belief that strangers have been replaced by familiar person(s)), reduplicative paramnesia (belief that a specific place has been duplicated and present in two different locations), or the mirror sign (inability to recognise the reflected image of oneself), are disorders of altered familiarity and sufferers incorrectly identifies or reduplicates persons, places, objects, or events (Moro et al., 2013). Literature on this subtype of delusion, whilst expanding, was mainly captured in case reports or series. CS have been reported to occur after deep brain stimulation (DBS)(Groth et al., 2018; Kyrtsos et al., 2015). In a 2017 case series (Groth et al., 2018), three PD patients (all of whom suffered motor fluctuations and mild cognitive impairment) experienced CS between 6 months to 5 years following DBS, two after subthalamic DBS and one after globus pallidus interna DBS, which improved on low-dose Quetiapine. Evaluation of two CS cases, with a subsequent systematic review (Cannas et al., 2017), led to final recommendations for gradual reduction of dopaminergic treatment, adjunct to appropriate antipsychotic use and psychological management of stressful events, until remission of psychotic symptoms, particularly if CS appears early during PD motor ON states.

1.3.2 Apathy in Parkinson's disease (incorporated publication)

<This section is presented as a published paper, focusing on the parts on apathy in PD. This article was published in Lazcano-Ocampo, C., Wan, Y. M., van Wamelen, D. J., Batzu, L., Boura, I., Titova, N., Leta, V., Qamar, M., Martinez-Martin, P., & Ray Chaudhuri, K. (2020). Identifying and responding to fatigue and apathy in Parkinson's disease: a review of current practice. *Expert review of neurotherapeutics*, *20*(5), 477–495. https://doi.org/10.1080/14737175.2020.1752669 *(Lazcano-Ocampo et al., 2020)*>

This is a narrative review, of which I am joint first author, on the latest pathophysiology, clinical phenomenology, as well as the most frequently used scales, for fatigue and apathy in PD with a focus on available therapeutic strategies. I have developed the research question with the guidance of my supervisor, Professor K. Ray Chaudhuri. I have coordinated all stages of manuscript development, particularly of the section on apathy, including definition of outline, literature search, literature selection, writing, incorporating suggestions, and submission. I have personally written the first draft of the abstract, and the entire section on apathy in PD. I have drawn tables 3 and 5 of the manuscript. My fellow co-first author, Dr. C. Lazcano-Ocampo, worked on the section on fatigue, while Dr. Van Wamelen and Dr. Lucia Batzu contributed to the draft of the other sections and figures of the manuscript. Other co-authors have reviewed the manuscript and provided their expert opinion on the topic.

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REVIEW

Identifying and responding to fatigue and apathy in Parkinson's disease: a review of current practice

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ABSTRACT

Introduction: Fatigue and apathy are two key non-motor symptoms in Parkinson's disease (PD), with documented negative impact on Quality of life (QoL) and a frequent burden for caregivers.

Areas covered: In this review, the authors comment on the latest pathophysiology, clinical phenomenology, the most frequently used scales for fatigue and apathy in PD with a focus on available therapeutic strategies.

Expert opinion:The identification of fatigue and apathy in PD is mainly hampered by the lack of a clear consensus on these subjective symptoms. The pathophysiological processes remain unclear, and the large variation in prevalence is likely due to the heterogeneous PD populations and the lack of an enriched cohort of people with fatigue and/or apathy as main symptoms. Treatment strategies, and especially level 1 evidence for specific treatments for fatigue and apathy in PD, remain scarce. The best evidence to date is doxepin, rasagiline and levodopa infusion therapy (for fatigue), and rivastigmine (for apathy). Further efforts should be made to properly identify these two major symptoms in PD, to correctly detect those who may benefit most from tailored personalized interventions.

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1. Introduction

Parkinson's disease (PD) is a neurodegenerative syndromic condition involving both motor and non-motor symptoms (NMS). Virtually omnipresent, NMS of PD often start a decade or more before motor symptoms manifest [1]. Among the known NMS, fatigue and apathy are two of the more troublesome ones reported [2].

1.1. Fatigue

Fatigue, from the Latin *fatigare*, is defined as an overwhelming sense of tiredness, lack of energy, and feeling of exhaustion, which is unrelated to physical activity [3]. Two main forms of fatigue exist: 1) *physiological fatigue*, which constitutes a reaction to intense and prolonged activity and, as such, is predictable and transient, and 2) *pathological fatigue*, which involves feelings of tiredness at rest and a disproportionate lack of energy that compromise daily activities and quality of life (QoL) for a prolonged period of time, usually more than 3 months [4,5]. A further distinction can be made between subjective fatigue and objective fatigue (fatigability); as these conditions do not necessarily correlate [6]. *Subjective fatigue* is a feeling of finding it tiring or troublesome to initiate a mental or physical activity for days to weeks, whereas *fatigability* refers to problems maintaining physical and mental effort at a certain level during a short period of time [6]. Subjective fatigue can be further categorized in physical and mental fatigue, where *physical fatigue* is described as a sense of disproportionate physical exhaustion despite the incentive to perform a task, whilst *mental fatigue* is the experience during and after prolonged activity involving cognitive tasks that require sustained attention and mental effort [7]. However, the severity of mental fatigue does not correlate well with physical fatigue in PD, suggesting a separate subjacent mechanism [8].

1.2. Apathy

The term 'apathy', introduced by the Stoics (Greek: *apatheia* (ἀπάθεια) meaning 'without feeling or suffering'), refers to the loss of motivation and lack of concern toward the external world. It was initially conceptualized by Marin et al. [9] but was

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Article highlights

- Fatigue and apathy are key, yet often undetected, non-motor symptoms in Parkinson's disease.
- Both symptoms have a tangible impact on quality of life in people with PD.
- The pathophysiology underlying these symptoms remains largely unclear and evidence supports both dopaminergic and non-dopaminergic pathways.
- The scale with best psychometric properties for fatigue so far is the Parkinson's Fatigue Scale, and for apathy is the Starkstein Apathy Scale.
- Treatment strategies for both symptoms lack level 1 evidence base.
- The best evidence for fatigue treatment is for doxepin, rasagiline, and levodopa infusion therapy.
- The best evidence for apathy treatment is for rivastigmine.
- Further efforts towards individualized strategy-driven research and treatment are needed.

later revised and adapted for PD by Starkstein et al. [10,11]. Absence of motivation is usually the cornerstone in defining apathy, which additionally includes a decrease in goal-oriented behavior and cognition, and a reduction in emotional expression [12].

Conventionally considered a unitary construct, apathy is currently represented by three key aspects with different clinical manifestations [13–15]:

a. *Affective-emotional apathy* – the impairment of linking affective and emotional signals with manifest behavior, expressed by emotional blunting and modified social interaction.
b. *Cognitive apathy or 'cognitive inertia'* – the impairment of conceiving and achieving goal-directed behavior, expressed by executive functioning.
c. *Behavioral apathy or 'auto-activation'* – the inability to activate and maintain spontaneous patterns of action and thought in the presence of spared ability to generate externally driven behavior, which affects both emotional and cognitive responses.

In this narrative review, we aim to summarize updated evidence-based recommendations on how to identify and respond to fatigue and apathy in PD.

2. Methods

A computerized search of PubMed, PsycINFO, EMBASE, CINAHL, the WHO International Clinical Trials Registry and the Cochrane Library of literature published up until December 2019 to identify all potentially eligible studies was conducted. For PubMed, we used the Medical Subject Heading (MeSH) term 'fatigue', or 'apathy', combined with the MeSH term 'Parkinson' or 'Parkinson's'. All MeSH terms were expanded to include all subheadings to identify all relevant articles. All potentially eligible studies were considered regardless of publication type. The Cochrane Database of Systematic Reviews and the reference lists of each article were also manually checked to identify additional studies. No language, publication date, or publication status restrictions were imposed. Selection and independent assessment of the abstracts were done by the research team from the Parkinson Foundation Centre of Excellence in non-motor research at King's College Hospital and King's College London. Disagreements were resolved by a consensus-based discussion.

3. Epidemiology

3.1. Fatigue

Fatigue in PD is more prevalent than in age-matched controls, even in early disease stages, with a clear negative impact on QoL, being described as one of the most three disabling symptoms by more than 50% of the people with PD (PwP) [16–18]. Its prevalence in PD ranges from 33% to 81% averaging to about 50%; these fluctuations in the estimated figures possibly attributed to differences in measurement methods and sampled populations [16]. To date, it seems to be that there is no correlation between fatigue and disease duration and motor symptoms, and could be associated to other non-motor symptoms such as anxiety, apathy, and sleep disturbances, as described in a recent meta-analysis [19]. Once fatigue is present, it is likely to persist or aggravate over time [16,20].

3.2. Apathy

Apathy has been reported in *de novo* PD, early in the disease preceding motor symptoms, and in advanced disease stages [21–24], being noted to progress parallel to the evolution of PD [25–27]. Due to its nature, occurrence of apathy in PD is likely underestimated. Reported prevalence ranges between 13.5% and 70% [28], with a recent meta-analysis reporting a pooled prevalence of 39.8% [12], although, similar to fatigue, these figures could be confounded by other comorbid NMS and the heterogeneity of the sampled populations and the measurement methods. The prevalence of apathy in PD excluding depression was about 42.8%, whilst its prevalence excluding cognitive impairment was reportedly in the range of 28%-39%, depending on methods of diagnosis [12]. The prevalence of pure apathy, after excluding both depression and cognitive impairment, is reported to be about 22.6% [12].

4. Pathophysiology

4.1. Fatigue

The understanding of fatigue pathophysiology has been a challenging concept, partly due to inconsistencies in fatigue definition and use of different methods of assessment across studies [29]. To date, and in spite of several efforts, it remains elusive to segregate the pathophysiology and understanding of fatigue from other NMS in PD, since it is not clear whether the occasional co-occurrence of these symptoms could be attributed to a common mechanism, like the degeneration of serotonergic pathways and abnormal activity and connectivity of limbic-cortical circuits [19], or to diagnostic bias [30].

No association was found between dopaminergic nigrostriatal degeneration, one of the hallmarks of PD pathology, and fatigue through neuroimaging studies [8,31], except for one study where nigrostriatal dopaminergic denervation assessed with [^{11} C] DTBZ PET was a significant predictor of fatigue in participants with mild PD [32] (Figure 1). Lack of association between fatigue and motor symptoms of PD could be another indirect indication that non-nigrostriatal dopaminergic dysfunction produces fatigue in PD [19], while the finding of reduced F-dopa uptake in the insular cortex of PD participants with fatigue might suggest a dysfunction of extrastriatal dopaminergic projections [8]. Interestingly, a link was reported between serotonergic denervation in the basal ganglia and associated limbic circuits using [^{11} C] DASB PET scan [8] (Figure 1). Modifications in serotonergic signaling could potentially affect the frontal-basal ganglia circuitry and integration of limbic input and motor functions and might represent a possible mechanism underlying fatigue in PD [19].

Dysfunction of circuits connecting the basal ganglia and medial frontal areas (frontal striato-thalamo-cortical loops) has also been suggested to be involved in fatigue pathophysiology [33]. In one study, fatigue perception was associated with decreased blood perfusion in the frontal lobes, suggesting that dysfunction in the frontal cortex might be a cardinal contributor to fatigue [34]. In an fMRI study conducted on a cohort of 'drug-naïve' patients with PD, fatigue was associated with decreased connectivity in the supplementary motor area and increased connectivity in the prefrontal and posterior cingulate cortices within the default mode network (DMN) [35].

Neuroinflammation may also be assumed to account for different levels of fatigue and disability seen in many patients with neurological and autoimmune diseases [36]. In a study with PD patients, fatigued subjects had elevated interleukin (IL)-6 serum levels compared to non-fatigued patients [37], while in another study, after controlling for possible confounders, high CRP levels in the CSF were significantly associated with more severe symptoms of fatigue and depression [38].

Finally, animal models have shown that the overexpression of alpha-synuclein in mice could diminish their performance over wheel-running compared with wildtype control, probably related to reduction of the daytime electrical activity of the suprachiasmatic nucleus neurons (SCN) and motor centers who are targets of the SCN [39,40]. Rat models have also supported the influence of neuroinflammation with a higher production of IL-1β which is not only related to central fatigue but other neurological conditions such as stroke, brain trauma, multiple sclerosis, Alzheimer's disease, PD, and chronic diseases like depression [41].

4.2. Apathy

The neural networks underlying apathy in PD provide a conjectural foundation to spearhead an exploration of cognitive, behavioral, and emotional domains of apathy [13], as well as investigate possible neuropsychological correlates of each domain.

Pre-clinical studies in rodents have proposed that apathy may stem from dysfunction of the dopaminergic mesocorticolimbic system, and additionally recommended that D3 R be targeted in the reversal of motivational deficits in PD [42]. Furthermore, it has been suggested that apathy represents the opposing end of a behavioral dopamine-dependent continuum from impulse control disorders (ICDs) in PD [43]. In support of the hypodopaminergic etiology, several studies suggested that apathy is mainly associated with deficits in the dopaminergic networks (Figure 2), as it is closely related to the brain reward system [44–46]. For instance, Thobois et al. compared the PET scans of 12 people with PD who suffered from post-DBS apathy with those who did not and demonstrated that the grow up with apathy had lower endogenous dopamine [47]. A recent study also revealed that apathy was inversely correlated to a marker of both dopamine and noradrenaline transporters ([11 C]RTI-32) in the ventral striatum [48]. The emergence of apathy after rapid reduction of anti-

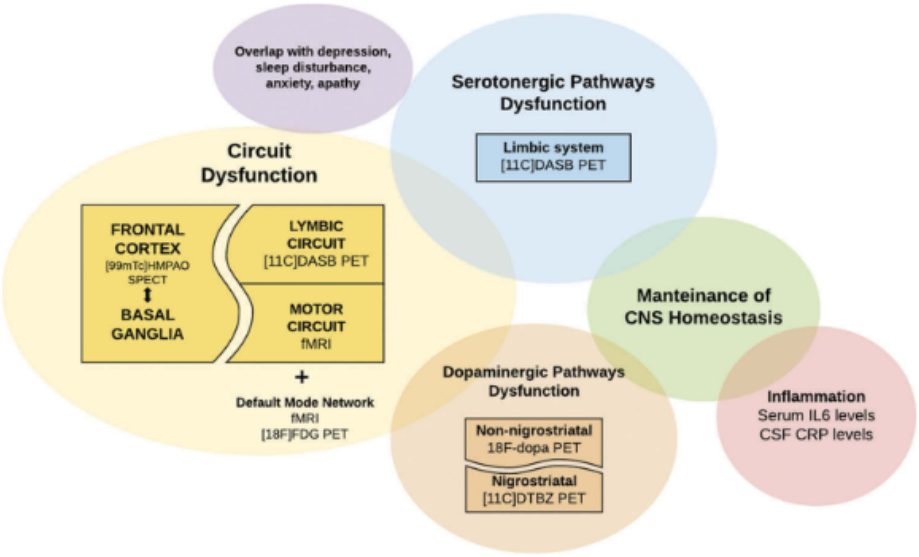

Figure 1. Different brain networks and neurotransmitter systems involved in Parkinson's disease fatigue.

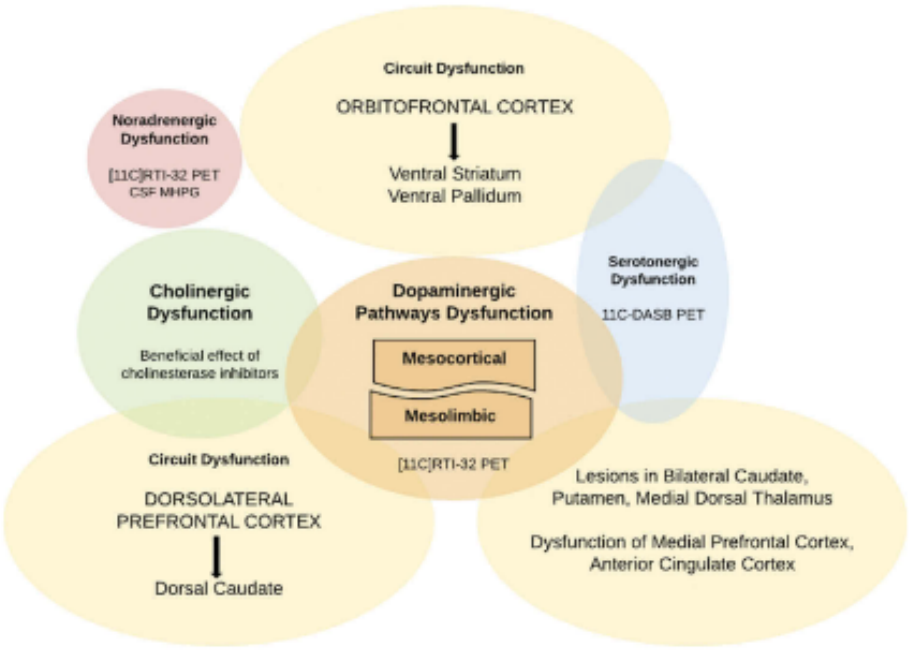

Figure 2. Circuit dysfunctions and different neurotransmitter systems involved in the pathophysiology of apathy.

parkinsonian drugs post-deep brain stimulation (DBS) [46] and the description of the positive influence of levodopa treatment on self-reported motivation in PD patients [45] also endorsed that apathy in PD is, at least in part, a dopamine-dependent syndrome.

On the other hand, the relationship between apathy and executive function [22], depression [21,22], and sleep disturbances [22] implicates additional non-dopaminergic origins. Mayeux et al. found a correlation between the CSF concentration of 3-methoxy-4-hydroxyphenylglycol (MHPG), the major metabolite of noradrenaline, and cognitive measures of bradyphrenia [49], which advocates that bradyphrenia (which is similar to the concept of apathy) in PD may be related to dysfunction of catecholaminergic pathways and the locus coeruleus. Evidence of a disruption in the serotonergic systems is also revealed by the 2016 study in *de novo* PD, when 15 patients with apathy primarily demonstrated greater serotonergic alteration in the ventral striatum, the dorsal, and the subgenual parts of the bilateral anterior cingulate cortices, as well as in the right-sided caudate nucleus and the right-sided orbitofrontal cortex, as compared to those without apathy [50]. Finally, the cholinergic systems may also play a vital modifying role on motivation in PD, given the robust link between PD apathy and cognitive impairment which is elaborated later in this text, and also based on the therapeutic benefit of cholinesterase inhibitors for treating apathetic behavior in some without depression and dementia [51].

In structural and functional imaging studies, apathy has been associated with the frontal cortex, basal ganglia, substantia nigra, anterior cingulate cortex, and orbitofrontal cortex in PD [52,53]. A 2010 study of apathy in PD revealed an association between apathy and decreased gray matter density in the anterior and posterior cingulate and bilateral inferior frontal gyri, as well as associated structures such as right precuneus, insula and bilateral precentral, inferior parietal, and inferior frontal cortex [53,54]. In addition, Skidmore and colleagues [54] reported a correlation of apathy with abnormal patterns of activation in the left supplementary motor cortex, the right orbitofrontal cortex, and the right middle frontal cortex, supporting the assumption that apathy in PD is related to orbitofrontal lobe dysfunction.

Studies of apathy in different neurodegenerative disorders have revealed that it may be a consequence of severe neuronal loss in the basal ganglia despite a lesser degree of prefrontal pathology, implying that apathy could be addressed as a 'prefrontal-like' syndrome due to lesions mainly affecting the basal ganglia. The failure to generate basal ganglia output to the frontal lobes and to select, extract, and augment the relevant incoming signal from background noise makes the transmission of the extracted signal to the prefrontal cortex (in order to maintain ongoing and generate new behavior) impossible [14,55].

In general, apathy is complex and multidimensional in etiology, with divergent mechanisms across different neurodegenerative disorders and across different stages of PD.

5. Description of symptoms

5.1. Clinical features of fatigue

Fatigue can go unrecognized by physicians, but given the significant impact on QoL in PD, and repercussions on public health care it is important not to miss this symptom [56,57].

Furthermore, it can significantly affect the caregiver's QoL when fatigue is associated with dementia [58], which could potentially increase the need of institutionalization. When addressing fatigue, it is important to ask the patients to describe their complaints, as fatigue is often referred to as

an unbearable tiredness, utter exhaustion, and a feeling of severe illness, which could be helpful to distinguish (a) from daytime sleepiness, as fatigue does not improve after sleeping, (b) from apathy as patients usually want to do activities but are limited due to lack of energy and (c) from depression, as it is not related to mood [18]. However, as fatigue overlaps frequently with these NMS, the approach to manage these patients in a holistic manner becomes a challenge, emphasizing on the need to take a comprehensive non-motor history aided by validated tools such as the NMS questionnaire. Time of onset can be used to rule out secondary causes of fatigue, such as other health issues (stroke, chronic diseases) or the concomitant use of medication that can worsen it, e.g. beta-blockers [59]. In addition, Kluger recommended considering the diurnal pattern of fatigue in PD, with it worsening during the afternoon. Fatigue can be a feature of non-motor fluctuation and is often associated with an off state [60], thus suggesting a dopaminergic basis in this scenario.

5.2. Clinical features of apathy

As a neuropsychiatric symptom, apathy in PD is often found to intersect with other neuropsychiatric syndromes such as depression, anhedonia, and anxiety. A study in 2017 assessed 40 Pw Pwith dementia and revealed that apathy was associated with advanced dementia, and could exist independent of depression [61]. The main differentiating clinical parameter between depression and apathy (once considered part of the depression symptomatology) is the mood, as it remains 'neutral' in the latter and negatively affected in the former [62]. While depression incorporates guilt and suicidal intentions, apathy does not often show such symptoms; rather, it identifies with emotional indifference or lack of emotional response to positive or negative events [63,64]. Apathy can indeed occur separately from depression in PD [65,66], and both independently exert a negative impact on QoL [66–68].

Symptoms exclusive to apathy are summarized in Table 1.

Studies examining apathy in neurodegenerative conditions have found that those with apathy have lower Mini-Mental State Examination (MMSE) scores than those without, and this have demonstrated impairment in impulse control, attention, visual and verbal memory, and verbal fluency [69]. Associated not only with PD dementia (PD-D) [61,70], apathy has also been found in PD patients with mild cognitive impairment (PD-MCI) and is postulated to be the key neuropsychiatric herald for the conversion to dementia [71]. Indeed, a very recent study [72] demonstrated apathy to be the staunchest behavioral predictor of early cognitive decline in PD.

Table 1. Exclusive symptoms of apathy.

Apathy symptoms
Reduced initiative
Reduced participation in external activity
Loss of interest in daily or social activities
Reduced interest in starting new activities
Reduced interest in the happenings of the external environment
Emotional indifference
Reduced emotional reactivity
Lack of concern about other people's feelings, or interests

For PwP, apathy exerts a negative impact on QoL [73] and poses significantly greater burden on the caregiver, which has negative implications on the caregiver's physical, emotional, and psychosocial well-being [74]. Increased caregiver distress, in turn, contributes to the QoL decline in PD, leading to an increased risk of premature institutionalization [75].

On the whole, apathetic Pw Pwere found to be more likely to have greater motor deficiency, major executive dysfunction, and a greater risk of developing dementia than those who were non-apathetic [26]. They are also more likely to have greater olfactory deficits, possibly due to overlapping dysfunction in associated brain regions [76]. The dimension of emotional blunting serves as a modifier for PD with apathy, leading to worse QoL and greater caregiver burden, even in the absence of dementia [77].

6. Measuring fatigue and apathy in PD

6.1. Sign-posting and screening with the non-motor symptoms scale

The NMS Scale (NMSS) [78] is a multidimensional tool, used to quantify a wide range of non-motor symptoms occurring in PD, each one scored for severity and frequency by the physician and evaluating a time frame of 1 month. The NMSS is composed of 30 items grouped into 9 domains, the collective sum of which comprises the total score. Fatigue, together with sleep disturbances, is a key component of domain 2 of the NMSS (sleep/fatigue domain) as well apathy in domain 3, and both can be scored based on the multiplication of its severity and its frequency [79]. The development of an updated version of the NMSS was launched in 2015 with the support of the International Parkinson and Movement Disorder Society (MDS) and the final version of the MDS-NMS is now published [80]. In this new scale, physical and mental fatigue is specifically addressed under the 'Others' domain and fatigue has also been included in an optional section targeting non-motor fluctuations (NMF) [80,81]. Furthermore, apathy is a specific domain in it (domain C) showing good domain-based clinimetric attributes in the first international validation study. In the context of a holistic NMS evaluation, the MDS-NMS provides a one-stop assessment of apathy as well as the ability to measure other possible comorbid NMS in an individual with PD.

6.2. Specific fatigue scales

Most subjective fatigue rating scales are self-reported questionnaires aiming to give a measure of individual perceptions of fatigue, nevertheless clinician-rated scales have also been probed to be useful (Table 2) In 2010, an MDS Task Force published a critical review on rating scales and provided recommendations on their endorsement for screening fatigue in PD and assessing its severity [82].

6.2.1. The fatigue severity scale (FSS)

The FSS [83] is the only 'recommended' fatigue scale for both screening and quantifying severity of PD subjective fatigue by the MDS Task Force. The FSS is brief and easy to administer.

comprehensive 8-item scale with satisfactory psychometric attributes designed for daily administration, and the Clinical Global Impression Scale (CGIS) [93], a rating instrument which can investigate all aspects of a chosen condition with a numerical measure (usually 5 or 7-point rating) for symptom severity. Interestingly, a recent study aiming to investigate the dimensionality of the constructs of fatigue identified the single-item Visual Analog Fatigue Scale (VAFS) as a potential reliable estimate for the overall sensation of excessive fatigue experienced by individuals with PD [94].

6.3. Scales for apathy

An arsenal of instruments is currently used to measure apathy (Table 3), which a few of the more important ones are described more extensively below, with most being self-reported subjective questionnaires. The Movement Disorder Society (MDS) Task Force to Assess the Clinimetric Properties of Apathy and Anhedonia Scales in PD [95] identified four apathy rating scales: the Apathy Evaluation Scale (AES); the abbreviated version of the AES, known as the Apathy Scale (AS); the Apathy Inventory (AI); and the Lille Apathy Rating Scale (LARS). The AS, AI, and LARS were specifically developed for PwP, but only the AS meeting criteria to be 'recommended' [95].

6.3.1. Apathy evaluation scale (AES)

The AES is a generic scale which has been specifically validated in PD population, including *de novo* PD [96], PD with comorbid dementia and depression [97,98], PD-MCI [99], as well as PD with STN-DBS [100]. There are three versions of this scale available: Patient (AES-S), Caregiver (AES-I), and Clinician (AES-C). The AES-C was one of the first instruments created to assess apathy in neurologic populations, and one of the first to quantify apathy based on a psychological definition. The AES-C has good internal consistency; however, those who are more cognitively impaired tend to score higher [101]. It has good interrater and test–retest reliability, and moderate item-total correlations. The informant- and patient-based versions have a good convergent validity, but concurrent validity with the NPIa is weak [97,101]. It reportedly has the highest sensitivity and specificity with both being 90% [96].

6.3.2. Starkstein apathy scale (AS)

The AS is a condensed and modified version of the AES developed by Marin et al., in 1991 [11]. It was specifically developed as a less demanding scale for people with PD, as compared to the AES. The reliability and validity of the original, patient-based, version of AS has been established [10], with excellent inter-rater reliability, test–retest reliability, and questionable-to-excellent internal

Table 3. Rating scales for apathy in Parkinson's disease.

Rating Scales to evaluate apathy in Parkinson's disease				
Scale	Time to complete	Number of items	Rater	Advantages
MDS – Non-motor Rating Scale (MDS-NMS)	15 – 40 minutes	52	Self-rated	• Holistic tool to assess apathy in the context of all nonmotor symptoms
Apathy Evaluation Scale (AES)	20 min	18	Self-report (AES-S) Informant (AES-I) Clinician (AES-C)	• Original quantitative scale assessing apathy • Has been extensively used in PD research • Suitable for all PD stages • Highest sensitivity and specificity of all apathy scales
Starkstein Apathy Scale (AS)	10–12 min	14	Self-Rated	• Informant version available • Brief and easy to complete • Suitable for all PD stages • Good sensitivity to change • Good balance of sensitivity and specificity • Recommended for screening and assessing severity by the MDS-Task Force
Lille Apathy Rating Scale (LARS)	20–25 min	33	Informant or self-rated	• Four composite subscales including intellectual curiosity, self-awareness, emotion, and action initiation • Sensitivity to change showed • Comprehensive and easy to use
Neuropsychiatry Inventory Apathy (NPIa) subscale	5 min	Screening question + 8 sub-questions	Informant-based interview	• NPI (complete scale) has been validated and extensively used in PD populations both with and without dementia
Ardouin Scale of Behavior in Parkinson's Disease (ASBPD) – Part II	NA (1 hour for the whole scale)	21 (whole scale)	Clinician-rated	• Evaluation of activity level, cognitive level, and emotional level
Apathy Inventory (AI)	NA	3	Self-rated	• Brief and easy to use • Informant version available • Assessment of frequency and severity of three domains: emotional blunting, lack of initiative and lack of interest
Frontal Symptoms Behavioral Scale (FrSBe) - Apathy Subscale	10 min	12	Informant, self-rated (2 versions)	• Brief and sensitive to change
MDS-UPDRS* (Part I)	30 min (whole scale)	13 (one for apathy)	Self-rated	• Extensively used in PD
Non-Motor Symptoms Scale (NMSS) – Mood/Apathy Domain	5 – 10 min (whole scale)	6 (30 for the whole scale)	Clinician-rated	• Brief and easy to administer

consistency [102,103]. As the instrument is based on a self-reporting system, those whose spontaneity is excessively low or have advanced dementia likely cannot answer the questions, which may limit the use of AS, but may be used in those with mild cognitive impairment [95]. The advantages of the AS are its brevity, its ease of administration, and its extensive worldwide use. It has been shown to be sensitive to change as well, especially in pharmacological treatment [104,105], as well as in treatment by DBS [106].

6.3.3. Lille apathy rating scale (LARS)

The LARS is a structured clinician-administered scale specially designed for PD and validated in a group of PD patients with and without dementia [107]. To date, it had shown sensitivity to change in two treatment studies and could discriminate apathy in PD from healthy controls [108]. It can be used in people with mild-to-moderate PD. However, it did not quite meet the MDS criteria for 'recommended' [95].

6.3.4. Neuropsychiatry inventory (NPI)- apathy (NPIa) subscale

The Neuropsychiatry Inventory (NPI) was developed to assess and measure neuropsychiatric disturbances in dementia [109]. The NPIa subscale (Item G) assesses apathy change over the past month or since the last evaluation. There is a lack of studies assessing the psychometric properties of the NPIa in PD. Despite this and it being a generic instrument, the NPI has been used extensively in the PD population [110–112] and it has been shown to be valid in PD populations both with and without dementia [110,113].

6.3.5. Ardouin scale of behavior in Parkinson's disease (ASBPD)

The ASBPD was a semi-structured clinician-conducted interview developed to evaluate several neuropsychiatric symptoms (NPS) and non-motor fluctuations, as existing scales do not identify all NPS present in those with PD [114]. Although considered to be overall reliable in detecting apathy, with acceptable internal consistency and test–retest reliability, studies of its convergent validity showed significant association with standardized rating scales measuring depression and anxiety, rather than with pure symptoms of apathy [114].

6.3.6. Apathy inventory (AI)

The AI is a three-item scale to assess global and subdomain apathy (emotional blunting, lack of initiative and lack of interest); one item for each domain [115]. This is a self-reported generic scale in which the user assesses his own behavior for each item (Yes/No), and then bisects a line reflecting severity of behavior on a 12-point scale ranging from mild to severe). Its brevity and ease of use made it attractive for use. However, although AI was disease-specific for evaluation of apathy in PD, no studies other than the original have used it in the PD population. Furthermore, it is copyrighted by CoBTeK – Association Innovation Alzheimer, and permission is needed before it can be used.

6.3.7. Frontal symptoms behavioral scale (FrSBe)

FrSBe [116] is a brief, reliable, and valid measure of three frontal behavioral syndromes: apathy, disinhibition, and executive dysfunction. It is sensitive to changes over time since it includes both baseline and current assessments of behavior. However, it needs to be purchased and is not freely available.

6.3.8. Movement disorder society–unified Parkinson's disease rating scale (MDS-UPRDS) Part I

The MDS-UPDRS [117] is a patient-rated scale, which retains the UPDRS structure of four parts with a total summed score, but the parts have been modified to provide a section that integrates non-motor elements of PD. It is a PD-specific scale and is available online although permission from the MDS is needed to use it. It has been translated into multiple languages and has been used in mild-to-moderate PD.

6.3.9. The MDS non-motor rating scale (MDS-NMS)

Apathy is a specific domain in the newly validated MDS-NMS (domain C) [81] and it shows good domain-based clinimetric attributes in the first international validation study. In the context of a holistic NMS assessment, the MDS-NMS provides assessment of apathy as well as the ability to measure other possible comorbid NMS in a patient using one tool.

7. Current therapy for fatigue and apathy

Although approximately one-third of PwP consider fatigue as the single most disabling symptom of their disease [118,119], treatment options are still very limited. In 2019, the MDS Evidence-Based Medicine (EBM) Committee published recommendations on treating PD-NMS [120] from which we based our recommendations for fatigue and apathy treatment, with the addition of recent evidence from both pharmacological and non-pharmacological perspectives (Table 4; Table 5).

7.1. Pharmacological treatment

7.1.1. Dopaminergic therapy

7.1.1.1. Levodopa. In the clinical trial, ELLDOPA (early PD enrolled in the Earlier vs. Later Levodopa), a total of 361 PD patients were enrolled and divided in four groups: carbidopa/levodopa 37.5/150 mg, 75/300 mg, and 150/600 mg per day vs. placebo [31]. After 40 weeks receiving medication and 2 weeks of washout period, increases in fatigue score from baseline to the final visit were noted, specifically in the placebo group whilst no significant change was observed in PD patients who had subjective fatigue from baseline. Previously, Lou et al. [121] described a reduction in physical fatigue in patients using levodopa, reaffirming that fatigue could have a dopaminergic etiology.

Similarly reflecting the overarching dopaminergic origins of apathy, a 2002 study showed that apathy levels (AS) of a group of PD patients without dementia or depression improved significantly under L-Dopa treatment [45].

7.1.1.2. Rotigotine. In the RECOVER trial, rotigotine was effective for both fatigue and apathy measured by the NMSS

Table 5. Therapeutic interventions for apathy in Parkinson's disease: randomized clinical trial, meta-analysis, and open-label studies.

Intervention	Study reference	Study design	Outcome measures	Results
Pharmacological				
Levodopa	Czenecki et al., 2002	Open label n = 23 PD (in both 'on' and 'off' states vs 28 controls)	AS	Improvement of AS apathy for those under levodopa treatment
Levodopa-carbidopa intestinal gel infusion (LCIG)	Martinez-Martin et al., 2015	Open label n = 87* 24 weeks	NMSS mood/apathy domain	Improvement of NMSS mood/apathy domain scores (apomorphine > LCIG)
	Dafsari et al., 2019	Open label n = 173* 24 weeks	NMSS mood/apathy domain	Improvement of NMSS mood/apathy domain scores (apomorphine > ULI or DBS STN)
Rotigotine	Hauser et al., 2016	RCT n = 122* 5 to 19 weeks	AS NMSS mood/apathy domain	No changes in AS score Improvement of NMSS mood/apathy domain scores
	Ray Chaudhuri et al., 2013	RCT n = 287* 4 weeks	NMSS mood/apathy domain	Improvement of NMSS mood/apathy domain scores in post-hoc analysis
Pramipexole	Leentjens et al., 2009	Meta-analysis of 7 RCT n = 1296*	UPDRS Part I item 4	Improvement of motivational symptoms
	Oguro et al., 2014	Open label, case-control n = 36* 8 weeks	Modified apathy scale	Pramipexole together with levodopa improved apathy
Ropinirole	Czernecki et al., 2008	Open label n = 8* 6 weeks	AS AI	Improvement of apathy in patients who had stopped all dopaminergic therapy after STN DBS
Piribedil	Thobois et al., 2013	RCT n = 37* 12 weeks	AS	Improvement of apathy in PD patients with apathy after DBS STN
Apomorphine	Martinez-Martin et al., 2011	Open label n = 17*	Item 8 of the NMSS mood/apathy domain	Improvement of NMSS mood/apathy (and especially Item 8) domain scores on apomorphine compared to control
	Martinez-Martin et al., 2015	Open label n = 87* 24 weeks	NMSS mood/apathy domain	Improvement of NMSS mood/apathy domain scores (apomorphine > LCIG)
Methylphenidate	Moreau et al., 2012	RCT n = 81* 12 weeks	LARS	Improvement of apathy in the subgroup of apathetic patients (N = 7)
Rivastigmine	Devos et al., 2014	RCT n = 101* 24 weeks	LARS	Improvement of apathy
Non-pharmacological				
rTMS	Oguro et al., 2014	Randomized double-blind, sham-controlled cross-over study n = 15* Area of stimulation: SMA 12 days	AS (Japanese translated)	Improvement of apathy
	Maruo et al., 2013	Randomized double-blind, cross-over study with sham stimulation n = 21* Area of stimulation: M1 3 days	AS	No improvement of apathy
	Fernandez and Bowers et al, 2016	Randomized sham-controlled double-blinded trial n = 24* Area of stimulation: Left prefrontal cortex 10 days	AES	Improvement of apathy immediately after rTMS, but no between-group differences.
Activity Therapy	Butterfield et al. 2017	Open label n = 34* 6–10 weeks (6-weeks of intervention)	AES	Improvement of apathy

Abbreviations: RCT = Randomized Control Trial, rTMS = Repetitive transcranial magnetic stimulation, AES = Apathy Evaluation Scale, AS = Starkstein Apathy Scale, LARS = Lille Apathy Rating Scale, AI = Apathy Inventory
* Total number of participants enrolled

and insight to apathy by caregivers, than by patients themselves.

Wang et al. conducted a meta-analysis on eight randomized placebo-controlled trials looking at the effect of rotigotine for the treatment of NPS [123]. The studies included a total of 1,675 PD patients, using NMSS to assess sleep/fatigue and mood/apathy. Three studies (Trenkwalder et al. 2011; Antonini et al. 2015 and Hauser et al.2016) [104,124,125]

showed a significant improvement of the sleep/fatigue domain in PD patients using rotigotine compared with the control group, but these items were not analyzed separately. Pertaining to apathy, this meta-analysis reported a significant improvement using NMSS in the studies by Antonini et al. (2015), Hauser et al. (2016), and Chung et al. [104,125,126]. It seems rotigotine could act on both dopaminergic and serotonergic receptor subtypes, improving not only fatigue and apathy but other NMS too [123].

7.1.1.3. Pramipexole. There is some controversy on the potential benefit of pramipexole on fatigue, since Shannon et al. reported fatigue as an adverse effect of its use [127], though the finding was not statistically significant. Later, Hauser et al. compared different versions of pramipexole, the immediate and the extended release, with placebo, showing that pramipexole was associated with the worsening of fatigue in PD patients [128]. Akihiko Morita et al. performed a multicenter cross-sectional study in 350 non-demented PD Japanese patients comparing the effect of dopaminergic treatment on fatigue, using the PFS [89]. Pramipexole was significantly more frequently used in PD patients without fatigue who were in an early stage of the disease, a finding that could be attributed to its agonist effect in D3-receptors, which are related with a good response of fatigue [89].

Regarding apathy, a 2009 meta-analysis of seven RCTs found that pramipexole has a beneficial effect on motivation (assessed with the UPDRS Part I item 4) [129]. When 22 participants with apathy but without depression were analyzed in a head-to-head comparison study examining the differential effects of dopamine agonists on NPS of PD [130], there was a significantly lower frequency of apathy in the pramipexole group (3.4%) compared to the ropinirole (8.5%) and levodopa (9.9%) groups, respectively. In another study, 1.5 mg daily of pramipexole together with L-DOPA improved apathy in PD patients within 8 weeks, compared with monotherapy with L-DOPA [131].

7.1.1.4. Ropinirole. In an open-label study, ropinirole was effective in improving apathy (AS) by 54% in eight patients who had stopped all dopaminergic therapy after STN DBS [46]. However, there are no clinical trials exploring the effect of ropinirole on fatigue in PD.

7.1.1.5. Piribedil. In 12-week double-blind randomized controlled trial of piribedil (a D2 and D3 receptor agonist) vs. placebo of 37 patients with apathy (AS score > 14) following STN DBS and initial withdrawal of dopamine agonist treatment, the apathy score was reduced on follow-up by 34.6% ($n = 19$) on piribedil 300 mg/day compared to 3.2% on placebo [105].

7.1.2. Monoamine oxidase inhibitors (MAOi)

7.1.2.1. Rasagiline. In a sub-study of the ADAGIO trial [88], the effects over fatigue of rasagiline 1 mg and 2 mg doses were compared with placebo using the PFS at baseline and at 72 weeks follow-up in early PD patients. Greater progression on severity of fatigue from baseline to follow-up was seen in the placebo group compared with the treatment arm ($p < 0.01$ for rasagiline 1 mg and $p < 0.001$ for 2 mg). This trial showed that rasagiline effectively slowed the progression of fatigue in early PD patients compared to placebo at follow-up, but it is important to notice that fatigue was not the main outcome. Later, Lim et al. compared rasagiline 1 mg with placebo at 12 weeks follow-up in 30 PD patients using the MFIS, with significant improvement in average MFIS scores for rasagiline compared to placebo groups [132].

7.1.3. Antidepressant medication

7.1.3.1. Doxepin. Doxepin, a tricyclic antidepressant with histaminergic antagonistic action, has been used successfully as treatment for insomnia in elderly patients. Ríos Romenets et al. conducted a randomized pilot study comparing non-pharmacologic treatment or doxepin (10 mg daily) versus placebo in a cohort of 18 PD patients who suffered from insomnia and as a secondary outcome, severity of fatigue was measured. The results showed that doxepin improved fatigue severity (FSS) compared with placebo and insomnia severity as well ($p < 0.03$) [133]. Although the results were positive, the number of participants was small and with a short follow up, for which larger studies focus on the effect of doxepin over fatigue are necessary.

7.1.3.2. Selective serotonin re-uptake inhibitors (SSRIs). Evidence for use of antidepressants to treat apathy in PD has been conflicting. In several studies, SSRIs have been reported to increase apathy in PD [134–136]. There are few quality studies that clarify the efficacy or differential indications of antidepressants in PD which prevents the existence of clear recommendations.

7.1.3.3. Bupropion. The noradrenaline–dopamine reuptake inhibitor bupropion increases the concentration of both neurotransmitters by having a weak and relatively selective effect on their pre-synaptic re-uptake [137,138]. It has been reported to improve motivation scores in patients with apathy syndrome, though not specifically in PD [139]. One Spanish review for antidepressants in PD concluded that Bupropion was likely useful for apathy in this population but acknowledged that evidence is at best Class IV (consensus or expert opinion only) with limited evidence to make firm recommendations [140].

7.1.3.4. Milnacipran. The selective serotonin and noradrenaline reuptake inhibitor (SNRI), Milnacipran, initially administered twice daily at 30 mg/day until subsequent adjustments as appropriate up to 60 mg/day from the second week over 12 weeks, improved apathy (reflected by AES) in an open-label trial among 8 PD patients with minimal side effects [141].

7.1.4. Psychostimulants

7.1.4.1. Modafinil. Although modafinil is often used as a treatment for excessive daytime sleepiness (EDS), there have been several studies looking into the effectiveness of this medication on fatigue in PD. Ondo et al. found no significant effect of modafinil on fatigue reported outcomes [142]. However, in other study with a smaller cohort of PD patients ($n = 19$), it was shown that modafinil was associated

with an improvement of physical fatigue compared with placebo, but there was no effect on mental fatigue [143,144]. It is not clear how modafinil improves fatigue, but in animal models, it seems to increase dopamine release in the nucleus accumbens by local GABAergic mechanisms and increases extracellular dopamine concentration in the prefrontal cortex [144].

7.1.4.2. Methylphenidate. Mendonça et al. performed a randomized, double-blind, placebo-controlled trial of methylphenidate in 36 PD patients, who received either methylphenidate (10 mg three times daily) or placebo for 6 weeks, using FSS and MFI total score to assess fatigue. At follow-up, no statistically significant differences were found between methylphenidate and placebo over fatigue in any score [86]. As such, the use of methylphenidate in relation to fatigue will require further analysis most with a larger cohort of patients. On other hand, methylphenidate (5 mg per day) was found to be beneficial for apathy in a case report [145] and in a small group of 7 patients treated with high doses of methylphenidate (1 mg/kg) for 90 days after STN DBS [146]. However, the assessment of apathy was a secondary outcome in the latter study.

7.1.4.3. Caffeine. Postuma et al. conducted a randomized controlled trial evaluating the effects of caffeine on motor and NMS with 61 PD patients, split between caffeine and a placebo arm. The patients receiving caffeine showed improvements in motor symptoms measured with UPDRS III but did not show improvements in fatigue impact on ADL nor fatigue severity, depression, and sleep disturbances [147].

7.1.5. Rivastigmine

In a double-blind placebo-controlled study of 31 PD patients who have moderate to severe apathy (evaluated with the LARS) but without dementia or depression, transdermal cholinesterase inhibitor rivastigmine (9.5 mg/day) was shown to significantly improve apathy after 6 months [51,148].

7.1.6. Antiglutamatergic drugs

7.1.6.1. Memantine. Memantine has been used for other NPS in PD, such as depression and anxiety, with modest benefit [149]. Ondo et al. carried out a single-center, double-blind, placebo-controlled pilot trial of memantine in 34 PD patients. Despite memantine titrated to 20 mg/day it was well tolerated, with fatigue severity and influence over ADL found not to be different compared with placebo after an 8 weeks follow-up [150].

7.1.6.2. Amantadine. Amantadine was found beneficial to ameliorate fatigue in other neurological conditions, such as multiple sclerosis [151]. Later, Rodriguez-Moran et al. described that the proportion of PD patients suffering fatigue measured with D-FIS, MFI, and VAFS was significantly lower in those who were on amantadine combined with dopaminergic therapy compared to other therapies [152]. As this favorable result was a secondary outcome, further trials focusing on the effects of amantadine on fatigue in PD are needed.

7.1.7. Advanced therapies

7.1.7.1. Apomorphine. The impact of chronic subcutaneous apomorphine infusion (Apo) was analyzed by Martinez Martin et al. in 2011 in a multicenter trial across Europe, showing a positive effect on fatigue and apathy in 17 PD later-stage patients measured with NMSS from baseline to 6 months of follow-up [153]. More recently, a larger cohort of patients were analyzed in EuroInf, a multicenter study comparing apomorphine and intrajejunal levodopa infusion (IJLI), resulting in better outcomes on fatigue for IJLI rather than Apo and more significant improvement on apathy for Apomorphine compared with IJLI [154]. The subsequent EuroInf 2 study, which compared deep brain stimulation, apomorphine, and levodopa infusion, did not find significant improvement in fatigue scores in PD patients in the apomorphine group compared with IJLI and DBS; however, fatigue and apathy were not analyzed independently, but only within their NMSS domains [155].

7.1.7.2. Intrajejunal levodopa infusion. Statistically significant improvement of fatigue scores from baseline to 6 months follow-up was described in a pilot multi-center study of intrajejunal levodopa infusion (IJLI); nevertheless, no correlation of improvement in fatigue item and QoL was found [156]. Consistent with earlier studies, GLORIA, EuroInf, and EuroInf 2 affirmed the benefits of IJLI on fatigue and apathy through longer follow-ups [154,155,157].

7.2. Non-pharmacological treatment

7.2.1. Bilateral subthalamic deep brain stimulation (STN DBS)

Largely used as an efficient treatment option for motor symptoms in PD, the benefits of DBS in ameliorating the burden of NMS in PD patients, specially fatigue, have recently been explored. Chou et al. described a cohort of 17 patients, who underwent bilateral STN DBS, completing the PFS and the Epworth Sleepiness Scale (ESS) before and 6 months post-surgery. No significant changes were observed in the severity of fatigue after bilateral DBS STN and ESS. However, the number of participants was small, and they were not selected based on fatigue but on motor symptoms [158]. Later, Dafsari et al. and the EuroInf 2 study described the effects of bilateral STN DBS on NMS in PD showing a strong benefit on fatigue at follow-up compared to baseline, with significant improvement in QoL [155,159].

Evidence pertaining to the impact of STN DBS on apathy in PD has been scanty and inconsistent. Pre-clinical studies in rodents have found chronic STN DBS to have profound and complex effects on behavioral motivation [160], reminiscent of apathy, which may contribute to the development of some apathetic symptoms independent of dopaminergic neurodegenerative processes or reduction in dopamine replacement therapy [161]. A 2006 study compared a series of 15 PD patients with a control group and concluded that poststimulation apathy (AES) results directly from STN DBS [106]. In 2009, the same group demonstrated that apathy could be induced by STN DBS in PD and not merely an effect of decreased levodopa post-DBS, with postoperative cortical metabolic abnormalities seen on ^{18}FDG-PET [162]. However,

the findings of a recent parallel open-label study (EARLYSTIM) yielded no significant change in apathy scores (ASBPD and AS) during the 2 years following STN DBS [163]. The worsening of apathy in 25% of patients 6 years after STN DBS was also thought to likely indicate disease progression, rather than the direct influence of DBS [164].

7.2.2. Transcranial direct current stimulation (tDCS)

In tDCS, a weak electrical current is delivered through two scalp electrodes by a portable battery-powered stimulator, thus modulating intrinsic neuronal activity in a polarity-specific manner and effecting cortical excitability [165]. In one randomized double-blind parallel study, 23 patients with PD were included and randomized to either tDCS plus occupational therapy or sham tDCS plus occupational therapy. Both groups received eight sessions of 20 minute of true tDCS or sham for two consecutive weeks; daytime sleepiness and fatigue were evaluated with ESS and FSS. Although tDCS did not improve daytime sleepiness just after the end of the sessions, or even at 3 months follow-up, a modest positive effect on fatigue was observed in patients receiving true tDCS compared to those on sham just after the treatment, which was not sustained at 3 months [157,158]. In future, longer follow-ups are recommended in studies exploring the effects of tDCS.

7.2.3. Repetitive transcranial magnetic stimulation (rTMS)

In rTMS, short low-frequency (≤1 Hz), high-frequency trains, or varying bursts of stimulation (such as the theta burst stimulation (TBS)) are administered through a coiled wire placed on the scalp, resulting in a magnetic-induced electric field which modifies cortical plasticity, with consequent changes in neuronal activity [165]. There are no specific studies regarding the effect of rTMS on fatigue in PD, although in general, rTMS has been probed to have some benefits for motor symptoms in PD but not for NMS [158,166]. In one study, rTMS stimulation improves the score in the Stroop test, which reflects attention and executive function associated with the frontal lobe [167], and was found to be significantly correlated with the AS score in PD [168,169].

A 2013 double-blind, placebo-controlled cross-over RCT of bilateral M1 foot area stimulation (high-frequency real rTMS) performed for 3 consecutive days did not significantly improve AS scores (n = 10) compared to that of sham stimulation (sham-rTMS) (n = 11) [170]. Similar findings were found in the ReStore Study done by Fernandez and Bowers examining the effect of high-frequency rTMS stimulation over the left prefrontal area in 16 PD patients with apathy (compared to that of sham treatment in 8 patients) daily for 10 days over a 2-week period: significant improvements in apathy (assessed with the modified AES) in both groups which was maintained over 3 months, but with no between-group differences [171]. A Japanese study in 2014, however, showed that rTMS stimulation over the supplementary motor area for 15 PD patients significantly improved both apathy (AS) and depression as compared to those given placebo stimulation [172].

7.2.4. Vestibular stimulation

Recently it has been proposed that caloric vestibular stimulation (CVS) may increase functional neuronal connectivity through the activation of cortical and subcortical ascending pathways involved in PD symptoms. One study compared CVS with placebo, reporting significant improvement of NMS such fatigue, in the CVS arm after 8 weeks of twice-daily treatment, and this improvement persisted after the treatment. Interestingly, most benefits occurred at 5 weeks after cessation of CVS. Even though the benefits returned to baseline after 6-month follow-up, this seems to be a promising non-invasive therapy and further studies with longer time of treatment are warranted [173].

7.3. Other therapies

7.3.1. Massage therapy

Traditional Japanese massage, which uses common massage techniques such as kneading, rubbing, tapping, and shaking in specific points in the body, has been proven to produce favorable outcomes in NMS of PD, used frequently as a complementary therapy. In addition, periodic session of massages may improve NMS such as fatigue in PD patients, suggesting that the stretch reflex and the muscle spindles stimuli during massage are associated with relaxation, and this could play a role relieving symptoms like fatigue [174].

7.3.2. Acupuncture

Acupuncture has been used as complementary treatment for many other conditions such as multiple sclerosis and cancer, with significant improvement of fatigue. In PD patients, both alternatives of acupuncture, the traditional and the sham were probed to be efficient to ameliorate the fatigue burden, which can be result of a placebo effect [175,176].

7.3.3. Exercise

Exercise has been tested by Canning et al. (2012), showing a trend of improvement on fatigue in PD patients who tried treadmill sessions [177]. However, Winward et al. (2012) did not find any changes in fatigue at follow-up, although they used a different exercise protocol than the former [178].

7.3.4. Activity therapy

In 2016, Butterfield et al. tested the effectiveness of the Parkinson's Active Living (PAL) program, one of the first behavioral therapy essentially a telephone-based 6-week activity scheduling and monitoring treatment regime integrating external cueing, which is designed to specifically target apathy in PD. Reduction in apathy levels, as reflected by the AES, was highly significant from baseline to post-intervention, with a moderate positive impact on patients' self-rated QoL (PDQ39) [179].

7.3.5. Multi-sensory stimulation/snoezelen

The objective of Multi-Sensory Stimulation/Snoezelen is to maintain or improve wellbeing by providing positive stimulation of the five senses (visual, auditory, tactile, olfactory, and gustatory stimulation). This behavioral intervention has been demonstrated in two high-quality randomized controlled trials to be effective for apathy in elderly patients with dementia, but no studies specific to PD patients have been identified [180].

8. Summary and key messages

Both fatigue and apathy remain two of the commonest and most disabling, yet often under-appreciated and under-recognized, NMS in PD. The span of these two NMS is considerable, ranging from the premotor stage to advanced and palliative PD, with a clear negative impact on quality of life and caregiver burden. Their pathophysiology remains largely unclear but seems to be linked to diverse factors, such as deficits in the prefrontal-ACC circuits, degeneration of multiple neurotransmitter pathways, primarily dopaminergic and serotoninergic, abnormal activity and connectivity of limbic-cortical circuits, and elevated levels of inflammatory markers in the central nervous system. Several scales have been developed to correctly assess both symptoms, while only the FSS and the Apathy Scale are 'recommended', the PFS is probably the best one for evaluation of fatigue in PD, and the newly developed MDS-NMS allows assessment of both using the same tool. To date, no specific treatment for fatigue and apathy in PwP has been found, although there are some promising pharmacological interventions such as Rivastigmine and apomorphine infusion (for apathy); and doxepin, rasagiline, and IJLI (for fatigue), for which further studies are needed. In addition, brain stimulation, vestibular stimulation, and DBS-STN appear to have beneficial effects. A holistic approach for both symptoms is needed in order to have an optimal management.

9. Expert opinion

Fatigue and apathy remain at the forefront of challenging symptoms in PD, not only pertaining to diagnosis but also especially relevant in relation to treatment. Given the relevance of both fatigue and apathy to QoL and caregiver burden in PD, an emphasis should be put on proper methods in identifying and addressing them. Based on the current evidence the most appropriate identification methods for assessing fatigue and apathy are the PFS and the AS, respectively. However, given the nature of both symptoms, great care should always be taken when assessing patients as there is significant clustering of fatigue and apathy within different NMS in PD, and with each other.

Further complicating the situation is the lack of clearly effective treatment strategies for these two debilitating NPS. The treatment for apathy is largely hampered by the lack of use of appropriate outcome measures, exemplified by the often used NMSS where apathy is not separated from the other items in the mood/cognition domain (now improved in the MDS-NMS being signposted as a specific domain), and by failing to make apathy a primary outcome of clinical trials. The same, although to a lesser extent, can be said for fatigue. Yet in this latter symptom, better evidence is available for at least some treatments. For instance, some dopaminergic medications appear to improve fatigue. Curiously, however, most pathophysiological and observational studies have reasoned against a dopaminergic origin of fatigue. This apparent discrepancy can be explained by the mechanisms outlined below.

The cause of fatigue and apathy in PD is complex and despite many advances in recent years, both in animal models and in PwP, the exact pathophysiology remains unclear. The latter is likely partly caused by the lack of uniform definitions of both fatigue and apathy in PD. This also causes problems when interpreting the results of clinical trials and observational studies. The heterogeneity in symptom definition is further underpinned by the use of largely non-enriched PD cohorts, exemplified by the use of random cross-sectional selection of PD participants in clinical research, without selecting the relevant ones in whom fatigue and apathy are key problems and who are most likely to respond to treatment.

Efforts regarding this have already been made by introducing the concept of specific NMS-dominant phenotypes in PD, for tailored interventional drug trials [181]. This would not require the development of novel instruments for fatigue and apathy in PD as many of tools have already shown their validity and usefulness, but we feel an endeavor should be made toward enriched study cohorts within the core concept of personalized medicine [1,182]. To this end, Cummings and his team have also recently published recommendations on the framework of clinical trials on apathy [183].

An early and holistic palliative approach is also recommended in tackling both fatigue and apathy in PD, such as setting up the interdisciplinary clinic model for both PwP and caregivers [184]. Close liaison between the different disciplines in the care plan facilitates communication and provides additional support for Pw Pwith fatigue and apathy, particularly regarding the integration of palliative care [185].

In five years from now, we expect clinical trials will focus on these crucial NMS since their management remains an unmet need and use of better signposting of both features with validated scales will provide enriched cohorts to study new interventional products and non-pharmacological measures. Key partners in patient charities, industry-based initiatives as well as policymakers' needs to drive such trials, which may also include repurposing of existing medications thus avoiding the huge bench to bedside costs of developing new molecules. Signals providing beneficial effects on fatigue are already available from several dopaminergic and non-dopaminergic agents and funding to initiate and complete large-scale studies providing level 1 evidence for management of fatigue and apathy in PD should be a major research strategy and priority in the 2020s [1,8,30,44,48,182].

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Addendum to the above publication:

Scales for Apathy

The Non-Motor Symptom scale (NMSS) is a clinician-rated scale developed specifically to assess non-motor symptoms (NMS) in PD. Apathy is assessed by a single question (Item 11 of Domain 3 – Mood/Apathy). Validation data for this single item (van Wamelen, Martinez-Martin, et al., 2021) showed poor to questionable internal consistency ($\alpha = 0.56 – 0.65$) (Chaudhuri et al., 2007; Martinez-Martin et al., 2009; Wang et al., 2009) and good test-retest (r=0.70-0.82) reliability (Koh et al., 2012; Martinez-Martin et al., 2009; Wang et al., 2009) . It also has good convergent validity with the MDS-UPDRS Part I (Apathy) (rs=0.80) (Martinez-Martin, Chaudhuri, et al., 2015). While the NMSS is a rater-administered scale which has been widely validated and used worldwide in

different languages, it is based entirely on the healthcare professional administering it. The clinimetrics of this particular scale, which has been validated across Asia, Europe, South America, and Australia, reflects this in two independent papers published in 2007 (Chaudhuri et al., 2007) and 2009 (Martinez-Martin et al., 2009). Apathy rating by the patients sometimes can involve proxy answering by the carer/caregiver though this is not integral to the NMSS.

Table S1. Overview of classification system of rating scales on the basis of their properties, as used by the Movement Disorder Society (MDS) in the development of the Appendix of ancillary scales to complement the MDS-sponsored revision of the UPDRS (MDS-UPDRS)

Classification	**Criteria**			**Total number of required criteria**
	Used in PD	Used in PD studies beyond original study	Satisfactory clinimetric assessment	
Recommended	X	X	X	3
Suggested	X			2
Listed	X	0	0	1

X, required criterion; 0, criterion should not be met

<This is adapted from (Fernandez et al., 2008; Leentjens et al., 2008)>

Most authors (Clarke et al., 2011; Leentjens et al., 2008; Radakovic et al., 2015) mutually agreed that there must be universal consensus about the definition of apathy as a construct before a gold standard assessment tool can be developed.

The 14-item Starkstein's Apathy Scale (SAS), as stated above, has good face validity, internal consistency (a=0.92), interrater (r=0.81), and 1-week test-retest reliability (r=0.90), although the latter two features were established in a population of only 11 PD patients (Starkstein et al., 1992). Using an independent neurologist's clinical impression of apathy status as the "gold standard" (Starkstein et al., 1992), SAS had 66% (low) sensitivity and 100% (very high) specificity in differentiating apathetic vs non-apathetic individuals in a group of 50 PD patients. The SAS also had good discriminant validity against depression (Pedersen et al., 2012), although the

demonstrating study was of poor quality. It also showed a sensitivity to change in therapy studies amongst PD patients (Czernecki et al., 2002; Drapier et al., 2006; Funkiewiez et al., 2006), although this was not psychometrically assessed. In general however, the quality of the determining studies for the psychometrics of SAS was assessed to be poor in the 2015 review (Radakovic et al., 2015) using the quality assessment of diagnostic accuracy studies (QUADAS) checklist, mainly due the lack of rigor in its methodology reporting and selection bias.

The Lille Apathy Rating Scale (LARS), supported by a French validation study of good quality (Sockeel et al., 2006) demonstrating acceptable internal consistency (a=0.74 -0.80), very good interrater (r=0.98), as well as 4-month test-retest (r=0.95) reliability properties of its total score and showing good sensitivity to change in treatment studies, was subsequently proposed to be the better instrument compared to SAS in assessing apathy in PD (Radakovic et al., 2015; Sockeel et al., 2006). However, a later validation study of lesser quality (Zahodne et al., 2009), conducted in English amongst probable idiopathic PD patients, only showed good internal consistency (a=0.82). Another study (Weintraut et al., 2016) also showed questionable discriminant validity (potentially strong overlap with depression). However, consisting of 33 items divided into 9 domains, it is the longest amongst the apathy rating instruments (taking 20-25 minutes to administer) which may be demanding for frail patients. There is an informant-based version of LARS useful for assessing apathy amongst patients with PD dementia, demonstrating good internal consistency (a=0.87), very good interrater (r=0.996), as well as "several days" test-retest (r=0.96) reliability (Dujardin et al., 2008). In the context of the MDS criteria, the LARS would have been reclassified under 'Recommended' now compared to its 'Suggested' status in 2008.

Dopaminergic Therapy

This 2002 controlled cross-over trial evaluated the impact of dopaminergic therapy on motivation, by comparing twenty-three non-dementing PD patients without depression, in both *on* levodopa versus *off* levodopa states, to 28 controls, using the Starkstein's Apathy Scale (SAS). For both patients and controls, two assessments separated by 24 hours were done. Overall, the findings showed that apathy amongst PD patients improved with levodopa treatment. However, there was no mention of the power calculation done, which made the robustness of the results unclear.

The RECOVER (Randomized Evaluation of the 24-hour Coverage: Efficacy of Rotigotine) trial (Ray Chaudhuri et al., 2013; Trenkwalder, Kies, et al., 2011) was a prospective placebo-controlled study which explored treatment effects on non-motor symptoms in PD using the Non-Motor Symptoms Scale (NMSS) as an exploratory outcome. Subjects were randomized 2:1 to receive either transdermal rotigotine patches (titrated to optimal dose over 1–8 weeks, starting at 2 mg/24 h and increasing to a maximum of 16 mg/24 h; optimal dose then maintained during the 4-week maintenance phase, during which dose adjustments (and alteration of levodopa dose) were not permitted. *Post hoc* analyses (Ray Chaudhuri et al., 2013) suggested that transdermal rotigotine may have a positive effect on apathy ($r = 0.47$; [$p < 0.0001$]) in patients with PD, based on the statistically significant differences in the individual scores of the mood/apathy domain of the NMSS. Of note, the "mood/apathy" domain of the clinician-rated NMSS consists of 4 apathy items, 1 mood item, and 1 anxiety item. The summation score of the 4 apathy items from the NMSS were not assessed independently from the full "mood/apathy" domain in this study. As such, the combined 4 apathy items of the NMSS deserve further evaluation as a potential primary outcome measure for clinical trials of apathy.

1.3.2.7 Conclusions

Apathy remains one of the commonest and most disabling, yet often under-appreciated and under-recognized, NMS in PD. The span of this specific NMS is considerable, ranging from the premotor stage to advanced and palliative PD, with a clear negative impact on quality of life and caregiver burden. Its pathophysiology remains largely unclear but seems to be linked to diverse factors such as deficits in the prefrontal-ACC circuits, degeneration of overlapping neurotransmitter pathways primarily that of acetylcholine, dopamine, and serotonin; abnormal activity and connectivity of limbic-cortical circuits; and elevated levels of inflammatory markers in the central nervous system. Several scales have been developed to assess apathy, although only the 14-item Apathy Scale (SAS) is considered "recommended" under the MDS criteria (Table S1). The SAS is also likely my preferred choice in clinical practice due to its ease of use, high specificity, and low overlap with depression, although I may conduct a more comprehensive better-quality validation study in future to further support its utility. However, amongst PD patients with neurocognitive impairment, I would prefer to use LARS (informant-based version) instead. The newly developed MDS-NMS allows assessment of apathy as well, along with other NMS, but is yet too new for any validation studies of its subscales to have been completed, thereby preventing a firm recommendation of its utility in this regard.

Chapter 2

Neuropsychiatric Fluctuations in Parkinson's Disease

2.1 Introduction

As much a non-motor disorder as a motor disorder, Parkinson's disease (PD) presents with a complex range of non-motor symptoms (NMS) from prodromal until the final palliative stage (Chaudhuri & Odin, 2010; Titova, Qamar, & Chaudhuri, 2017) . Varying degrees of neurodegeneration affecting different nuclei promote non-motor endophenotypes of PD, adding to the heterogeneity of PD (Chaudhuri & Odin, 2010; Titova, Qamar, & Chaudhuri, 2017).

Despite the major advances in our current understanding of PD since the "shaking palsy" described by James Parkinson 2 centuries ago, L-dopa, which had been in clinical use since the 1960s, remains the gold standard of treatment (Ray Chaudhuri et al., 2018). Nevertheless, the use of chronic oral L-dopa in PD is associated with evolution of motor and nonmotor complications, such as drug-induced dyskinesias in many patients after more than 5 years of exposure, with up to 30% developing these within the first 2 years (Aquino & Fox, 2015; Fahn et al., 2004; Stocchi et al., 2014). Motor fluctuations (MF)are usually characterized by several patterns of motor OFF periods, with a majority coinciding with non-motor fluctuations (NMFs), first described by Hillen and Sage in 1996 (Hillen & Sage, 1996). NMFs have also shown a circannual fluctuation, with the impact seen largest in cardiovascular, sleep, and hallucinations domains (van Wamelen et al., 2019).

Convergent evidence (Bayulkem & Lopez, 2010; Riley & Lang, 1993) demonstrated that NMFs had been characterized into:

(i) Neuropsychiatric (including psychotic symptoms, hypomania/mania, depression, apathy, visual hallucinations, confusion, fatigue),

(ii) Autonomic (including sweating, facial flushing, abdominal bloating discomfort, urinary frequency and urgency, dyspnoea, blood pressure changes peripheral oedema) and,

(iii) Sensory (including pain, internal tremor, akathisia, numb-ness, dysesthesia)

Certain NMF has been found to involve a greater degree of disability than MF themselves (LeWitt & Chaudhuri, 2020; Storch et al., 2013). The clinical spectrum and the frequency of these symptoms are often underestimated as changes in NMS are not always time-locked to those of motor manifestations (Rascol et al., 2005; Raudino, 2001; Richard et al., 2001). NMFs do not always correlate with motor function (Chaudhuri et al., 2005; Richard et al., 2001; Storch et al., 2015), despite the close link established between dopaminergic therapy intake and improvement in NMFs (Chaudhuri & Schapira, 2009; Honig et al., 2009; Stacy et al., 2010).

Poor recognition complicating the subsequent management of NMF has increasingly been acknowledged as a key unmet need and a major determinant of health-related quality of life (QoL) in people with Parkinson's disease (PwP) (LeWitt & Chaudhuri, 2020). As such, the objective of this review is to assess the existing literature pertinent to neuropsychiatric fluctuations of Parkinson's disease and highlight an important area to which little attention has been applied previously.

2.2 Contributions and Collaborations

I wrote the entire sections on the fluctuations of PD psychosis, PD Anxiety, PD Apathy, PD depression, PD fatigue, as well as PD cognition. I also contributed the two summarizing tables. My colleague (YHL) helped with the literature search and contributed to the sections on pathophysiology as well as methodology, as well as provided input about the conclusions drawn at the end.

2.3 Methods

My colleague (YHL) and I helped to search in four major databases (PubMed, SCOPUS, EMBASE, PsycINFO) with the relevant controlled terminology specific to the database (e.g. Medical Subject Headings in PubMed) through to 2 February 2022. The search strategy included the search terms "Parkinson disease", "hallucinations", "delusions", "psychotic disorder", "apathy", "fatigue", "anxiety", "depression", "cognition", "non-motor symptoms", "neuropsychiatric", "fluctuat*", "evolution", "evolv*", "trajectory", combined using appropriate Boolean operators. Further sources of information were obtained by a manual search of the reference lists of previously identified articles, as well as selected reviews.

Included articles were reviews and original research studies published in English, inclusive of human studies diagnosed with PD according to the Movement Disorder Society (Postuma et al., 2015) or UK Parkinson's Disease Society Brain Bank Diagnostic Criteria (Hughes et al., 1992). Studies that reported on neuropsychiatric fluctuations in PD, specifically regarding psychosis, anxiety, depression, apathy, fatigue, and cognition, were retrieved and read in full.

2.4 Clinical spectrum

Prevalence of NMF in PwP who suffered from MF varies from 17% to 100%, with neuropsychiatric fluctuations being the most common and disabling (Brun et al., 2014; Gunal et al., 2002; Hillen & Sage, 1996; Picillo et al., 2016; Seki et al., 2013; Storch et al., 2013; Witjas et al., 2002), with one study reporting poor correlations with motor function (Bayulkem & Lopez, 2010). The wide prevalence range reported was likely due to heterogenous study design and methodology, in what remains an underfunded area, fraught by logistic and physician-led barriers (Hurt et al., 2019a, 2019b).

One recent prospective, multicenter, cross-sectional study which assessed motor OFF and ON states via self-ratings at home in 100 fluctuating L-dopa treated PD patients (Storch et al., 2013), utilising a modified version of the Non-Motor Symptom (PD-NMS) scale, showed that NMF was present in all, with each (100%) suffering at least two NMS. Most NMS occurred during L-dopa-induced motor ON and worsened during OFF states; some however, such as concentration difficulties, fatigue, depression, and anxiety, were noted during OFF periods only (Riley & Lang, 1993). Anxiety and depression showed a particularly intense interdependence to motor OFF symptoms since both were related to postural instability and freezing of gait. The timing of mood fluctuations has been shown to be comparable to MFs in terms of onset. In general, however, psychiatric OFF periods had a considerably longer duration (median: 3-4 hours) compared to that of motor OFF periods (median: 2 hours)(Ossig et al., 2017).

Throughout the course of PD, certain NMS increase in frequency whereas others decrease, differing from the more linear progression of motor features (Antonini et al., 2011; Titova & Chaudhuri, 2018). It has been shown that NMS that improve were those already responding to dopaminergic therapy, suggesting that optimizing dopaminergic therapy improves a range of NMS as well as NMF (Titova & Chaudhuri, 2018; Titova, Padmakumar, et al., 2017). However, as dopamine depletion worsens with disease progression, physiological stimulation with pharmacotherapy will become more challenging, resulting in increase in the severity and frequency of NMF, similar to that of MFs (Jellinger, 2012b). The risk of developing NMF includes females, early-onset PD, longer disease duration, and patients who received higher doses of L-dopa (Calabresi et al., 2010; Olanow et al., 2006; Stacy et al., 2010). More recently, a study found a strong temporal correlation between the motor OFF condition and the OFF neuropsychiatric condition, presenting with more severe anxiety, depression, apathy, and impaired concentration (Del Prete et al., 2022). In general, the frequency and severity of both MFs and NMFs increase with PD progression.

L-dopa-induced NMF also involves the wearing-off phenomenon that occurs late at night or early morning, recognized as the EMO period (Hillen & Sage, 1996; Picillo et al., 2016; Storch et al., 2013).Apart from the wearing- off phenomenon, NMS such as anxiety, pain, and fatigue can complicate dyskinesias, especially during peak dose and diphasic dyskinesias (Storch et al., 2013). Apathy or panic attacks can be disabling aspects of severe NMFs, and these symptoms sometimes overshadow the motor OFF period(Riley & Lang, 1993).NMS occurrence is much more frequent in motor OFF than ON, though certain NMFs can present even in the absence of MFs (Chaudhuri et al., 2005; Picillo et al., 2016; Riley & Lang, 1993).

2.5 Pathophysiology

Despite the expansive elucidation and advances in the understanding of MF patho-mechanisms, NMFs in PD remain poorly characterized and understood. MF development has been associated with the effect of pulsatile non-physiological dopaminergic stimulation combined with the natural progression of PD, with current evidence supporting an interplay of pre- and postsynaptic events(Calabresi et al., 2010; Chase et al., 1989; Cilia et al., 2014; Olanow et al., 2006).

The most important presynaptic factor is non-continuous delivery of L-dopa to the brain because of intermittent oral dosing. Progressive dopaminergic denervation of nigrostriatal terminals with advancing PD leads to reduced presynaptic dopamine storage capacity, such that fluctuations in L-dopa plasma levels increasingly erratic, translating into oscillations of synaptic DA and result in pulsatile activation of postsynaptic DA receptors (Olanow et al., 2006; Ray Chaudhuri et al., 2018). Striatal output activity becomes altered by supersensitivity of DA receptors in parallel with structural and molecular changes, leading to altered signal processing in striatal neurons. Serotonergic maladaptive plasticity with sprouting of striatal serotonin terminals with ectopic dopamine release, as well as excessive glutamatergic activity in corticostriatal and

subthalamopallidal projections, contribute to altered activity patterns in basal ganglia thalamocortical networks (Ray Chaudhuri et al., 2018). Ultimately, the combination of disease progression or pathology and pharmacokinetic and pharmacodynamic mechanisms lead to motor complications (Martinez-Fernandez et al., 2016).

As mentioned earlier, NMFs do not always synchronise to those of MFs nor correlate consistently with motor function. This finding suggests the possibility of different pathophysiological mechanisms in the emergence of MF and NMF. On the other hand, dopaminergic therapy intake leads to substantial improvement in fluctuating NMS, such as apathy or pain (Cantello et al., 1986; Chaudhuri & Schapira, 2009).

The heterogeneity of Parkinson's is also underpinned by a complex pathophysiology which ranges from misfolding of alpha-synuclein to amyloid and tau protein deposition, neuroinflammation, mitochondrial dysfunction, genetic and epigenetic factors, as well as the brainstem origin of the condition (Titova & Chaudhuri, 2018; Titova, Padmakumar, et al., 2017).The clinical phenotypic variations, therefore, represent the consequence of widespread brain and peripheral Lewy body pathology and not only a single neuronal structure, such as the substantia nigra or isolated loss of the dopamine neurotransmitter system(Jellinger, 2012b; Todorova et al., 2014). The neurotransmitter systems affected are widespread and the convergent in the dopaminergic, cholinergic, noradrenergic, and serotonergic pathways amongst others (Titova, Padmakumar, et al., 2017). Degeneration of these neurotransmitter systems results in complicated interactions between both the dopaminergic and nondopaminergic deficits that ultimately underlie NMF(Martinez-Fernandez et al., 2016).

2.5.1 PD Psychosis Fluctuations

Emergent literature over the past decade has depicted the chronological and clinical cascade of psychosis in Parkinson's disease (PDP) to be distinct from that of other psychotic

disorders such as schizophrenia or substance-induced psychosis (Ffytche et al., 2017; Ravina et al., 2007). Despite the rapidly developing evidence, the kinetics of PDP fluctuation have been little addressed.

Current evidence revealed minor hallucinations, or more specifically *presence* hallucinations, are the most prevalent of PDP (Fenelon & Alves, 2010), affecting 40% of PD patients, and can be elicited even in the *de novo* untreated phase of PD. Isolated *passage* or *presence* hallucinations were reported to occur more than once a month but less than once a week; if concurrent, occurrence would then be more than once a week (Pagonabarraga et al., 2015; Papapetropoulos et al., 2008).

Of the major hallucinations, visual hallucinations are the commonest, typically well-circumscribed and likely modulated by past experiences (Ffytche et al., 2017; Molho & Factor, 2013). These are sudden in onset, recurring in nature, often occurring several times in a day (Barnes & David, 2001; Ravina et al., 2007), and frequently experienced five or less times in a week (Barnes & David, 2001; Ravina et al., 2007). Hallucinations usually vary with motor fluctuations (Riley & Lang, 1993), and will often disappear when confronted.

In general, hallucinations are fleeting in duration, lasting seconds to minutes, although few would last up to hours (Barnes & David, 2001; Papapetropoulos et al., 2008). Longer spells may occur in the morning or evening, often in surroundings of low ambient stimulation (Barnes & David, 2001; Factor et al., 2017; Ravina et al., 2007). Classically associated with the motor ON state, hallucinations can also occur in the motor OFF state (Riley & Lang, 1993; Storch et al., 2015; Witjas et al., 2002), particularly in patients with PD dementia (Storch et al., 2015). Hallucinations may also be associated with the light cycle (Papapetropoulos et al., 2008), although evidence on this has been conflicting (Ravina et al., 2007). Van Wamelen et. al has also demonstrated that seasonal variations in hallucinations exist, with higher scores in the Non-

Motor Symptom Scale (NMSS) during the winter months compared to the summer months (van Wamelen et al., 2019).

Hallucinations of other modalities rarely arise in isolation (Goetz et al., 2011; Goetz et al., 2005; Solla et al., 2021), often occurring with visual hallucinations in later stages of the disease. More severe hallucinations coincided with cognitive fluctuators amongst PwPs with dementia (PDD) (Varanese et al., 2010). Consensus remains that PD hallucinations are related to a particular disease endophenotype, rather than to a real perceptual oscillation (Pagonabarraga et al., 2015).

Delusions have been associated more with the PD motor OFF state (Nissenbaum et al., 1987) can also be more persistent across both motor ON and OFF states (Storch et al., 2015). Reports of delusions are mostly in case studies (McNamara & Durso, 1991; Solla et al., 2015). Nihilistic delusions such as Cotard syndrome (Solla et al., 2015) has been reported as sudden in onset, and markedly improved with administration of levodopa dose, along with amelioration of end-of-dose dyskinesias and akathisia. This was successfully treated by shortening the intervals between levodopa doses.

2.5.2 PD Anxiety Fluctuations

PD anxiety accounts for 42% of an adverse impact on QoL independent of motor fluctuations (Quelhas & Costa, 2009; Storch et al., 2013). Described as often occurring years before the onset of motor symptoms, oft-diagnosed anxiety disorders in PD are generalized anxiety disorder (GAD), social phobia, and anxiety disorder not otherwise specified (NOS)(Broen et al., 2016).

Evidence of the relationship between plasma L-dopa levels and anxiety has been heterogenous. More of those with motor fluctuations suffer from GAD that those without. Recurrent PD anxiety disorder NOS are frequently associated with motor fluctuations from end-

of-dose "wearing-off" period (Erdal, 2001; Pontone et al., 2009), well as mood fluctuations (Erdal, 2001; Richard et al., 2001). This, along with the precipitation of anxiety by dopamine withdrawal, suggests the involvement of shared integral pathophysiological processes, rather than merely a psychological response to the variability in the motor symptoms.

Associated with an early age of PD onset(Brown et al., 2011; Dissanayaka et al., 2010; Leentjens et al., 2011; Vazquez et al., 1993) and the postural instability gait impairment PD subtype (Dissanayaka et al., 2010; Khoo et al., 2013), PD anxiety has been reported to affect women more (Picillo et al., 2016), and occurred more frequently during motor OFF states (Fauser et al., 2015; Maricle, Nutt, & Carter, 1995; Storch et al., 2013; Witjas et al., 2002), typically in the early morning (Ossig et al., 2016; Rizos et al., 2014). Symptoms last a median length of 3-4 hours(Ossig et al., 2017), longer than that for motor OFF periods. Although often associated with comorbid fluctuating depression, PD anxiety can exist independently (Richard et al., 2004) and has been said to occur one hour before the onset of the dyskinetic ON state (Ossig et al., 2017), suggesting a high degree of unpredictability. Fauser et. al's study noted that PD anxiety was prevalent among the "unstable fluctuators" with a high intraindividual variability in symptom severity and frequency, particularly within the motor OFF state (Fauser et al., 2015).

Panic attacks occur in about 60% of PD (Seki et al., 2013), almost exclusive to the motor OFF periods (Ossig et al., 2017; Vazquez et al., 1993), with sufferers usually needing higher doses of levodopa treatment (Eriksson et al., 1984; Raudino, 2001; Seki et al., 2013). PD panic attacks are described to start with marked malaise, along with an ascending burning peripheral paraesthesiae, associated with an overwhelming fear, progressing to motor freezing and aggravated tremor, autonomic symptoms such as sweating or flushing, palpitations, choking sensation, difficulty breathing, and a urinary urgency.

Panic episodes are ameliorated by intake of a new dose of levodopa, although the effect is not always consistent (Maricle, Nutt, & Carter, 1995; Ossig et al., 2017; Siemers et al., 1993). Relief

by levodopa, even when it occurs, appears to be transient, with possible significant rebound anxiety after about 2 hours from intake. The extent of change in anxiety did not coincide with that of motor change, implying an underlying distinct isolated process (Erdal, 2001; Maricle, Nutt, & Carter, 1995; Vazquez et al., 1993).

2.5.3 PD Apathy Fluctuations

Apathy is another key neuropsychiatric symptom with a tangible negative impact on QoL in PD (Barone et al., 2009; Benito-Leon et al., 2012; Oguru et al., 2010). Dujardin et. al 2007 demonstrated that 30% of the fluctuating PD group suffered from moderate-to-severe clinical apathy (Lille Apathy Rating Scale (LARS) ≥ -16)(Dujardin et al., 2007), indicating a significant lack of action initiation compared to the stable PD group, as well as markedly lower emotional responses than healthy controls. In general, there is an increased prevalence of apathy over time amongst PD patients, although curiously there is an impersistent pattern in its trajectory noted, with less than half experiencing persistent apathy after 4 years (Ou et al., 2020). Once again, evidence of association with motor fluctuations were not always consistent, although a recent study utilizing the Parkinson's Kinetigraph (PKG) along with the Neuropsychiatric Fluctuations Scale (NFS), demonstrated a strong temporal association between motor OFF and apathy in 18 PwPs (Del Prete et al., 2022). All this overall suggests the unpredictability of the kinetics of apathy in PD.

2.5.4 PD Depression Fluctuations

PD-specific pathology related to the mesocorticolimbic dopaminergic projection plays a crucial role for the pathophysiology of depression in PD (Poewe, 2008; Titova & Chaudhuri, 2018). Depression in PD have been associated with dopaminergic loss in the anterior striatum which has been hypothesized due to the degeneration of dopaminergic projections from the ventral

tegmental area(Rodriguez-Blazquez et al., 2021; Vriend et al., 2014). Reduced cortical cholinergic activity has also been suggested to correlate inversely with depression (Bohnen et al., 2007). Other neurotransmitter deficiencies affecting mesocortical norepinephrinergic and serotonergic projections, such as cortico-limbic norepinephrinergic denervation through cell loss in the locus coeruleus and serotonergic denervation via serotonergic cell loss in the raphe nucleus, also resulted in depressive features (Jellinger, 2012b; Titova & Chaudhuri, 2018).

At higher dopaminergic stimulation, neuropsychiatric ON symptoms such as impulsivity will develop and when stronger dopaminergic stimulation occurs; neuropsychiatric ON symptoms will be exacerbated, resulting in aggression and confusion(Martinez-Fernandez et al., 2016; Martinez-Martin, Reddy, et al., 2015). This dopamine stimulation hypothesis is supported by correlations for some neuropsychiatric NMF including depression (Ossig et al., 2016; Witjas et al., 2002).

Mood fluctuations occur in about 7%-72% of the PD population (van der Velden et al., 2018), and were more prevalent in PwPs with younger age of disease onset (Racette et al., 2002) . There was a strong association with MFs, as well as with psychosis, dementia, and non-fluctuating clinical depression (Racette et al., 2002).

Depression moodswings frequently respond with treatment of MFs, but correlation of symptom severity may be poor (Classen et al., 2017). Depression has been stated to occur one hour before the onset of the dyskinetic ON state, like that of anxiety (Ossig et al., 2017). An old case report characterised daily crying spells in parallel with bouts of depression lasting 30-45 minutes, which resolved once dopaminergic medication doses were increased (Riley & Lang, 1993). A recent meta-analysis reported that on average, 34.9% of PwPs with MFs also frequently have fluctuations in depression, and that the rate of depressive fluctuations was higher than those reported in PwPs without MFs (van der Velden et al., 2018). This temporal relationship is, however, inconsistent across literature, with 12%-18.2% of depression fluctuating either only in

motor ON states or independent of MFs entirely (Pontone et al., 2011; Storch et al., 2013; Witjas et al., 2002)

2.5.5 PD Fatigue Fluctuations

Often the most distressing neuropsychiatric symptom reported in fluctuating PD with adverse impact on QoL (Barone et al., 2009), fatigue has been reported in early PD(Storch et al., 2013) and prevalent in up to 60% of patients(Witjas et al., 2002). PD fatigue is largely associated with OFF states (Barone et al., 2009; Lazcano-Ocampo et al., 2020; Witjas et al., 2002), although some may beg to differ(Ossig et al., 2016, 2017). In terms of circadian profiles, fatigue tends to peak in the evening (Ossig et al., 2016) but otherwise showed relatively stable frequencies over the 24-hour period.

Like PD anxiety, there is an increased unpredictability in terms of PD fatigue frequency and severity across both motor ON and motor OFF states, but particularly in the latter (Fauser et al., 2015; Storch et al., 2013). PD fatigue was the main neuropsychiatric symptom reported to be most frequently oscillating in tandem with motor fluctuations (Ossig et al., 2016), although concordance rate was low. Storch et. al. 2013 (Storch et al., 2013) has also reported that QoL was worse in patients suffering PD fatigue only in motor ON state, compared to those across both motor ON and OFF states; although there were discrepant accounts of this in literature, some citing no effect of motor state on the nexus between PD fatigue and decreased QoL(Gallagher et al., 2010).

2.5.6 PD Cognitive Fluctuations

Early cognitive presentations such as subjective cognitive decline (SCD) or mild cognitive impairment (MCI) can occur prior to or at the time of Parkinson disease (PD) diagnosis, or even later in the disease course, with varying rate of progression. A recent study has shown that PwPs

with MCI (PD-MCI) may revert to normal cognition and then develop cognitive impairment later, which is typically in line with motor progression and the occurrence of other NMS (Aarsland et al., 2021).

Cognition in patients with advanced PD have been linked with degenerative extrastriatal dopamine D2 and D3 receptor function in thalamus, anterior cingulate, dorsolateral prefrontal and temporal cortex (Brooks & Pavese, 2011). The initial stages of cognitive decline in patients with PD were closely related to gray matter atrophy in left hippocampus and thalamus, which serve as potential imaging biomarkers for PD-mild cognitive impairment, whereas PD with dementia is associated with selective disruption of corticostriatal connectivity (Chen et al., 2016). Disruption of network including medial prefrontal, anterior cingulate and posterior cingulate cortex, the precuneus, and the inferior parietal lobe may play a key role in executive dysfunction in PD(Gao & Wu, 2016). In terms of cognitive fluctuation, the presenting features include slowness of thinking, difficulty in memorizing, mental emptiness, or mental hyperactivity(Witjas et al., 2002). Cognitive fluctuations respond in a rather complex manner to dopaminergic stimulation, where attention deficits improve, but executive functions deteriorate (Nieoullon, 2002). The more stable the levodopa availability, the less cognitive fluctuations emerge, assuming that the underlying mechanisms are eventually regulated by dopamine(Cools, 2006).

Concentration and attention fluctuations are more frequently reported with increased severity in motor OFF state (Chaudhuri et al., 2005; Delis et al., 1982; Storch et al., 2015; Witjas et al., 2002). Cognitive fluctuators within the cohort of PwPs with dementia (PDD) exhibited a similar cognitive and behavioural profile to patients suffering from dementia with Lewy bodies (DLB) (Varanese et al., 2010). However, PDD cognitive fluctuators demonstrated significantly slower simple reaction times, vigilance accuracy, and choice reaction times than non-fluctuators, but were overall better if compared to patients with Alzheimer's disease (AD), except in cognitive reaction time (Ballard et al., 2002; Varanese et al., 2010). Frontal impairment in PDD fluctuators

was also more pronounced than that in non-fluctuators (Varanese et al., 2010). The level of disability from cognitive fluctuations was found to be correlated with slowness of thinking, with 58% oscillating during the motor OFF state (Witjas et al., 2002), although no relationship was found between NMFs and PD severity or duration.

2.6 Assessments

Assessment and quantification of neuropsychiatric NMF is challenging due to the variable manifestations. As PwP may develop NMFs preceding or after experiencing MFs, isolated NMF can be difficult to identify, with high potential for misdiagnosis(Storch et al., 2013). For instance, severe anxiety-related states could be misdiagnosed as dopamine dysregulation syndrome (DDS) in relation to excessive L-dopa intake and dyskinesias(Storch et al., 2013). Neurobehavioural syndromes with varying severities, such as impulse control disorders (ICDs) and DDS, which are intrinsically related to L-dopa intake, can be falsely mislabelled as NMFs (Storch et al., 2013). Complicating the NMF profile, a recently described phenomenon termed "metacognitions", where MFs can induce anticipatory "thinking," which, in turn, can worsen the severity of the fluctuations and increase OFF period distress (Ray Chaudhuri et al., 2018).

One option is the Wearing-Off Questionnaire (WOQ), which was also recommended by The Movement Disorders Task Force; although it has been noted that this scale focus mainly on motor evaluation (Antonini et al., 2011). There is also the 20-item self-administered Neuropsychiatric Fluctuations Scale (Schmitt et al., 2018) available, but this mainly cater to drug-related NMFs and did not encompass the full range of neuropsychiatric symptoms; for instance, fluctuating PD psychosis was not assessed. The 27-item self-administered Non-Motor Fluctuation Assessment (NoMoFA) is also a valid and reliable questionnaire, capturing both static and fluctuating non-motor symptoms in PD (Kleiner et al., 2021).

The recent PD-NMS scale has been validated for NMF using selected items (Storch et al., 2015). It is the first comprehensive and global instrument that includes the assessment of the NMF. The MDS-NMS includes an 8-item Non-motor Fluctuation (NMF) Subscale, spanning the neuropsychiatric (depression, anxiety, thinking or cognition disabilities), autonomic (bladder symptoms, excessive sweating) and sensory (restlessness, pain and fatigue) features (Rodriguez-Blazquez et al., 2021). The first validation study of MDS-NMS noted that depression, apathy, psychosis, orthostatic hypotension, and urinary and gastrointestinal problems were significantly more prevalent in moderate-severe Hoehn and Yahr (HY) stages than in mild disease (Rodriguez-Blazquez et al., 2021).

The International Movement Disorder Society has also listed various rating scales for the assessment of NMS including the Non-Motor Symptom Questionnaire (NMS-Quest) and the Non-Motor Symptom Scale (NMSS). The NMS-Quest is a 30-item questionnaire designed as screening tool, with a specificity of approx. 89% for all NMS(International Parkinson and Movement Disorder Society). Diary reporting of NMS coupled with ambulatory-sensor–based monitors for objective measurement of motor fluctuations may potentially play a role to ascertain NMF in the future (Ray Chaudhuri et al., 2018).

2.7 Treatment

Overall, NMF can be directly or indirectly ascribed to dopaminergic dysfunction in PD. As NMS were often described in the PD motor OFF states, improvement in motor OFF will lead to improvement in both NMS and NMF. For this reason, the main approach to NMFs should mirror that of MFs, aiming at continuous, non-pulsatile dopaminergic stimulation which more closely resemble the natural steady state of the striatum (Witjas et al., 2007). Current available continuous non-oral pharmacological therapies in PD include the transdermal Rotigotine (RTG) or Rivastigmine patch, as well as infusion therapies such as Apomorphine

(APO) or Intrajejunal Levodopa (IJLI) (Chaudhuri et al., 2013; van Wamelen et al., 2018). To date, literature evaluating the response of NMF to specific therapies is lacking(Chaudhuri, Healy, et al., 2006; Seppi et al., 2019).

The first step in approaching NMF should be to exclude adverse effects of existing medications (Classen et al., 2017; Franke & Storch, 2017). NMFs in PD generally respond to dopaminergic therapeutic adjustments in the same way as MFs (Stacy et al., 2010). Improvement of MFs can provide an initial therapeutic template in improving NMF, even though there may not be a pathophysiological link between both. The correlation of symptom severity can also be unreliable(Classen et al., 2017).

The following step would be to introduce L-dopa dose fragmentation, use of long-acting L-dopa formulations or dopamine agonists, as well as initiation of dopamine-enhancing therapies such as catechol-O-methyltransferase or monoamine oxidase-B inhibitors(Hillen & Sage, 1996; Rascol et al., 2005; Smith et al., 2015). In a cross-over study of oral L-dopa challenge with L-dopa/carbidopa controlled-release formulation versus immediate-release formulation, only fluctuating patients showed elevation in mood with the immediate-release(Kulisevsky et al., 2007).

COMT inhibitors have been an established first-line strategy to manage motor fluctuations for over 25 years, and are the only adjunct class to directly address the peak-trough variations in plasma levodopa levels that clinically manifest as wearing-off fluctuations(Riederer et al., 2007). An open-label study that investigated the effectiveness and safety of third generation COMT inhibitors, opicapone, in PwP with MFs showed that opicapone also provided a positive effect in several NMS, particularly mood and cognition (Reichmann et al., 2020).

Safinamide, a novel drug with dopaminergic and glutamatergic mechanisms, improved not only motor complications in advanced PD but also ameliorated depression in a controlled clinical trial (Borgohain et al., 2014). Significant benefit was reflected in the Beck Depression

Inventory-II (BDI-II), the NMSS mood/apathy domain, and the Parkinson's Disease Questionnaire-39 (PDQ-9) emotional well-being scores at 6 months (Labandeira et al., 2021), which showed that Safinamide was well tolerated and improved overall NMS burden and QoL in PwP with severe or very severe NMS burden(Santos Garcia et al., 2021).

Several studies provided evidence that dopamine D3 agonists improved mood symptoms, particularly depression and apathy(Barone et al., 2010; Chaudhuri et al., 2013). Rotigotine offers a continuous drug delivery pattern, particularly compared with oral dopaminergic therapies, and has a good tolerability profile(Raeder et al., 2021).A post-hoc analysis of a double-blind trial of transdermal dopamine agonist rotigotine versus placebo in PwP with MF suggested an improvement in the NMSS domains of pain, "sleep/fatigue" and "mood/ apathy" (Kassubek et al., 2014; Ray Chaudhuri et al., 2013). Rotigotine could be considered as a treatment option, with a multimodal action in managing both motor dysfunction and depression, in relation to personalising treatment and avoiding the use of adjunct antidepressants in selected cases (Raeder et al., 2021).

Apomorphine infusion represents a minimally invasive and easily reversible treatment option, which now has high-level evidence for its efficacy and good safety profile, and should be considered in PwPs with uncontrollable MFs (Ossig et al., 2016). Despite the few studies, existing evidence showed that apomorphine has an overall beneficial effect on NMS of PwP, including neuropsychiatric symptoms, sleep disturbances, pain, urinary dysfunction, and impulse control disorders (Martinez-Martin, Reddy, et al., 2015; Rosa-Grilo et al., 2016).

Treatment with levodopa-carbidopa intestinal gel (LCIG) avoids the irregular absorption of oral L-dopa caused by impaired gastric emptying, by providing a more-stable L-dopa plasma concentration and resulting in continuous dopaminergic stimulation. Chaudhuri et al reported positive associations between NMSS baseline burden & improvement of especially sleep/fatigue and mood/ cognition in PwPs during treatment with LCIG (Ray Chaudhuri et al., 2019).

In a 2-year follow-up PD cohort, it was found that deep brain stimulation of the subthalamic nucleus (STN-DBS) significantly reduced the number and severity of autonomic and psychiatric NMF in the OFF state, whereas sensory NMF completely disappeared in the ON state (Ortega-Cubero et al., 2013). Witjas and colleagues found a 58% total reduction in NMF postsurgery using the NMF scale, noting a 30% decline in neuropsychiatric NMFs. In a recent randomized controlled Earlystim study, neuropsychiatric NMF improved after STN-DBS, whereas they tend to worsen in the best medical treatment group (Lhommee et al., 2018).

A recent real-life cohort compared the QoL, nonmotor and motor outcomes between PwP undergoing STN-DBS, IJLI, and APO respectively. Interestingly, the domain of sleep/ fatigue, mood/cognition, perceptual problems/hallucinations, urinary, sexual functions improved in patients who underwent STN-DBS, whereas the sleep/fatigue, mood/cognition, gastrointestinal domain were improved substantially for patients who had IJLI therapy. Improvement in mood/cognition, perceptual problems/hallucinations, attention/memory were obvious among patients who received APO therapy (Dafsari et al., 2019).

***Table* 2.1 Overview of the papers captured for each neuropsychiatric fluctuation**

Study	Type of study	Number of PD participants & duration of monitoring	Mean age (years) (SD or %)	Mean H&Y (SD or %)	Mean disease duration (years), (SD or %)	Cognitive assessment	Outcome measures	Results
PD Psychosis Fluctuation								
(Hardie et al., 1984)	Cross-sectional study	• 20 PD patients • Diaries recorded over 5 days	56.85 (6.23)	• 3.95(1.19)	• 11.9 (3.42)	Not assessed	• Self-scoring diaries Webster Disability Rating Scale	• 1 patient had low mood with delusions of guilt/unworthiness in PD motor OFF states. • 1 patient had paranoid delusions in PD motor OFF states.
(Nissenbaum et al., 1987)	Case series	• 9 PD motor fluctuators	51.4 (11.1)	• 4 (0.6)	• 11.2 (3.9)	Unclear	• Psychiatric mental state examination • Semi-structured interview on depression and anxiety • Tests on orientation, digit span, 10-word verbal learning test.	• Hallucinations and/or delusions can occur in the PD motor OFF state. Hallucinations more common amongst PD patients at night.
(Fernandez et al., 1992)	Cross-sectional study	• 30 PD hallucinators • 20 PD non-hallucinators	• 65 (8.8) (hallucinators) • 54 (11.5) (non-hallucinators)	• 3.6 (0.5) (hallucinators) • 3.2 (0.6) (non-hallucinators)	• 12.5 (5.7) (hallucinators) • 11.2 (4.9) (non-hallucinators)	MMSE (SD): • 23.9 (6.3) (hallucinators) • 29.2 (1.3) (non-hallucinators)	Personal interview from patients with help from caregivers and relatives.	37% hallucinators experienced mainly in the evening and at night. 8 patients' VH associated with "off" periods. No association with medication dose or duration.

(Haeske-Dewick, 1995)	Cross-sectional study	• 16 PD hallucinators • 20 PD non-hallucinators	• 72.1(7.34) (hallucinators) • 67.3 (10.34) (non-hallucinators)	• 3 (1) (hallucinators) • 2 (1) (non-hallucinators)	• 10.5 (8) (hallucinators) • 5.5 (6) (non-hallucinators)	MMSE (SD): • 26 (6.5) (hallucinators) • 29 (2.5) (non-hallucinators)	Unspecified self-report questionnaire	Hallucinations usually occurred at night
(Sanchez-Ramos et al., 1996)	Cross-sectional study	• 55 PD hallucinators • 159 PD non-hallucinators	• 70 (10.3) (hallucinators) • 66 (9.18) (non-hallucinators)	• 3.2 (0.9) (hallucinators) • 2.3 (0.8) (non-hallucinators)	• 8.6 (5.6) (hallucinators) • 6.3 (5.4) (non-hallucinators)	MMSE (SD): • 21.8 (6.6) (hallucinators) • 27.3 (2.4) (non-hallucinators)	Unspecified questionnaire	62% of patients stated they experienced visual hallucinations in the "on" state. Hallucinations were more common at night. Higher anticholinergic and bromocriptine in non-hallucinator group.
(Fenelon et al., 2000)	Cross-sectional study	• 86 PD hallucinators • 109 PD non-hallucinators	• 73.9 (7.0) (hallucinators) • 67.5 (9.6) (non-hallucinators)	• 2.5 (0.6) (hallucinators) • 1.8 (0.8) (non-hallucinators)	• 12.9 (7.5) (hallucinators) • 8.5 (5.6) (non-hallucinators)	• 64.6 % dementia (DSM) (hallucinators) • 6.1% (non-hallucinators)	Unspecified semi-structured questionnaire in French	21 had auditory hallucinations. Formed VH occurred in 48 (22% of whole sample). Minor hallucinations occurred in 25.5% of the sample. Hallucinations occurred predominantly at night.
(Goetz et al., 2001)	Prospective longitudinal study	• 29 hallucinators • 60 PD non-hallucinators • Interviewed at 6, 18, & 48 months	• 73.9 (7.0) (hallucinators) • 67.5 (9.6) (non-hallucinators)	H+Y 2-3 while in PD motor ON state	13.1 (7.5) (hallucinators) 9.0(6.2) (non-hallucinators)	MMSE (SD): • 25.5 (3.2) (hallucinators) • 27.7 (3.0) (non-hallucinators)	• UPDRS • Rush Hallucination Inventory	• Frequency of hallucinations increased (at least 3x/week)over 4 years. • Presence of hallucinations predicts continued hallucinations.
(Barnes & David, 2001)	A systematic review of case series, surveys, case-control studies &	• 6 studies • 316 hallucinators *vs* 806 comparators	↑ Age associated with visual hallucinations	↑ disease severity associated with visual hallucinations	↑ disease duration associated with visual hallucinations	↑ cognitive impairment associated with visual hallucinations	Unclear	Hallucinations - intermittent, lasting seconds to minutes - occurred at least once a week - sudden in onset - tend to occur in dim lighting - unrelated to medications

	• A cross-sectional phenomenological survey	• 21 PD patients (hallucinators) vs 23 non-hallucinators	67.6 (6.52) (hallucinators) vs 63.23 (10.82) (non-hallucinators)	3.47(0.63) (hallucinators) vs 2.95(0.57) (non-hallucinators)	11.76 (5.42) (hallucinators) vs 8.30(4.38) (non-hallucinators)	MMSE (SD): 26.7(1.4) (hallucinators) vs 27.6(1.1) (non-hallucinators)	Unspecified questionnaire described as a typed A4 booklet investigating general visual changes in PD.	52.4% had visual hallucinations only in dim lighting.
(Witjas et al., 2002)	• Cross-sectional study	50 PD motor fluctuators (end-of-dose akinesia with an "off " period lasting at least 1 hour, "on-off " phenomenon, peak-of-dose and diphasic dyskinesia, & dystonia).	66.2(8.5)	• 2.3 (0.9) for PD motor ON & 3.8(0.8) for PD motor OFF;	12.7 (5.4)	MMSE(SD): 27.1 (2.5)	• UPDRS • Schwab & England scale • Structured questionnaire with 54 questions about NMF manifestations.	46% had hallucinations during motor ON state
(Ravina et al., 2007)	• Narrative review	45 articles on clinical features & outcomes	Unclear	• Unclear	Unclear	Unclear	Unclear	• Hallucinations: - occur at least once a week, lasting seconds to minutes. - Occur several times per day. - Tend to occur in times of low ambient stimulation (e.g. evenings). - Tend to persist chronically once established. - Early hallucinators more likely to have persistent visual hallucinations during the day with frightening content & with non-visual hallucinations.
(Papapetropoulos et al., 2008)	• Cross-sectional	• 70 (total sample size) over 6 months. • 31 PD hallucinators *vs* 39 PD non-hallucinators	• 64.3 (10.2) (Total sample size) • 64.3(10.5) (hallucinators) 53.9(10) (non-hallucinators)	• 2.5 (0.7)	9 (5.4)	MMSE (SD): 25.6(4.5)	UM-PDHQ (not validated at the time of this study)	• 56% hallucinations occurred once per week or more. • Hallucinations instantaneous (<1 sec) in 10 (32.3%), of medium duration (<10 sec) in 18 (58.1%) patients. • Hallucinations - prolonged duration (>10sec) in 1 PD patient.

								• 64.5% hallucinations single modality. • 77.5% visual hallucinations • 42% Hallucinations occurred more in ON phase. • More than half of hallucinations sudden in onset, occurred anytime, 12.9% gradual. • 2 (6.5%) hallucinations occurred after changes in treatment. • NOT associated with light cycle. NOT associated with cognitive impairment.
(Shiotsuki et al., 2010)	• Case report	• One housewife	• 64 years of age	H&Y IV	6 years	MMSE 20/30 FAB 11/18	NA	Delusional misidentification disorder (Capgras syndrome) only in PD motor OFF state; relieved with increased levodopa dosage.
(Pagonabarraga et al., 2016)	• Prospective longitudinal	• 50 *de novo* PD (100 control); • 21 with mH followed up for 4.4±1.5 (Range 2-8) years; 6 lost to follow-up.	• 68.8 (10) (PD) 66.4(10) (healthy controls)	1.9 (0.2)	22.8 (10)	PD-CRS: 85.0±18	• MDS-UPDRS Part I • The authors' own semi-structured interview for psychosis	• Hallucinations present more than once per week. • Combined presence/passage hallucinations – more than once a week. • Isolated presence/passage hallucinations – more than once a month but less than once a week. • Passage hallucinations – fleeting • mH started 3 months to 9 years before PD diagnosis; about 33% started starting 20.8±28 months (7 months to 8 years) before the onset of the first parkinsonian

								motor symptoms (no dopaminergic drug initiated) • mH remained stable in more than half during follow-up, worsened in over 35%, and disappeared in less than 10% of the patient population. • Stable mH experienced weekly/monthly; did not develop major hallucinations. • 14.2% progressed to dementia; had worsening mH and developed major hallucinations with loss of insight. • No delusions in *de novo* patients and controls (unable to assess paranoid, jealousy, theft, self-referential delusions) • Healthy controls : mostly presence hallucinations; 1-2 times/year.
(van Wamelen et al., 2019)	Retrospective cross-sectional study	• 372 PD patients • Divided into three groups based on ecological seasons: (1) Winter: November – February (2) Spring : March – June (3) Summer: June - October	Age of onset (years) (1) Winter: 57.8(12.1) (2) Spring : 58.4 (11.7) (3) Summer: 58.3(11.8)	(1) Winter: 2.3 (0.9) (2) Spring :2.4 (1.0) (3) Summer: 2.3(0.9)	(1) Winter: 6.7(6.2) (2) Spring : 5.2(4.9) (3) Summer: 5.4(5.1)	Unspecified	• NMSS • HADS • PDSS • ESS	Seasonal differences were observed for the NMSS domain 4 (perceptual problems), worse scores during the winter and improved in the summer.
PD Anxiety Fluctuation								
(Girotti et al., 1986)	Cross-sectional study	• 21 non-demented PD patients/ 21 healthy controls.	• PD patients: 58 (8.1)	Not assessed	11 (4.8)	Stated non-demented	• Duvoisin scale test • Gerlach's rating scale for hyperkinesia	Anxiety occurred mainly in the PD motor OFF state

		• PD patients evaluated twice in two sessions on different days, within one week, once when on and once when off, according to a randomised sequence	Controls: 57.8 (7)				• Computerised assessment of reaction and movement times. • Benton visual orientation line test • Modified set-test • Modified Randt memory test • Rene Zazzo's attention test • BPRS	
(Nissenbaum et al., 1987)	Case series	9 PD motor fluctuators	51.4 (11.1)	• 4 (0.6)	• 11.2 (3.9)	Unclear	• Psychiatric mental state examination • Semi-structured interview on depression and anxiety • Tests on orientation, digit span, 10-word verbal learning test.	• Anxiety occurred more frequently in the PD motor OFF state.
	Clinical survey	31 PD motor fluctuators	64.4(9.4)	• Median H&Y (Range): - ON: 2 (1-4) - OFF: 3(3-5)	54 (8.2)	Not assessed	• Questionnaire survey on mood/anxiety	• Anxiety fluctuations not reliably linked to motor fluctuations, dopaminergic dose or PD severity. • Anxiety fluctuations worse in PD motor OFF state. • Anxiety fluctuations strongly related to age and depressive fluctuations.
(Menza et al., 1990)	Cross-sectional study	• 10 PD motor fluctuators • Completed scales over 3 days: during an "off' period on day 1, during an "on" period on day 2, & during an "on with dyskinesia" period on day 3. Cycle	Not stated	Not stated	Not stated	Not assessed	• POMS-BI • VAS for depression & anxiety	Anxiety fluctuations parallel motor fluctuations in PD patients.

		repeated 5 times for a total of 5 ratings for each state.						
(Riley & Lang, 1993)	Case series	6 PD patients	68.3 (6.47)	Not stated	6 (3.9)	Unclear	NA	One case described anxiety mainly more pronounced in the PD motor OFF state, which improved with switch to controlled realease dopaminergic medications.
(Vazquez et al., 1993)	Cross-sectional study	31 PD patients with panic attacks (PA); comparators = 100 PD patients without panic attacks (CS)	• PA: 64 (8.4) CS: 66(11)	• PA: 3 (0.9) • CS: 2.5 (1)	Stated that most patients had disease duration 6-12 years.	Unclear	• UPDRS • HPS • HAS • HAM-D	• Typical PA - begins acutely with a marked sensation of malaise, paraesthesias, burning feelings, aches, sometimes ascending from the feet, sometimes, initiating in the face, chest, etc, accompanied by a feeling of fear or panic, an intense motor freezing, a coarser tremor than usual, sweating or flushes, tachycardia, choking, dyspnea, or urgency to urinate. • PA tended to appear 2 years later than dyskinesias and motor fluctuations. • PA group has more motor fluctuations. • PA occurred more frequently in the PD motor OFF state (90.3%). • PA strongly correlated with depression rates. • Anxiety improves on levodopa
(Maricle, Nutt, & Carter, 1995)	Open-label uncontrolled	• 15 PD motor fluctuators with a minimum of 9h without antiparkinsonian	61 (8)	3.6 (1.1)	10 (4)	Not assessed	VAS to quantify mood & anxiety at 30-min intervals from 8am-	• Improvement in anxiety fluctuations with levodopa infusion lasted ~2hours,

	exploratory pre-post clinical study	medications before infusions. • IV levodopa infusion at 1 mg/kg/h from 9-11am. Carbidopa (25 mg) was administered 8am,10am, & 12pm. Motor disability monitored every 30min from 8am-2pm by tapping speed, timed walking, & tremor/ dyskinesia scores.					2pm (separate by participant & caregiver)	with significant rebound anxiety afterwards. • Anxiety effects precede motor effects. • Anxiety effects parallel mood effects.
(Maricle, Nutt, et al., 1995)	Double-blind randomised controlled trial with allocation concealment.	• 8 PD motor fluctuators with a minimum of 9h without antiparkinsonian medications before infusions. • IV levodopa infusions: high dose (1 mg/kg/hr), low-dose (0.5 mg/kg/hr), & placebo (normal saline) between 9-11am on 3 consecutive days. Carbidopa (25 mg) administered at 8am,10am, & 12pm. Motor disability monitored every 30min from 8am-2pm by tapping speed, timed walking, & tremor/ dyskinesia scores	• 70 (19)	• 3.6 (0.9)	• 10.5 (1.6)	Not assessed	VAS to quantify mood & anxiety at 30-min intervals from 8am-2pm (separate by participant & caregiver)	• Improvement in anxiety proportional to levodopa dose with longer duration & greater peak effect (effect size moderate to large) compared to placebo. • Anxiety occurs more in motor OFF states
(Richard et al., 2001)	Case series	• 16 PD motor fluctuators • Completed hourly diary for mood/ anxiety/motor function over seven consecutive days.	• 62 years	• Mean H&Y: 2.7	• Unclear	Not assessed	• BDI • GDS • Zung Anxiety Scale • VAS on mood/anxiety/motor states.	• Anxiety fluctuations can be independent from motor fluctuations (authors suggested that different neurobiologic mechanisms may underpin emotional and motor fluctuations)

								• No consistent relationship detected between anxiety fluctuations with history of anxiety disorders or existing medications.
(Erdal, 2001)	Cross-sectional study	• 36 PD patients (14 PD motor fluctuators; 22 PD motor non-fluctuators)	• 69.81 (9.69)	• PD motor fluctuators: 2.36 (0.92) • PD motor non-fluctuators: 1.64 (0.63)	• PD motor fluctuators: 9 (6.4) • PD motor non-fluctuators: 5.41 (5.29)	• PD motor fluctuators: MMSE 26.64 (3.25). • PD motor non-fluctuators: MMSE 26.55 (3.26)	• ADL Scale • BDI • SDS • STAI	State and trait anxiety significantly more amongst PD motor fluctuators compared to PD motor non-fluctuators.
(Raudino, 2001)	Cross-sectional study	• 47 PD patients (16 motor fluctuators; 22 motor&non-motor fluctuators)	• 70.6 (9.9)	• 3.06 (0.96) (motor fluctuators) • 3.02 (0.96) (non-motor fluctuators)	• 83.2 (38.5) months (motor fluctuators) • 95.9 (58.1) (non-motor fluctuators)	Unclear	• Self-composed semi-structured interview re: motor & non-motor fluctuations. • Webster Disability Rating Scale	• Anxiety fluctuations occurred in 10.5% of the sample. • Anxiety fluctuations occurred in the PD motor OFF state & is associated with motor fluctuations
(Witjas et al., 2002)	Cross-sectional study	50 PD motor fluctuators (end-of-dose akinesia with an "off " period lasting at least 1 hour, "on-off " phenomenon, peak-of-dose, and diphasic dyskinesia, & dystonia).	• 66.2(8.5)	• 2.3 (0.9) for PD motor ON & 3.8(0.8) for PD motor OFF	• 12.7 (5.4)	MMSE(SD): 27.1 (2.5)	• UPDRS • Schwab & England scale • Self-composed structured questionnaire with 54 questions about NMF manifestations.	• 88% had anxiety during motor OFF state. • Anxiety fluctuations associated with greater level of disability.
(Gunal et al., 2002)	Cross-sectional study	• 85 PD patients • Evaluated over 6 months	• 66.2 (9.3)	• Median H&Y (Range): 2.16 (1-5)	• 7.8 (6.1)	MMSE >25	• UPDRS • Standard questionnaire on sensory/ autonomic/ psychiatric symptoms	• Anxiety fluctuations more in the PD motor OFF state. • Psychiatric fluctuations associated with higher levodopa dose but not duration of levodopa use.
(Richard et al., 2004)	Double-blinded randomised placebo-controlled	• 6 PD mood & motor fluctuators.	• 65.2 years	2.7 (0.42)	• 11.83 (5.74)	Not assessed	• standardized clinical examination by experienced	• No consistent correlations between anxiety fluctuation with plasma levodopa levels.

	trial; allocation concealment was done.	• Two treatment days: (i) Active oral carbidopa/ levodopa (and active entacapone in the case of subjects who had been taking it with their carbidopa/ levodopa) according to their usual dosage regimen & a placebo levodopa infusion (8 am–4 pm) with placebo oral carbidopa (& placebo entacapone if indicated). (ii) Placebo oral carbidopa/ levodopa & an active levodopa infusion (8 am–4 pm) with active oral carbidopa (& active entacapone if indicated). • Completed VAS at 30-minute intervals during the infusions. • Completed hourly diary for mood/ anxiety/motor function over seven consecutive days.					movement disorder physicians, who further characterized motor fluctuations as any or all the following: (1) dyksinesias, (2) wearing off, and (3) "on–off" fluctuations. • UPDRS III • SCID • VAS on mood/anxiety/motor states. • GDS • BDI • ZAS	• No impact of an underlying psychiatric disorder or existing antidepressant medications on response to the levodopa infusions.
(Pontone et al., 2009)	Cross-sectional study	• 127 PD patients	• 67 (11)	I-18 (number of patients), I ½-2 II-64, II ½-23, III-14, IV-5, V-1	• 7.9 (5.5)	MMSE (SD): 28.1 (1.8)	• UPDRS • SCID (DSM-IV-TR) • Questionnaire on non-motor fluctuations	• Current prevalence of anxiety disorders 43% • Lifetime prevalence of anxiety disorders 49% • Commonest anxiety diagnosis = Anxiety disorder NOS • Panic disorder associated with earlier age of PD onset, higher rates of motor fluctuations, as well as morning dystonia.

(Seki et al., 2013)	Cross-sectional study	• 464 PD patients	• 70.8 (8.4)	• 2.6 (0.9); •	• 6.6 (5)	Not assessed	WOQ-19	• 60% PD patients experience panic attacks • Presence of panic attacks associated with higher doses of levodopa treatment.
(Storch et al., 2013)	Cross-sectional study (NoMoFlu-PD study)	• 100 advanced PD patients	• 68.4 (9.7)	• 2.7 (0.9) for PD motor ON & 3.4(0.9) for PD motor OFF	• 11.3(6.2)	MMSE>23	• A semi-structured interview using standardized clinical examination by experienced movement disorder physicians. • UPDRS III • NMS-Q • WOQ-9 • A visual analogue scale (NMF-VAS) displayed to the patients during the examination ranging from 0% (no symptoms) to 100% (most severe symptom possible)	• Anxiety reported more in motor OFF state compared to motor ON • Anxiety associated with motor fluctuations but can occur independently. • Presence of anxiety associated with worse quality of life.
(Rizos et al., 2014)	Multicenter cross-sectional study	• 320 PD patients	• 70 (range 42-90)	• 2.7(2)	• 7 (range 0-24)	Not assessed	• UPDRS • PDSS • NMSQuest	Anxiety is associated with 'early morning off' periods in PD.
(Storch et al., 2015)	Cross-sectional study	• 73 Advanced PD patients • NMS fluctuations assessed over 1-month period.	• 68.2 (9.7)	• 2.7 (1.0) for PD motor ON & 3.4(0.9) for PD motor OFF	• 11.6(6.3)	MMSE>23	• A semi-structured interview using standardized clinical examination by experienced movement disorder physicians. • UPDRS III • NMSQ • WOQ-9 • NMSS (modified) - severity & frequency of NMS reported only within motor ON	• Anxiety worse in PD motor OFF states compared to ON High concordance between NMSS and WOQ-9

							($NMSS_{On}$) or OFF ($NMSS_{Off}$) state over the last month.	
(Fauser et al., 2015)	Cross-sectional study	• 38 PD fluctuators • Self-reported frequency and severity of NMS in a series of five patient-perceived motor ON and OFF periods	• 65.6 (8.2)	• 2.4 (0.9) for PD motor ON & 3.1(1.0) for PD motor OFF;	• 10.3(7.0)	MMSE>23	• A semi-structured interview using standardized clinical examination by experienced movement disorder physicians. • UPDRS III • Home diary with list of ten NMS to be rated at home as "present" or "absent" during five patient-perceived motor ON and OFF & • A visual analogue scale (NMF-VAS) ranging from 0% (no symptoms) to 100% (most severe symptom possible). • Diary data dichotomized to (i) "instable" fluctuators reported a respective NMS within 1–4 of 5 assessments of a given motor state. (ii) "stable" fluctuating subjects presented with a specific NMS during either all or none of the investigated motor state.	• Anxiety occurred significantly amongst "instable" PD NMS fluctuators within motor OFF state. • Anxiety demonstrated significantly higher intraindividual variability in symptom severity during PD motor OFF state.
(Ossig et al., 2016)	Cross-sectional study	• 15 PD motor fluctuators • 17 PD motor non-fluctuators • 15 controls	• 62.9 (6.6) (PD, fluctuators)	• 2.2(0.5) (PD, fluctuators)	• 10.5(3.3) (PD, fluctuators)	MoCA (SD): • 27.5(2.4) (PD, fluctuators)	• Modified diary for motor dunction with four different motor states (asleep, motor	• Anxiety fluctuation is associated with motor fluctuations.

		• Completed a pair of motor diary & NMS diary over 5 consecutive days	• 66.4 (9.6) (PD, non-fluctuators) • 62.1 (6.9) (Healthy controls)	• 2.4(0.4) (PD, non-fluctuators)	• 4.3(2.8) (PD, non-fluctuators)	• 27.1(2.0) (PD, non-fluctuators) • 27.1 (1.6) (Healthy controls)	OFF, ON without dyskinesia, ON with dyskinesia) • A novel NMS diary asking to rate 9 key NMS, including psychiatric NMS such as anxiety	• Switches between motor states and anxiety seen more frequently in PD motor fluctuators. • Anxiety switches can be independent of motor switches with a concordance rate of 25.9-42.9% in PD motor fluctuators • In PD motor fluctuators, anxiety (and motor OFF state) more pronounced in the morning, early afternoon, and evening.
(Ossig et al., 2017)	Cross-sectional study	• 15 PD motor fluctuators • 17 PD motor non-fluctuators • Home diaries were completed by rating NMS as absent (defined herein as NMS ON state) or present (NMS OFF state) and motor function for every hour for 5 consecutive days. Timing and kinetics were analyzed by synchronizing motor OFF periods and subsequent cross-classification of NMS OFF periods for each motor OFF hour into 2×2 contingency tables.	• 62.9 (6.6) (PD, fluctuators) • 66.4 (9.6) (PD, non-fluctuators)	• 2.2(0.5) (PD, fluctuators) • 2.4(0.4) (PD, non-fluctuators)	• 10.5(3.3) (PD, fluctuators) • 4.3(2.8) (PD, non-fluctuators)	• 27.5(2.4) (PD, fluctuators) • 27.1(2.0) (PD, non-fluctuators)	• Modified diary for motor function with four different motor states (asleep, motor OFF, ON without dyskinesia, ON with dyskinesia) • A novel NMS diary asking to rate 9 key NMS, including psychiatric NMS such as anxiety	• Anxiety is present for a longer duration (3–5 hours) compared to motor OFF periods (2 hours; $p < 0.05$) • Anxiety occurred one hour before the start of dyskinetic ON state.
(Rodriguez-Blazquez et al., 2021)	Cross-sectional study	• 402 PD patients	• 67.42 (9.96)	• Median H&Y 2 (IQR: 2-3)	• 8.2 (5.9)	• MoCA ≥ 21	• CISI-PD • MDS-NMS (including NMF subscale) • NMSS	• Anxiety fluctuations worsen with increased PD severity.

							• MDS-UPDRS	• Fatigue was the most prevalent NMS in patients with NMF
(Del Prete et al., 2022; Fauser et al., 2015)	Cross-sectional study	• 18 PD motor and non-motor fluctuators (self-reported, caregiver-reported, or directly observed by clinician). • PKG worn for 6 consecutive days to identify motor ON & OFF periods; NFS completed during the motor ON & OFF periods for 3 consecutive days while wearing PKG.	63 (8.60)	Not stated	• 10 (3.90)	• MMSE : 26.13 1.58) • Mattis DRS: 139.50 (1.80)	• PKG • NFS	• Worse anxiety in the PD motor OFF state. • No correlation between non-motor ON scores with the PD motor ON state.
(Pontone et al., 2022)	Cross-sectional study	• 200 PD patients	65.21 (7.71)	76.2% H&Y 2	9.09 (5.81)	MoCA 26.74 (2.90)	• HAM-A • HAM-D • PAS • WoQ-9 • S&E Scale • Symbol Digit Modality Test • Stroop Color-Word T-score	• Anxiety worse in the PD motor OFF state compared to ON. • Anxiety fluctuations causes distress & lowers quality of life in Parkinson's. • High anxiety in the PD motor OFF associated with higher depression and greater disability. • 'Anxious fluctuators' more likely to be male and to have a family history of anxiety disorders.

PD Apathy Fluctuation								
(Dujardin et al., 2007)	Cross-sectional study	• 159 PD patients - 47 non-demented motor non-fluctuators (stable PD) - 73 non-demented PD fluctuators - 39 with PD dementia • 58 healthy controls	• Stable PD: 62 (11.38) • PD fluctuators: 60.47(8.23) • PD dementia: 68.56 (8.91) • Healthy controls: 61.34 (10.98)	Not stated	• PD with apathy: 8.76 (7.17) • PD without apathy: 8.05 (6.14)	Mattis DRS: • Stable PD: 136.96 (4.60) • PD fluctuators: 134.33 (5.69) • PD dementia: 118.67 (7.84)	• UPDRS III • LARS • MADRS	• 30% of the motor PD fluctuators suffered from moderate-to-severe clinical apathy compared to stable PD& healthy controls. • Apathy more pronounced amongst PD patients with dementia compared to PD motor fluctuators.
(Ou et al., 2020)	Prospective cohort study	• 188 PD patients with baseline disease duration < 3 years. • Follow-up over 4 years	Baseline: 58.1 (10.7)	1.9 (0.4)	Baseline: 1.5 (0.8)	Baseline MoCA: 25.5 (3.5)	• UPDRS III • LARS	• Prevalence of apathy increased 1.5 fold with disease progression (18.6 to 28.8%) • An impersistent pattern noted with less than half experiencing persistent apathy after 4 years.
(Del Prete et al., 2022)	Cross-sectional study	• 18 PD motor and non-motor fluctuators (self-reported, caregiver-reported, or directly observed by clinician) • PKG worn for 6 consecutive days to identify motor ON & OFF periods; NFS completed during the motor ON & OFF periods for 3 consecutive days while wearing PKG.	63 (8.60)	Not stated	10 (3.90)	• MMSE : 26.13 (1.58) • Mattis DRS: 139.50 (1.80)	• PKG • NFS	• Worse apathy in the PD motor OFF state. • No correlation between non-motor ON scores with the PD motor ON state.

PD Depression Fluctuation								
(Hardie et al., 1984)	Cross-sectional study	• 20 PD patients • Diaries recorded over 5 days	56.85 (6.23)	3.95(1.19)	11.9 (3.42)	Not assessed	• Self-scoring diaries • Webster Disability Rating Scale	Mood fluctuations parallel PD motor fluctuations; worse in PD motor OFF states.
(Cantello et al., 1986)	Case-control study	• 18 PD motor fluctuators – "typical end-of-dose deterioration" *vs* • 12 nursing-home patients with chronic active rheumatoid arthritis (RA) • Each subject assessed four times (2x mobile & 2x immobile)over a week	• 18 PD motor fluctuators: 64.4 (6.6) • 12 RA patients: 66.2 (7.6)	I, IV and V: 0 pts II: 10 pts III: 8 pts	• 18 PD motor fluctuators: 7.2 (3.4) • 12 RA patients: 8.7 (4.9)	**MMSE** • 18 PD motor fluctuators: 28.2 (3.2) • 12 RA patients: 28.4 (2.8)	• Hachinski Ischaemic Score • DSM-III for depression • Activation & Euphoria Scale • NUDS • BDI (Italian translated) • Mood & Behaviour Self-rating Scale	• Depression more common in PD during the motor ON state compared to RA. • Depression worse in PD during the motor OFF state compared to RA • Severity of depression did not correlate with duration of illness in PD, in contrast to RA.
(Menza et al., 1990)	Cross-sectional study	• 10 PD motor fluctuators • Completed scales over 3 days: during an "off' period on day 1, during an "on" period on day 2, & during an "on with dyskinesia" period on day 3. Cycle repeated 5 times for a total of 5 ratings for each state.	Unspecified	Unspecified	Unspecified	Unspecified	• POMS-BI • VAS for depression & anxiety	• Mood fluctuations parallel motor fluctuations in PD patients. • Low mood occurred more frequently in the PD motor OFF state and improved in the PD motor ON state. • Mood is worst during the PD motor OFF and 'ON with dyskinesia" states.
(Riley & Lang, 1993)	Case series	• 6 PD patients	• 68.3 (6.47)	Unspecified	• 6 (3.9)	Unspecified	NA	Two cases described depression to be mainly worse in the PD motor OFF state which improved with less PD motor OFF states after dopaminergic medications were titrated.

(Maricle, Nutt, & Carter, 1995)	Open-label uncontrolled exploratory pre-post clinical study	• 15 PD motor fluctuators with a minimum of 9h without antiparkinsonian medications before infusions. • IV levodopa infusion at 1 mg/kg/h from 9-11am. Carbidopa (25 mg) was administered 8am,10am, & 12pm. Motor disability monitored every 30min from 8am-2pm by tapping speed, timed walking, & tremor/ dyskinesia scores.	• 61 (8)	3.6 (1.1)	• 10 (4)	Not assessed	VAS to quantify mood & anxiety at 30-min intervals from 8am-2pm (separate by participant & caregiver)	• Improvement in mood fluctuations with levodopa infusion lasted ~2hours, with significant rebound depression afterwards. • Mood effects precede motor effects. • Mood effects parallel anxiety effects
(Maricle, Nutt, et al., 1995)	Double-blind randomised controlled trial with allocation concealment.	• 8 PD motor fluctuators with a minimum of 9h without antiparkinsonian medications before infusions. • IV levodopa infusions: high dose (1 mg/kg/hr), low-dose (0.5 mg/kg/hr), & placebo (normal saline) between 9-11am on 3 consecutive days. Carbidopa (25 mg) administered at 8am,10am, & 12pm. Motor disability monitored every 30min from 8am-2pm by tapping speed, timed walking, & tremor/ dyskinesia scores.	• 70 (19)	• 3.6 (0.9)	• 10.5 (1.6)	Not assessed	VAS to quantify mood & anxiety at 30-min intervals from 8am-2pm (separate by participant & caregiver)	• Improvement in mood proportional to levodopa dose with longer duration & greater peak effect (effect size moderate to large) compared to placebo. • It was an hour after the low-dose infusion before mood started to improve. • On high-dose infusion, mood improved for 2 hours longer than on low-dose, but then dropped noticeably below pre-infusion levels (?rebound effect) • Depression is worse in PD motor OFF state.
(Raudino, 2001)	Cross-sectional study	• 47 PD patients (16 motor fluctuators; 22 motor&non-motor fluctuators)	• 70.6 (9.9)	• 3.06 (0.96) (motor fluctuators) • 3.02 (0.96) (non-motor fluctuators)	• 83.2 (38.5) months (motor fluctuators) • 95.9 (58.1) (non-motor fluctuators)	Unspecified	• Self-composed semi-structured interview re: motor & non-motor fluctuations. • Webster Disability Rating Scale	• Depressive fluctuations occurred in 7.9% of the sample. • Depressive fluctuations occurred in the PD motor OFF state & is associated with motor fluctuations.

(Richard et al., 2001)	Case series	• 16 PD motor fluctuators • Completed hourly diary for mood/ anxiety/motor function over seven consecutive days.	• 62 years	Mean H&Y: 2.7	Unclear	Not assessed	• BDI • GDS • Zung Anxiety Scale • VAS on mood/anxiety/motor states.	• Depressive fluctuations can be independent from motor fluctuations (authors suggested that different neurobiologic mechanisms may underpin emotional and motor fluctuations) • Depression and trajectory trajectory tended to parallel each other, though not consistently. • No consistent relationship detected between anxiety fluctuations with history of anxiety disorders or existing medications.
(Racette et al., 2002)	Case-control study via retrospective records review	• 70 PD mood fluctuators • 100 PD mood non-fluctuators • 70 PD motor fluctuators & mood non-fluctuators • Evaluated over 5 years	• Mood fluctuators: 55.4 (range 26-78) • PD mood non-fluctuators: 62.9 (range 30-81) • Motor fluctuators & mood non-fluctuators: 58.1 (range 28-70)	Unclear	• Mood fluctuators: 12.2 • PD mood non-fluctuators: 6.3 Motor fluctuators & mood non-fluctuators: 9.9	Not stated	• Modified H&Y scale • DSM-IV diagnoses of anxiety disorder due to a general medical condition" or "mood disorder due to a general medical condition"	• Mood fluctuations associated with younger age of onset. • Mood fluctuations associated with motor fluctuations • Mood fluctuations associated with psychosis, dementia, and nonfluctuating clinical depression.
(Witjas et al., 2002)	Cross-sectional study	50 PD motor fluctuators (end-of-dose akinesia with an "off " period lasting at least 1 hour, "on-off " phenomenon, peak-of-dose, and diphasic dyskinesia, & dystonia).	• 66.2(8.5)	2.3 (0.9) for PD motor ON & 3.8(0.8) for PD motor OFF	• 12.7 (5.4)	MMSE(SD): 27.1 (2.5)	• UPDRS • S&E scale • Self-composed structured questionnaire with 54 questions about NMF manifestations.	• Depressive fluctuation occurred mainly in the PD motor OFF state. • Depressive fluctuation was associated with greater level of disability.

(Richard et al., 2004)	Double-blinded randomised placebo-controlled trial; allocation concealment was done.	• 6 PD mood & motor fluctuators. • Two treatment days: (iii) Active oral carbidopa/ levodopa (and active entacapone in the case of subjects who had been taking it with their carbidopa/ levodopa) according to their usual dosage regimen & a placebo levodopa infusion (8 am–4 pm) with placebo oral carbidopa (& placebo entacapone if indicated). (iv) Placebo oral carbidopa/ levodopa & an active levodopa infusion (8 am–4 pm) with active oral carbidopa (& active entacapone if indicated). • Completed VAS at 30-minute intervals during the infusions. • Completed hourly diary for mood/ anxiety/motor function over seven consecutive days.	• 65.2 years	2.7 (0.42)	11.83 (5.74)	Not assessed	• standardized clinical examination by experienced movement disorder physicians, who further characterized motor fluctuations as any or all the following: (1) dyksinesias, (2) wearing off, and (3) "on–off" fluctuations. • UPDRS III • SCID • VAS on mood/anxiety/motor states. • GDS • BDI • ZAS	• ~30% had mood improvement with levodopa infusions. • No consistent correlations between mood fluctuation with plasma levodopa levels. • No impact of an underlying psychiatric disorder or existing antidepressant medications on response to the levodopa infusions.
(Kulisevsky et al., 2007)	Randomized double-blind crossover studty	• 14 PD patients (7 stable, 7 wearing-off) • Patients monitored for motor status, mood, anxiety, and plasma LD levels 1 hour before and 6 hours after an oral dose of immediate release & controlled release LD formulations.	61.6 (9.5)	2.2 (0.5)	7.15 (4.0)	MMSE: 27.6 (2.0)	• BDI • STAI • VAS for mood & anxiety	• Mood fluctuators are sensitive to type of motor response (stable/ wearing off) to oral LD & kinetic profile of LD formulations • Mood elevation peaked at 2 hours after immediate release LD

(Storch et al., 2013)	Cross-sectional study (NoMoFlu-PD study)	100 advanced PD patients	• 68.4 (9.7)	2.7 (0.9) for PD motor ON & 3.4(0.9) for PD motor OFF	11.3(6.2)	MMSE>23	• A semi-structured interview using standardized clinical examination by experienced movement disorder physicians. • UPDRS III • NMS-Q • WOQ-9 • BDI-1A • PDQ-8 • A visual analogue scale (NMF-VAS) displayed to the patients during the examination ranging from 0% (no symptoms) to 100% (most severe symptom possible).	• Depression more severe in motor OFF state compared to motor ON • Depression associated with motor fluctuations but can occur independently. • Depressive fluctuations associated with the worst quality of life compared to other NMS fluctuations.
(Fauser et al., 2015)	Cross-sectional study	• 38 PD fluctuators • Self-reported frequency and severity of NMS in a series of five patient-perceived motor ON and OFF periods	• 65.6 (8.2)	• 2.4 (0.9) for PD motor ON & 3.1(1.0) for PD motor OFF;	10.3(7.0)	MMSE>23	• A semi-structured interview using standardized clinical examination by experienced movement disorder physicians. • UPDRS III • Home diary with list of ten NMS to be rated at home as "present" or "absent" during five patient-perceived motor ON and OFF & • A visual analogue scale (NMF-VAS) ranging from 0% (no symptoms) to 100% (most severe symptom possible).	• Depression occurred significantly amongst "instable" PD NMS fluctuators within motor OFF state. • Depression demonstrated significantly higher intraindividual variability in symptom severity during PD motor OFF state.

							• Diary data dichotomized to (iii) "instable" fluctuators reported a respective NMS within 1–4 of 5 assessments of a given motor state. "stable" fluctuating subjects presented with a specific NMS during either all or none of the investigated motor state.	
(Ossig et al., 2016)	Cross-sectional study	• 15 PD motor fluctuators • 17 PD motor non-fluctuators • 15 healthy controls • Completed a pair of motor diary & NMS diary over 5 consecutive days	• 62.9 (6.6) (PD, fluctuators) • 66.4 (9.6) (PD, non-fluctuators) • 62.1 (6.9) (Healthy controls)	• 2.2(0.5) (PD, fluctuators) • 2.4(0.4) (PD, non-fluctuators)	• 10.5(3.3) (PD, fluctuators) • 4.3(2.8) (PD, non-fluctuators)	MoCA (SD): • 27.5(2.4) (PD, fluctuators) • 27.1(2.0) (PD, non-fluctuators) • 27.1 (1.6) (Healthy controls)	• UPDRS • S&E Scale • PDQ-39 • NMSS • BDI • Modified diary for motor dunction with four different motor states (asleep, motor OFF, ON without dyskinesia, ON with dyskinesia) • A novel NMS diary asking to rate 9 key NMS, including psychiatric NMS such as depression.	• Depressive fluctuation is associated with motor fluctuations. • Depressive fluctuations higher in motor non-fluctuators than in controls. • Switches between motor states and depression seen more frequently in PD motor fluctuators. • Depressive switches can be independent of motor switches with a concordance rate of 25.9-42.9% in PD motor fluctuators • In PD motor fluctuators, depression (and motor OFF state) more pronounced in the morning, early afternoon, and evening.
(Ossig et al., 2017)	Cross-sectional study	• 15 PD motor fluctuators • 17 PD motor non-fluctuators • Home diaries were completed by rating NMS as absent (defined herein as NMS ON state) or present (NMS OFF state) and motor	• 62.9 (6.6) (PD, fluctuators) 66.4 (9.6) (PD, non-fluctuators)	• 2.2 (0.5) (PD, fluctuators) 2.4(0.4) (PD, non-fluctuators)	• 10.5(3.3) (PD, fluctuators) 4.3(2.8) (PD, non-fluctuators)	• 27.5(2.4) (PD, fluctuators) • 27.1(2.0) (PD, non-fluctuators)	• Modified diary for motor function with four different motor states (asleep, motor OFF, ON without dyskinesia, ON with dyskinesia)	• Depression is present for a longer duration (1.5-4 hours) compared to motor OFF periods (2 hours; $p < 0.05$) • Depression occurred one hour before the start of dyskinetic ON state.

		function for every hour for 5 consecutive days. • Timing and kinetics were analyzed by synchronizing motor OFF periods and subsequent cross-classification of NMS OFF periods for each motor OFF hour into 2×2 contingency tables.					• A novel NMS diary asking to rate 9 key NMS, including psychiatric NMS such as depression	
PD Fatigue Fluctuation								
(Witjas et al., 2002)	Cross-sectional study	50 PD motor fluctuators (end-of-dose akinesia with an "off " period lasting at least 1 hour, "on-off " phenomenon, peak-of-dose, and diphasic dyskinesia, & dystonia).	66.2(8.5)	2.3 (0.9) for PD motor ON & 3.8(0.8) for PD motor OFF	12.7 (5.4)	MMSE(SD): 27.1 (2.5)	• UPDRS • Schwab & England scale • Self-composed structured questionnaire with 54 questions about NMF manifestations.	• More than half had fatigue during motor OFF state. • Fatigue fluctuations generally paralleled motor fluctuations.
(Storch et al., 2013)	Cross-sectional study (NoMoFlu-PD study)	100 advanced PD patients	68.4 (9.7)	2.7 (0.9) for PD motor ON & 3.4(0.9) for PD motor OFF	11.3(6.2)	MMSE>23	• A semi-structured interview using standardized clinical examination by experienced movement disorder physicians. • UPDRS III • NMS-Q • WOQ-9 • BDI-1A • PDQ-8 • A visual analogue scale (NMF-VAS) displayed to the patients during the examination ranging from 0% (no symptoms) to 100% (most severe symptom possible)	• Fatigue reported more in motor OFF state compared to motor ON • Fatigue associated with motor fluctuations but can occur independently. • Presence of fatigue, especially in PD motor ON state, associated with worse quality of life.

(Fauser et al., 2015)	Cross-sectional study	• 38 PD fluctuators Self-reported frequency and severity of NMS in a series of five patient-perceived motor ON and OFF periods	65.6 (8.2)	• 2.4 (0.9) for PD motor ON & 3.1(1.0) for PD motor OFF;	10.3(7.0)	MMSE>23	• A semi-structured interview using standardized clinical examination by experienced movement disorder physicians. • UPDRS III • Home diary with list of ten NMS to be rated at home as "present" or "absent" during five patient-perceived motor ON and OFF & • A visual analogue scale (NMF-VAS) ranging from 0% (no symptoms) to 100% (most severe symptom possible). • Diary data dichotomized to (iv) "instable" fluctuators reported a respective NMS within 1–4 of 5 assessments of a given motor state. "stable" fluctuating subjects presented with a specific NMS during either all or none of the investigated motor state.	• There were no significant differences between the occurrence of fatigue amongst "instable" PD NMS fluctuators within motor ON or OFF states. • Fatigue demonstrated higher intraindividual variability in symptom severity during PD motor OFF state.
(Ossig et al., 2016)	Cross-sectional study	• 15 PD motor fluctuators • 17 PD motor non-fluctuators • 15 healthy controls Completed a pair of motor diary & NMS diary over 5 consecutive days	• 62.9 (6.6) (PD, fluctuators) • 66.4 (9.6) (PD, non-fluctuators)	• 2.2(0.5) (PD, fluctuators) • 2.4(0.4) (PD, non-fluctuators)	• 10.5(3.3) (PD, fluctuators) 4.3(2.8) (PD, non-fluctuators)	MoCA (SD): • 27.5(2.4) (PD, fluctuators) • 27.1(2.0) (PD, non-fluctuators) 27.1 (1.6) (Healthy controls)	• UPDRS • S&E Scale • PDQ-39 • NMSS • BDI • Modified diary for motor dunction with four different motor states (asleep, motor	• Fatigue was the most frequent NMS in PD motor fluctuators. • Fatigue fluctuation worse in PD motor OFF state. • Fatigue tended to peak in the morning and remain stable for the rest of the day for PD motor fluctuators, peak

			62.1 (6.9) (Healthy controls)				OFF, ON without dyskinesia, ON with dyskinesia) • A novel NMS diary asking to rate 9 key NMS, including psychiatric NMS such as fatigue.	in the early afternoon for PD motor non-fluctuators, compared to peaking in the evening for healthy controls. • Switches of motor state and fatigue seen more in PD motor fluctuators • Fatigue fluctuations occurred independent of motor fluctuations.
(Ossig et al., 2017)	Cross-sectional study	• 15 PD motor fluctuators • 17 PD motor non-fluctuators • Home diaries were completed by rating NMS as absent (defined herein as NMS ON state) or present (NMS OFF state) and motor function for every hour for 5 consecutive days. • Timing and kinetics were analyzed by synchronizing motor OFF periods and subsequent cross-classification of NMS OFF periods for each motor OFF hour into 2×2 contingency tables.	• 62.9 (6.6) (PD, fluctuators) 66.4 (9.6) (PD, non-fluctuators)	• 2.2(0.5) (PD, fluctuators) 2.4(0.4) (PD, non-fluctuators)	• 10.5(3.3) (PD, fluctuators) 4.3(2.8) (PD, non-fluctuators)	• 27.5(2.4) (PD, fluctuators) • 27.1(2.0) (PD, non-fluctuators)	• Modified diary for motor function with four different motor states (asleep, motor OFF, ON without dyskinesia, ON with dyskinesia) • A novel NMS diary asking to rate 9 key NMS, including psychiatric NMS such as fatigue	• No temporal connection between fatigue and dyskinetic motor ON state periods. • Fatigue occurred independent of motor fluctuations.
(Del Prete et al., 2022)	Cross-sectional study	• 18 PD motor and non-motor fluctuators (self-reported, caregiver-reported, or directly observed by clinician) PKG worn for 6 consecutive days to identify motor ON & OFF periods; NFS completed during the motor ON & OFF periods for 3 consecutive days while wearing PKG.	• 63 (8.60)	• Not stated	• 10 (3.90)	• MMSE : 26.13 (1.58) • Mattis DRS: 139.50 (1.80)	• PKG • NFS	• Fatigue mainly experienced in the PD motor OFF state (75%). • No correlation between non-motor ON scores with the PD motor ON state.

PD Cognition Fluctuation								
(Delis et al., 1982)	Case report	Single college-educated man with PD	51 years of age	Unspecified	10 years	• Complete neuropsychological examination done in the PD motor ON state • Only tests requiring a verbal response done in the PD motor OFF state	• WAIS • Stroop test • Wechler Memory scale (including digit span) • Verbal fluency test • Boston Naming Test • Benton Visual Recognition test • Articulatory agility assessed by speech therapists	**In both PD motor ON & OFF states:** • Intact digit span, auditory continuous performance, mental control tasks • Equivalent immediate recall **PD motor ON state:** • Perseveration & impulsivity seen on constructional tasks. • Visuospatial memory severely impaired. • Verbal memory moderately impaired. • Verbal abstraction mildly impaired. • Verbal fluency good **PD motor OFF state** • Delayed initiation to naming • Verbal perseveration noted • Poor articulatory agility • Impaired delayed memory • More circumlocutory errors on confrontation naming
(Brown et al., 1984)	Case-control study	• 16 PD motor fluctuators • 25 matched normal controls • Subjects evaluated on two occasions, once when in PD motor ON and once when OFF state.	• 45.1 (9.3) (PD) • 57.6 (12.9) (normal controls)	Not assessed	11.2 (4.3)	Unclear, though stated not demented	• An unspecified disability rating scale, rating 39 symptoms of Parkinson's disease on a 0-3 scale (0 indicating no impairment and 3 indicating severe impairment) • WAIS	• Fluctuations in cognition tended to be relatively mild despite severe motor fluctuations. • Affect/arousal state important determinant of cognitive function.

							• The MAHT • Subjective Affect/Arousal score computed from a series of 13 scales to assess subjective response to anti-anxiety & antidepressant drugs	
(Girotti et al., 1986)	Cross-sectional study	• 21 non-demented PD patients/ 21 healthy controls. • PD patients evaluated twice in two sessions on different days, within one week, once when on and once when off, according to a randomised sequence	• PD patients: 58 (8.1) • Controls: 57.8 (7)	Not assessed	11 (4.8)	Stated not demented	• Duvoisin scale test • Gerlach's rating scale for hyperkinesia • Computerised assessment of reaction and movement times. • Benton visual orientation line test • Modified set-test • Modified Randt memory test • Rene Zazzo's attention test • BPRS	No significant change in cognitive performance was observed between PD motor ON and OFF states.
(Gotham et al., 1988)	Open label Randomized controlled study	• 16 PD patients • 16 controls • PD patients completed evaluations in both PD motor ON and OFF state, over one week	• 64.4 (5.9) (PD) • 65.2 (5.4) (controls)	Unclear	9.9 (range 2-28)	Stated not to have dementia	• Parkinson's disease rating scale • WAIS • PASAT • WCST • VVCALT • Word Fluency Tasks • Subject-ordered Pointing Tasks • Subjective Affect/Arousal score computed from a series of 13 scales to assess subjective response to anti-anxiety & antidepressant drugs	• Cognitive fluctuations worse in PD motor OFF than ON. • Affect-arousal state not an important determinant of cognitive function.

(Meco et al., 1991)	Cross-sectional study	10 PD motor fluctuators	57(range 49-64)	Unclear	7 (range 2-10)	MMSE ≥ 18	• Toulouse-Pieron test of attention • Digit span • Reaction Times test • Rey forms 1 and 2 • Maze test • Maudley Adjective check list • Webster rating Scale	Despite large motor fluctuations, no significant differences in attention, cognitive performance, or mood between PD motor ON and OFF states.
(Witjas et al., 2002)	Cross-sectional study	50 PD motor fluctuators (end-of-dose akinesia with an "off " period lasting at least 1 hour, "on-off " phenomenon, peak-of-dose, and diphasic dyskinesia, & dystonia).	• 66.2(8.5)	• 2.3 (0.9) for PD motor ON & 3.8(0.8) for PD motor OFF	• 12.7 (5.4)	MMSE(SD): 27.1 (2.5)	• UPDRS • S&E scale • Self-composed structured questionnaire with 54 questions about NMF manifestations.	• Slowness of thinking was the commonest reported cognitive fluctuation (58%). • Slowness of thinking occurred mainly in the PD motor OFF state.
(Ballard et al., 2002)	Case-control study	• 278 (50 PD, 48 PDD, 50 DLB, 80AD, 50 healthy controls)	• 75 (4.2) (PD) • 73.7 (6.2) (PDD) • 77.3 (4.8) (DLB) • 78.6 (7) (AD) • 76.3 (5.4) (controls)	Unclear	Unclear	MMSE • 27.2(2.4) (PD) • 19.8 (5.1) (PDD) • 16.1 (4.8) (DLB) • 17.6 (4.5) (AD) • 28.4 (1.7) (controls)	• UPDRS • Newcastle:Columbia University Scale of psychopathology in AD • NPI • Stroop test • Benton visual retention test • Judgement of Line Orientation test • Section B CAMCOG • Newcastle: Cambridge assessment of mental disorders in the elderly.	• PD patients had significantly greater impairment of cognitive reaction time than healthy controls, though comparable deficit to AD patients. • PD patients did not have fluctuating attention.
(Varanese et al., 2010)	Case-control study with cluster analysis	• 78 patients (27 PDD, 33 DLB, 18 AD) • 20 healthy controls	• 71 (4.2) (PDD) • 73.3 (8.4) (DLB) • 74.1 (5.1) (AD) • 73.05 (9.21) (controls)			MMSE • 20.22 (2.47) (PDD) • 19.94 (4.99) (DLB) • 18.56 (4.38) (AD) • 27.95 (1.76) (controls)	• UPDRS • CAF • DRS-2 • NPI • Mayo sleep questionnaire	• PD cognitive fluctuators have a significantly higher prevalence of hallucinations. • PDD fluctuators shared similar cognitive deficit profile (impairment in

								attention/ initiation/perseveration cognitive domains) to DLB
(Storch et al., 2015)	Cross-sectional study	• 73 Advanced PD patients • NMS fluctuations assessed over 1-month period.	• 68.2 (9.7)	2.7 (1.0) for PD motor ON & 3.4(0.9) for PD motor OFF	11.6(6.3)	MMSE>23	• A semi-structured interview using standardized clinical examination by experienced movement disorder physicians. • UPDRS III • NMSQ • WOQ-9 • NMSS (modified) - severity & frequency of NMS reported only within motor ON ($NMSS_{On}$) or OFF ($NMSS_{Off}$) state over the last month.	• Cognitive fluctuations worse in PD motor OFF states compared to ON • High concordance between NMSS and WOQ-9

PD: Parkinson's disease; PDD: PD dementia; DLB: Dementia of Lewy Body; AD: Alzheimer's Disease; LD: levodopa; mH: minor hallucinations; NMS: Non-Motor Symptoms; NMF: Non-Motor Fluctuations; H&Y: Hoehn & Yahr; IQR: Interquartile Range; MMSE: Mini-Mental State Examination; PD-CRS: Parkinson's Disease-Cognitive Rating Scale; NMS-Q: Non-motor Symptom Questionnaire; NMSS: Non-Motor Symptom Scale; MoCA:Montreal Cognitive Assessment test; SCID: Structured clinical interview for DSM-IV; DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision; WOQ-9: Wearing-off Questionnaire (9-item); UPDRS III: United Parkinson's Disease Rating Scale Part III; NMF-VAS: Non-Motor Fluctuation Visual Analogue Scale; BPRS: Brief Psychiatric Rating Scale; ADL scale: Activities of Daily Living scale; GDS: Geriatric Rating Scale; BDI: Beck's Depression Inventory; ZAS: Zung Anxiety Scale; HPS: Hamilton's scale for anguish; HAS:Hamilton Anxiety Scale; PAS: Parkinson Anxiety Scale; HADS: Hospital Anxiety Depression Scale; PDSS: Parkinson's disease sleep scale; ESS: Epworth sleepiness scale; HAM-A: Hamilton Anxiety Scale; HAM-D: Hamilton Depression Rating Scale; SDS: Zung Self-rated Depression Scale; STAI: State-Trait Anxiety Inventory; POMS-BI: Profile of Mood States; LARS: Lille Apathy Rating Scale; MADRS: Montgomery & Asberg Depression Rating Scale; DRS-2: Dementia ratings Scale-2; Mattis DRS: Mattis Dementia Rating Scale; PKG: Parkinson's Kinetigraph; NFS: Neuropsychiatric Fluctuation Scale; CISI-PD: Clinical Impression of Severity Index for PD; MDS-NMS: Movement Disorders Society-Non-Motor-Rating Scale; MDS-UPDRS: Movement Disorders Society-Unified Parkinson's Disease Rating Scale: S&E Scale: Schwab & England Scale; NUS: Northwestern Disability Scale; WAIS: Wechler Adult Intelligence Scale; PASAT: Paced Auditory Serial Addition Task; WCST: Wisconsin Card Sorting Test; VVCALT: Visual-Visual Consitional Associative Learning Test; MAHT: Modified Alice Heim Test; CAMCOG: Cambridge Cognitive Examination; CAF: Clinician Assessment of Fluctuation Scale

***Table* 2.2. Summarizing the Kinetics and Clinical Associations of Specific Neuropsychiatric Symptoms**

Neuropsychiatric PD symptom	Kinetics of fluctuations	Related to PD medications?	Related to fluctuating motor symptoms?
Psychosis	• Hallucinations: sudden onset, last seconds-minutes (possibly hours, in morning or evening. o *Minor*: once/week to once/month o *Major*: several times/day, <5 times/week. • Delusions: sudden in onset	Yes, but not always	Hallucinations: ON>OFF Delusions: OFF>ON
Anxiety	• Occurs in the early morning, duration is about 3 hours, with high intraindividual variability for severity and frequency • May occur one hour before onset of dyskinetic ON state	Yes, but not always Significant rebound anxiety after about two hours from medication intake.	OFF>ON Duration of anxiety longer than motor fluctuation period.
Apathy	• Unclear; Impersistent in trajectory	Yes, but not always	OFF>ON
Depression	• May occur one hour before onset of dyskinetic ON state	Yes, but not always	OFF>ON Duration of depression longer than motor fluctuation period.
Fatigue	• Tends to peak in the evening, but relatively stable diurnal frequencies otherwise.	Yes, but not always	OFF>ON
Cognition	• PD-MCI may revert back to a normal cognition during the course of PD, but may still decline to PD dementia later. • Concentration and attention mainly affected – slow simple and choice reaction times as well as vigilance accuracy.	Yes, but not always, and contradictory response from selected cognitive domains	OFF>ON

PD-MCI: Mild cognitive impairment in Parkinson's disease

2.8 Conclusion

Neuropsychiatric fluctuations frequently parallel PD motor fluctuations, although these can also occur independently. With the generally adverse impact of neuropsychiatric fluctuations (particularly that of anxiety, depression, and fatigue) on quality of life in PwPs (Ray Chaudhuri et al., 2018; Storch et al., 2013), its identification and management become more crucial than ever, given the therapeutic implications. The underlying pathogenic mechanism of neuropsychiatric fluctuations remain unclear, although with improvement of neuropsychiatric fluctuations in line with continuous dopaminergic therapy (Table 2.1), pulsatile dopaminergic dysfunction may be part of the underlying cause, similar to PD motor fluctuations. Specific symptomatic treatment would be the first-line option for non-fluctuating NMS, while fluctuating symptoms may be treated by solely adjusting dopaminergic therapies (Chaudhuri & Schapira, 2009). Most of the studies are observational in nature. To date, well-designed double-blind trials with a main focus on psychiatric fluctuations in PD have yet to be conducted.

Chapter 3

A systematic review of the use of psychosis measurement scales in Parkinson's and assessment of their validity & reliability

3.1 Introduction

As part of measurement-based healthcare, quality quantification of psychosis severity paves a way to assess risk, monitor prognosis, track response to treatment, and estimate burden of care for both patients and caregivers across a wide range of neurodegenerative diseases, aside from serving as a key platform for advancing research and clinical care. Precise psychosis severity rating scales provide detailed information from as early as pre-prodromal disease stages and can also serve as prognostic tools. These instruments are also useful in gauging the link between psychosis severity with healthcare costs and delivery in the clinical setting. The recognition that the severity of psychosis is associated with cognitive (Peters et al., 2015) and functional decline(Peters et al., 2015; Scarmeas et al., 2005), as well as to nursing-home placement (Aarsland et al., 2000; Scarmeas et al., 2005; Steele et al., 1990), underlined the need for rapid identification of psychotic symptoms and for tools to provide steadfast monitoring throughout the course of treatment.

As outlined in the introductory chapter, one of the main objectives of this thesis was to explore the clinical profile of psychosis in Parkinson's disease (PD), with the information leading to the development of a comprehensive one-stop assessment of psychosis severity specific to PD later in chapter 6.

Imprecise operational definitions of psychosis in PD, and utilization of assessment methods with questionable reliability and validity have undermined investigations into this area. Currently, there are several instruments of psychosis severity in active use, but the comparative

characteristics of each are generally diverse and inadequate in encompassing the range and nature of psychotic features in PD.

To our knowledge, the present practice thus far involved adapting and applying pre-existing psychosis rating scales meant for patients with primary psychotic disorders like schizophrenia (SCZ), with very few of *de novo* design. Of these, not many have been validated amongst patients with that disease in question. Comparison of scales is particularly challenging because many were created for other purposes (screening or diagnosis), in a myriad of clinical settings and users, and incorporating different features or behaviours. In addition, many scale reviews did not focus on clinimetric properties (the science of clinical measurements) of the instruments involved, which are important for their ability to detect the presence of psychosis, evaluate its severity, and track the effects of treatment.

There has not been a referential tool for rating psychosis severity in PD that can be said to truly capture the complete phenomenology of psychosis to date. A systematic review by The Movement Disorders Society Task Force on Rating Scales have offered recommendations on which psychosis scales (screening or diagnostic) were most appropriate (Fernandez et al., 2008) for use. However, this review was conducted more than a decade ago, with scarcely any updated ones since (Fernandez, 2013). Meanwhile, research into PD psychosis has much advanced, with the advent of new rating scales (*Table* 3.1), and fresh validation studies on existing ones. There is a need for updated work, particularly to address the clinimetric properties of these instruments.

3.2 Aims and Objectives

Under the circumstances, I conducted a literature review aiming to assess the psychometric properties of existing psychosis severity instruments used in PD, in preparation to develop an appropriate scale.

For this review, psychosis severity is defined as the cumulative intensity of multi-domain symptoms associated with PD psychosis, and psychosis severity instruments defined as those which track these symptoms on a continuous, quantitative scale.

My main objective was to present a comprehensive systematic review of psychosis severity instruments used in PD identified from extant literature through 2021. My secondary aim was to assess the psychometrics of the most used psychosis rating scales in PD, leading to suitable recommendations for the most appropriate psychosis severity scales specific for PD.

3.3 Contributions and Collaborations

I wrote the entire manuscript with revisions after input from other co-authors.

3.4 Methods

3.4.1 Search Strategy

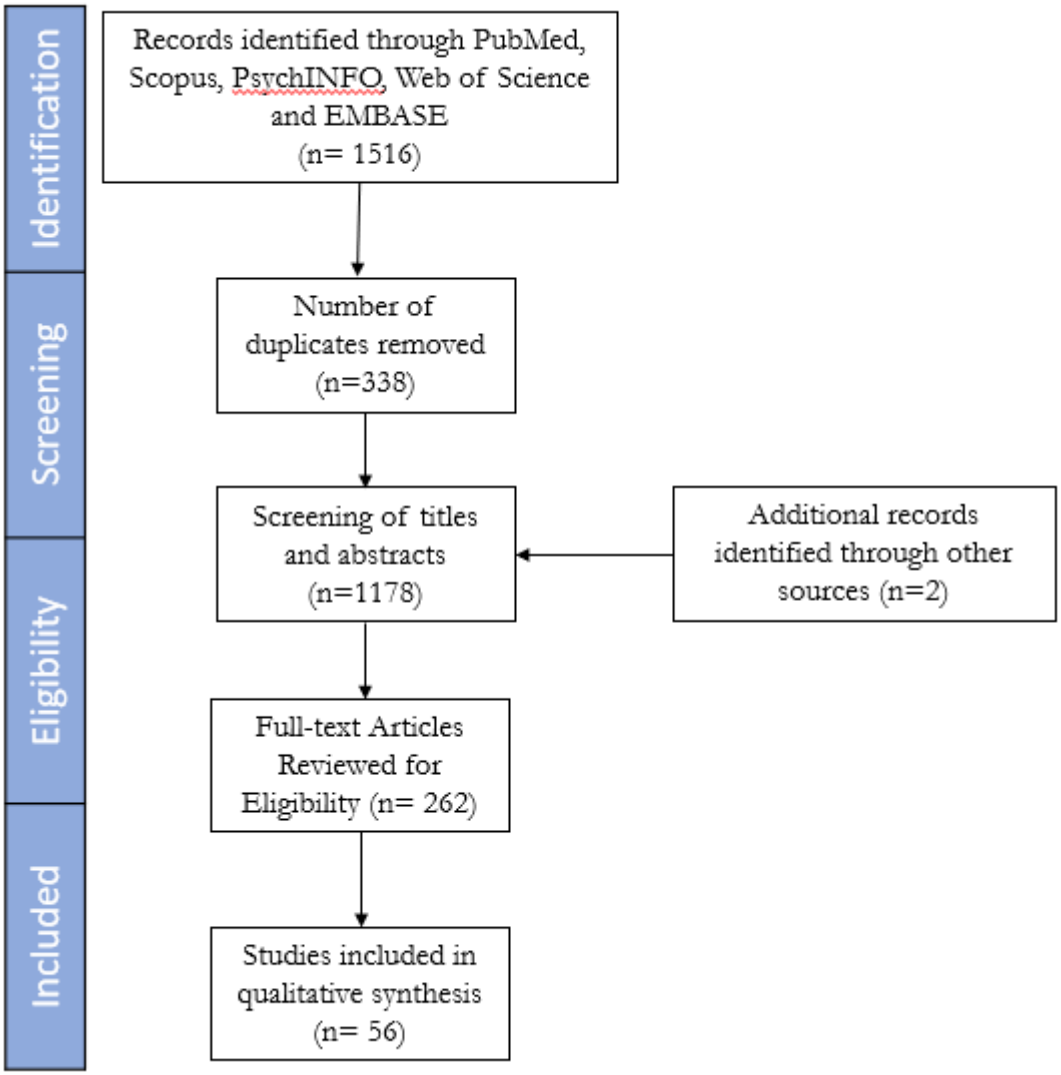
The initial approach was informed by the PRISMA(Preferred Reporting Items for Systematic Reviews and Meta-analysis)(Liberati et al., 2009) guidelines.

Articles were identified by assembling results of a comprehensive search across 3 databases: PubMed (Medline), Embase, and PsychINFO. The PubMed advanced search engine was used to search Medline (from 1950); OvidSP was used to individually search Embase (from 1974) and PsychINFO (from 1806). We tried to identify in a comprehensive manner all measures used to operationalize psychosis severity in PD as aforementioned. Our searches were inclusive through February 22, 2022. Search strategies were specifically tailored for the database they were being applied to.

For a more comprehensive search and to minimise bias, we conducted a hand review of the reference lists of all articles identified (backward snowballing), as well as through all subsequent

citations (forward snowballing). We augmented our strategy by appraising previously published reviews of psychosis instruments.

***Figure* 3.1: PRISMA Diagram on the inclusion of studies**



3.4.2 Selection Criteria

Identified articles underwent an initial screening based on title and abstract. Duplicates were then removed and any manuscript that did not meet criteria excluded. The remaining articles underwent

full text screening for final eligibility by a panel of three independent reviewers (including myself). The references of these studies were then examined to retrieve the original validation studies for the selected scales.

3.4.3 Eligibility Screening

To avoid unwarranted exclusion of any validation studies, we limited the stringency of our inclusion criteria to the following:

(i) The scale has been applied in studies involving patients diagnosed with PD according to established international criteria.

(ii) An appropriate measure of validity/reliability had been utilised; with quantitative data acquired for scale evaluation.

(iii) The instrument was required to use numeric ratings of psychosis severity or intensity of psychotic symptoms.

3.4.4 Data Extraction

Upon selection, the following data was extracted from the articles: author, year of publication, index scale (scale being validated), reference scale (scale compared against index scale), and quantitative data on four outcome measures- internal consistency, inter-rater reliability, test-retest reliability, and validity.

Not all studies had evaluated all four outcome measures mentioned above. For example, some validation studies did not compare index scale performance against a reference scale. In these cases, the data of such studies was included for comparison of reliability, but not for validity.

3.4.5 Quality and Risk-of-Bias Assessment

The QUADAS-2 (Whiting et al., 2011) was used for the quality and risk of bias assessment of the studies that met our eligibility criteria. This tool was utilised as it has been specifically designed and recommended for diagnostic accuracy studies. The *Robvis* tool (https://www.riskofbias.info/welcome/robvis-visualization-tool) was used to apply the QUADAS-2 and generate a graphical result.

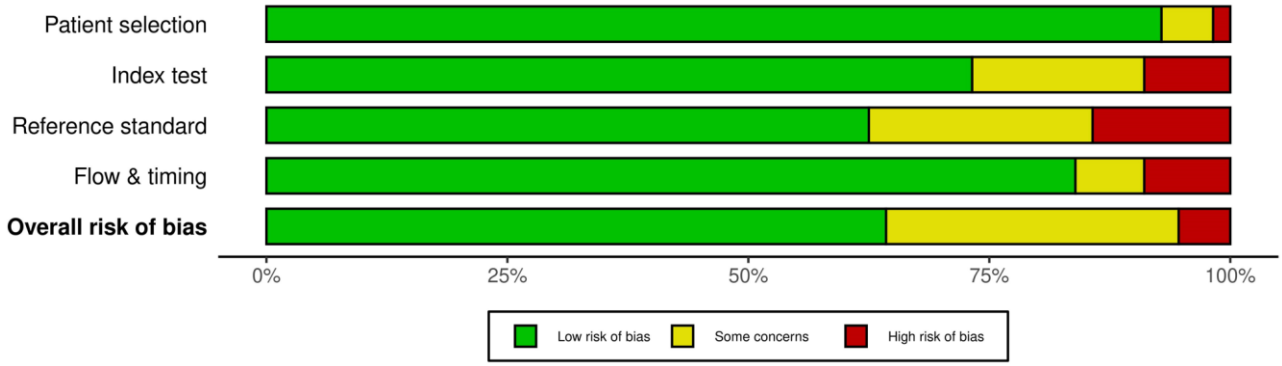
The QUADAS-2 consists of 4 domains assessing patient selection, index test, reference standard, and flow and timing. Each domain is assessed in terms of risk of bias. This tool allows for signalling questions to be tailored according to the scope of the systematic review.

The QUADAS-2 is designed specifically for diagnostic accuracy tests, involving an index test compared against an existing gold standard reference test, which is lacking in the field of evaluating PD psychosis. Therefore, some of the signalling questions of the QUADAS-2 Tool could not be appropriately answered for certain studies. However, at the time that this academic project was conceptualised in 2017, this was the tool recommended for use and this is therefore implemented.

3.5 Results

An overview of article selection has been summarized in the PRISMA diagram (*Figure* 3.1). A total of 56 validation studies were included and analysed in this systematic review. The characteristics of these studies are summarized in *Table* 3.1. As I wished to complement the work of Fernandez et. al, and not duplicate it, this review will update the characteristics of some of the scales already discussed (*Table* 3.1), as well as elaborate in more detail on the scales devised after 2008.

Figure 3.2a Summary Plot using the QUADAS-2



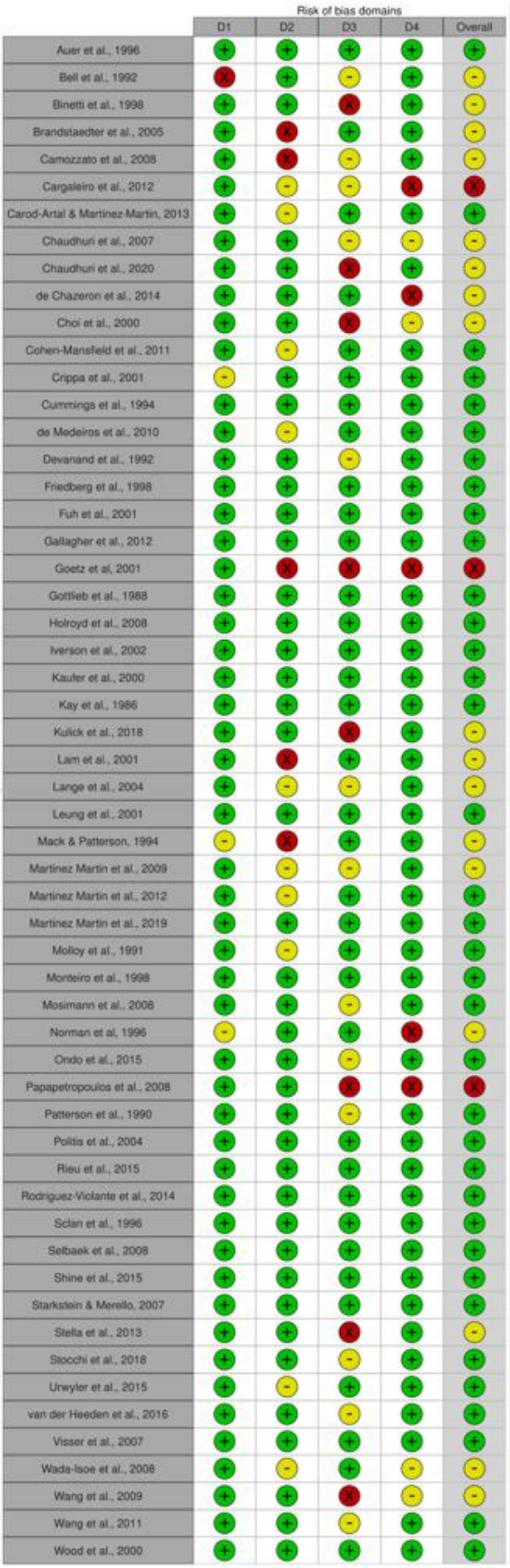


Figure 3.2b. The Risk of Bias table using the QUADAS-2

Domains:
D1: Patient selection.
D2: Index test.
D3: Reference standard.
D4: Flow & timing.

Judgement
High
Some concerns
Low

3.5.1 The Non-Motor Symptom Scale (NMSS)

The NMSS, developed and validated in 2007, is a 30-item rater-administered scale which provides a thorough and detailed assessment of non-motor symptoms in PD (Chaudhuri et al., 2007). It includes the following 9 domains: cardiovascular/falls, sleep/fatigue, mood/cognition, perceptual problems, attention/memory, gastrointestinal, urinary, sexual function, and miscellaneous, with translations into several languages. The whole scale takes 10 to 15 minutes to complete.

The NMSS burden scores (Chaudhuri et al., 2013) were marked as such :

(i) No NMS burden – NMSS score of 0;

(ii) Mild – Scores 1-20;

(iii) Moderate – NMSS scores 21-40;

(iv) Severe – NMSS scores 31-70;

(v) Very severe – NMSS scores 71 or higher

Three relevant validation studies(Carod-Artal & Martinez-Martin, 2013; Martinez-Martin et al., 2009) were retrieved, which revealed moderate correlations between the NMSS 'perceptual problems/hallucinations' domain and SCOPA-PC score (rs= 0.53), the NPI (rs= 0.40), as well as the Hallucinations/psychosis section of the MDS-UPDRS Part I (rs=0.70) (Martinez-Martin, Chaudhuri, et al., 2015).

Strengths: The NMSS assesses for non-motor burden in PD, including psychosis. It has also been shown to be able to track symptom change over time (Dafsari et al., 2019; Honig et al., 2009; Martinez-Martin, 2011). It considers the frequency and severity (distress level) of both hallucinations and delusions.

Limitations: The single items each for hallucinations and delusions of the NMSS are unable to capture the full heterogeneity of PD psychosis, with a narrow window for measuring clinical change. Interrater reliability was also never tested. There were high floor effects and low internal consistency of NMSS Domain 4 (Perceptual Problems) (Chaudhuri et al., 2007), as well as low correlation between NMSS scores and motor measurement scores (van Wamelen, Martinez-Martin, et al., 2021).

***Table* 3.1: Scales used to measure severity of psychosis among Parkinson's Disease patient population**

No.	Measure	Completion time	Form of administration	Availability	Interrater-reliability	Internal Consistency	Reproducibility (Test-retest reliability)	Association with other tools [d]	Key references
1	**BPRS**	15-30 min	Trained rater	Figure 1 of Overall et. al, 1962	Item 10 (Hallucinations) & Item 11 (Unusual thought content): 0.58 – 0.66 [b] 0.76-0.78 [c]	0.76- 0.91[a]	0.78-0.91[c]	PANSS: 0.82-0.92 SAPS: 0.88-0.92	(Crippa et al., 2001; Hedlund, 1980; Nicholson et al., 1995; Overall, 1962; Schutzwohl et al., 2003; Shafer, 2005)
2	**BEHAVE-AD BEHAVE-AD-FW E-BEHAVE-AD**	15-20 minutes	Caregiver-reported Clinician-administered	E-BEHAVE-AD: Appendix of Auer et. al, 1996	0.94-0.96 [c]	BEHAVE-AD: 0.40-0.60[c] BEHAVE-AD-FW (Paranoid & delusional ideation and Hallucinations): 0.91-0.97[c]	[c] 0.65 – 0.96 * (for 6 categories except for Hallucinations due to absence of variance in the latter)	NPI(Hallucinations and Delusions): 0.74-0.76[d]	(Cohen-Mansfield & Golander, 2011; Harwood et al., 1998; Monteiro et al., 2001; Monteiro et al., 1998; Patterson et al., 1990; Reisberg et al., 1987)
3	**NPI – Delusions & Hallucinations sections**	15-30 min (whole scale) 3-5 min (delusions and Hallucinations sections)	Caregiver	Copyrighted	0.96 – 1.00 [c]	NPI-10: 0.76-0.88[a] C-NPI-12: 0.69 – 0.78[a] H-NPI-10: 0.76[a] K-NPI-Q: 0.85[a] N-NPI-NH: 0.83[a]	NPI-10: 0.80-0.98[c] NPI-12: 0.79-0.86[c] C-NPI-12: 0.94-0.96[c] BP-NPI-12: 0.71-0.82[c]	BEHAVE-AD: 0.74-0.76 H-BPRS : 0.602	(Choi et al., 2000; Cummings, 2020; Cummings, 1997; Cummings et al., 1994; Kaufer et al., 1998; Kaufer et al., 2000; Leung et al., 2001)

						BP-NPI-12: 0.70[a]	NPI-Q: 0.80[c] NPI-NH: 0.76[c] K-NPI-Q: 0.635[c]		
4	**SAPS** **SAPS-PD** **eSAPS-PD**	>30 min	Rater	SAPS-PD described in the website which needs paid subscription for access to the scale: https://eprovide.mapi-trust.org/instruments/scale-for-assessment-of-positive-symptoms-for-parkinson-s-disease-psychosis eSAPS-PD: Appendix A of Kulick et. al, 2018	SAPS: 0.84[c]	SAPS: 0.48[a]	SAPS: 0.54[c] SAPS-PD: 0.54-0.64[c]	PANSS Positive (SAPS): 0.31-0.89 BPRS (SAPS): 0.89-0.98	(Andreasen, 1984; Kulick et al., 2018; Norman et al., 1996; Voss et al., 2013)
5	**PANSS**	30-40 min	Trained Rater	Available online	0.82[c]	0.73-0.87[a]	0.77-0.89[c]	SAPS: 0.77	(Kay, 1990; Kay et al., 1987)
6	**DBRI– 6 questions on psychosis**	5-15 min	Caregiver	Appendix of International Psychogeriatric Association, 1996, webpage.	Nil	Nil	0.75[c]	BPC: 0.69-0.73	(International Psychogeriatric Association, 1996; Molloy et al., 1991)
7	**TUHARS**	5-15 min[¥]	Rater	Appendix of Wada-Isoe et. al, 2008.	Nil	0.88	Nil	PPQ Section B: 0.965	(Wada-Isoe et al., 2008)
8	**NEVHI**	8-10 min	Rater	Found in Mosimann et. al, 2008	Nil	0.71	Nil	I-NEVHI vs NPI-4 : 0.56 MDS-UPDRS 1.2: 0.57	(Holiday et al., 2017; Mosimann et al., 2008)

								NPI-VH: 0.10	
9	**PPQ**	5-15 min	Rater	Appendix of Brandstaedter et.al, 2005.	Nil	0.68[a]	Nil	BPRS-E (Portuguese): 0.36	(Brandstaedter et al., 2005; Cargaleiro et al., 2012)
10	**UM-PDHQ**	5-15 min	Rater	Appendix of Papapetropoulos et. al, 2008.	Nil	Nil	Nil	Nil	(Papapetropoulos et al., 2008)
11	**Baylor Hallucination Questionnaire (Updated)**	10 min	Rater	Figure 1 of Ondo et. al, 2015	0.87[c]	Nil	0.86[c]	Nil	(Ondo et al., 2005) (Ondo et al., 2015)
12	**Rush Hallucination Inventory**	>30 min	Rater	Nil	Nil	Nil	Nil	Nil	(Goetz et al., 2001)
13	**PPRS**	5-15 min	Rater	Appendix I of Friedberg. al, 1998.	0.80-0.99[d]	0.71[a]	0.06-0.70 [d]	BPRS: 0.92	(Friedberg et al., 1998)
14	**SEND-PD (Psychosis subscale)**	10-15min[¥]	Rater	Appendix I of Martinez-Martin et. al, 2012	Nil	0.73[a]	Nil	SCOPA-PC: 0.53-0.66 MDS-UPDRS 1.2: Hallucinations (Item 4): 0.92 Total psychotic subscale: 0.64	(Martinez-Martin et al., 2012; Rodriguez-Violante et al., 2014)
15	**SCOPA-PC [First three questions]**	5-10 min	Rater	Appendix of Visser et. al, 2007	Hallucinations : 0.68[b] Illusions : 0.88[b] Paranoid ideation : 0.92[b]	0.68[a]	0.71-0.80[c]	NPI (hallucinations and paranoid ideation) : 0.34-0.68 *	(Visser et al., 2007)

					Total score : 0.95[c]			NMSS(perceptual problems): 0.53	
16	**NMSS**	10-15 min (whole scale)	Rater	Figure 1 of Chaudhuri et. al, 2007.	Nil	0.37-0.44[a]	0.77-0.86[c]	NPI: 0.40 MDS-UPDRS 1.2: 0.70 SCOPA-PC: 0.53	(Chaudhuri et al., 2007; van Wamelen, Martinez-Martin, et al., 2021)
17	**MDS-UPDRS 1.2**	10 minutes	Rater	Published on Movement Disorder Society (MDS) website Page 2143 of Goetz et.al, 2008	Nil	0.79-0.85[a]	0.92[c]	SAPS (hallucinations& delusions score): 0.65 NMSS: 0.70 PPRS: 0.86 UPDRS Part I: 0.76	(Barrett et al., 2017; Gallagher et al., 2012; Goetz et al., 2008; Martinez-Martin et al., 2013)
18	**PSAS**	5-15 min[¥]	Rater	Appendix A (supplementary material) of de Chazeron et. al, 2015.	0.74 – 1.00 [b]	0.49 - 0.77[d]	0.62 - 0.87 [b]	UPDRS part 1 item 2: [d] 0.10 – 0.70* Total score : 0.44	(de Chazeron et al., 2015)
19	**PsycH-Q**	10 min	Self	Available from the authors of Shine et. al 2015 upon request	Nil	0.696-0.923[a]	0.928[b] (0.869 - 0.961) over 2.2 months	SCOPA-PC (delusions): 0.34* SCOPA-PC (hallucinations) : 0.64* NPI-Q (Hallucinations): 0.37 * NPI-Q (Delusions): 0.51* PPQ (Hallucinations):	(Shine et al., 2015)

								0.58 * PPQ (delusions): 0.38*	
20	**ASBPD Part III (Hyperdopaminergic) Item 2**	¥15-20min for Part III Item 2 (1 hour for the whole scale)	Trained Rater	Supplementary information of Rieu et. al, 2015.	0.65[b]	Psychotic symptoms: 0.68[a]	0.68[b]	PANSS (hallucinations): 0.84 PANSS (delusions): 0.43	(Rieu et al., 2015)
21	**SENS-PD**	20 min	50% rater; 50% Self	Supplement 2 file of van der Heeden et. al, 2016.	Nil	0.67[a] (Psychotic symptoms section) 0.78-0.84[a] (whole scale)	0.40-0.87[b]	MDS-UPDRS (non-motor section): 0.64	(van der Heeden et al., 2016)
22	**PDCS**	15-20 min	Rater	Figure 1 of Stocchi F. et. al, 2018 Free for download from https://www.parkinsoneurope.org/get-involved/the-parkinsons-disease-composite-scale/	Hallucinations (Item 12) : 0.79 [b] Non-motor section : 0.96[c]	0.57 [a] 0.49 [d]	0.95 – 0.99[c]	MDS-UPDRS 1.2: 0.73	(Balestrino et al., 2019; Martinez-Martin et al., 2019; Stocchi et al., 2018)
23	**MDS-NMS (Psychosis Domain D)**	15 - 40 min (Whole Scale)	Trained Rater	Published on Movement Disorder Society (MDS) website. Appendix of Chaudhuri et. al, 2019.	0.98 – 1.00[b] 0.99[c]	0.72[a]	0.26-0.68[b] 0.66[c]	MDS-UPDRS 1.2: 0.49 NMSS(Hallucination/ perceptual): 0.57	(Chaudhuri et al., 2020; Martinez-Martin et al., 2020)

[a] : Cronbach's alpha; [b]: k_w (weighted kappa) ; [c] : Intraclass correlation coefficient; [d] : Spearman's rho; * $p<0.05$; : ¥ : estimated by author (YM Wan)

PD: Parkinson's disease; ASBPD: Ardouin Scale of Behaviour in Parkinson's Disease; BPC: Behaviour Problem Checklist; BPRS: Brief Psychiatric Rating Scale; H-BPRS: Hellenic translated Brief Psychiatric Rating Scale; BEHAVE-AD : Behavioural pathology in Alzheimer's disease rating scale; E-BEHAVE-AD: Empirical Behavioural pathology in Alzheimer's disease rating scale; BEHAVE-AD-FW : Behavioural pathology in Alzheimer's disease rating scale Frequency-Weighted Severity Scale; NPI: Neuropsychiatric Inventory; BP-NPI: Brazilian Portuguese Neuropsychiatric Inventory; NPI-10: Neuropsychiatric Inventory (10 items); NPI-12 : Neuropsychiatric Inventory (12 items); NPI-4 : Neuropsychiatric Inventory (4 items); NPI-NH : Neuropsychiatric Inventory Nursing-Home; NPI-Q: Neuropsychiatric Inventory Questionnaire; BP-NPI-12: Brazilian Portuguese Neuropsychiatric Inventory (12 items); C-NPI-12: Chinese Neuropsychiatric Inventory (12 items); H-NPI-10: Hellenic Neuropsychiatric Inventory (10 items); K-NPI-Q: Korean Neuropsychiatric Inventory Questionnaire; NEVHI : North-East Visual Hallucinations Interview; I-NEVHI : Informant-based North-East Visual Hallucinations Interview; MDS-UPDRS 1.2: United Parkinson's Disease Rating Scale Part I item 1.2:Hallucinations and Psychosis (Movement Disorder Society sponsored revision); DBRI : Dysfunctional Behaviour Rating Instrument; NMSS : Non-Motor Symptoms Scale; PANSS: Positive and Negative Symptom Scale; PPQ: Parkinson Psychosis Questionnaire; PPRS : Parkinson Psychosis Rating Scale; PSAS : Psycho-Sensory hallucinations Scale; PsycH-Q : Psychosis and Hallucinations Questionnaire; SCOPA-PC : Scales for Outcomes in Parkinson's Disease – Psychiatric Complications; SENS-PD : SEverity of predominantly Nondopaminergic Symptoms in PD; TUHARS : Tottori University Hallucination Rating Scale; UM-PDHQ : University of Miami Parkinson's disease Hallucinations Questionnaire

3.5.2 The Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS)

The MDS-UPDRS, adapted from the well-known UPDRS in 2006, is a structured mixed-administered scale with a total summed score, consisting of the following four sections:

(i) I - Nonmotor Experiences of Daily Living;

(ii) II - Motor Experiences of Daily Living;

(iii) III- Motor Examination;

(iv) IV - Motor Complications.

All items have five response options with uniform anchors of 0 – normal, 1 – slight, 2 – mild, 3 – moderate, 4 – severe. Psychosis was measured via the rater-administered single question 1.2 Hallucinations and Psychosis, with the following response options : 0 - No hallucinations or psychotic behaviour; 1 – Illusions or non-formed hallucinations, but patient recognizes them without loss of insight; 2 – Formed hallucinations independent of environmental stimuli and no loss of insight; 3 – Formed hallucinations with loss of insight; 4 – Patient has delusions or paranoia. The whole scale takes approximately 30 minutes to complete, with about 10 minutes for each section.

MDS-UPDRS Part I showed low floor and ceiling effects. Internal consistency is good (α for Part I = 0.79). Interrater reliability was not tested. Test-retest reliability was excellent (ICC 0.77-0.86). Convergent validity with the SAPS, NMSS, PPRS, and UPDRS Part I showed moderate-to-high correlations.

Strengths: The MDS-UPDRS question 1.2 is brief and easy to administer.

Limitations: The single question can only serve for screening purposes, and not for quantification of disease severity. It is not sufficient to capture the full spectrum of psychosis in PD.

3.5.3 The Scale for Evaluation of Neuropsychiatric Disorders in Parkinson's Disease (SEND-PD)

This questionnaire is composed of 12 items for interview categorised into 3 domains (Psychotic symptoms, Mood/Apathy, Impulse control disorders), with each severity item scoring from 0 (absent) to 4 (very severe). The domain of psychotic symptoms is defined by four questions, as follows:

1. Irritability—Aggressiveness: does he/she usually proffer threats or express him/herself in a violent manner?

2. Delusions: does he/she refer ideas of events which are not really happening, such as being cheated or tricked, being a victim of violence or being followed or even chased?

3. Misidentification: does he/she mistake some persons for others, say some person is a different one, or assign false identities to people surrounding him or her?

4. Hallucinations: does he/she perceive things that are not happening or are not real, such as hearing voices, seeing inexistent objects, or being touched?

Internal consistency was good for the SEND-PD, although no further data on interrater- or test-retest reliability was available.

Strengths: The SEND-PD is a brief and PD-specific scale, which encompasses hallucinations/ delusions, and includes irritability-aggressiveness.

Limitations: Insufficient psychometric data for a true recommendation of this scale. The SEND-PD also does not capture minor hallucinations, and thus fails to depict the full phenomenology of PD psychosis.

3.5.4 The SCales for Outcomes in Parkinson's Disease-Psychiatric Complications (SCOPA-PC)

Originally developed in Dutch, the SCOPA-PC is a rater- administered semi-structured questionnaire that was adapted from the Parkinson Psychosis Rating Scale (PPRS), addressing both psychotic and compulsive complications in PD. The SCOPA-PC consists of seven items addressing perceptual (5 items) and compulsive behaviour (2 items): "Hallucinations," "Illusions," "Paranoid ideation," "Altered dream phenomena," "Confusion," "Sexual preoccupation," and "Compulsive behaviour", with each item rated on a scale from 0 (no symptoms) to 3 (severe symptoms). The whole scale can be completed in approximately 5-10 minutes. For the item denoting 'Hallucinations' and 'Illusions/Misidentification of persons', the following were the response anchors: 0 – absent; 1 – mild, complete insight, non-threatening; 2 – moderate, partial insight, can be convinced, may be threatening; 3 – severe, no insight, cannot be convinced, may be associated with heightened emotional tone, agitation, and aggression. For the item describing 'Delusions', the following were the response options: 0 – absent; 1 – mild, associated with suspiciousness; 2 – moderate, associated with tension and excitement; 3 – severe, accusations of persons, aggression, and/or lack of cooperation (i.e. refusal to eat and/or take medication).

Overall internal consistency is moderate ($\alpha = 0.68$). Interrater reliability for the items on hallucinations and paranoid ideation were good. Test-retest reliability was excellent (ICC 0.71-0.80). Convergent validity with the corresponding elements of NPI and NMSS showed low-moderate correlations.

Strengths: The SCOPA-PC is a brief and PD-specific scale. It allows for measurement of change over time. Insight is also accounted for in this scale.

Limitations: Like the PPRS, the single items for hallucinations and delusions fail to completely depict the phenomenology of PD psychosis. The item on 'Illusions' was also peculiarly worded to include misidentification of persons which may be misinterpreted to include delusions of misidentification common in PD that did not seem to be the developers' intent. Finally, the anchors requested for multiple condensed questions which may limit the characteristics of the psychotic symptom elicited.

3.5.5 The Psycho-Sensory hAllucinations Scale (PSAS)

Derived in 2007 from existing scales such as the Psychotic Symptom Rating Scales (PSYRATS) (Haddock et al., 1999), the Rush Hallucination Inventory (Pappert et al., 1999), and the Tottori University Hallucination Rating Scale (TUHARS)(Wada-Isoe et al., 2008), the PSAS defined four domains (auditory, visual, olfactory, gustatory, cenesthetic hallucination modalities) with non-overlapping descriptive questions classified into firstly the presence or absence of hallucinations, and then a qualitative as well as quantitative part later (frequency, duration, unpleasant or negative aspects, conviction, impact, control), with the addition of 'sound intensity' only for auditory hallucinations. The quantitative section was based on the same structure as the PSYRATS with a 5-level severity subscale except for 'conviction' item (from 0 – absent to 4 - severe or extreme). An additional item on 'guardian angel' (which was an early description of *presence* hallucination) was added into the PSAS but there was no quantitative option anchored due to the nature of this symptom according to the authors (Visser et al., 2007).

Overall internal consistency is good (standard; $r \geq 0.20$). Interrater reliability for this scale and test-retest reliability was good (*Table* 3.1). Convergent validity with the UPDRS part 1 item 2 was good for olfactory and gustatory hallucinations (r=0.70, p<0.05), moderate for auditory (r=0.43, p<0.05) and visual hallucinations (r=0.33, p<0.05), but very low for cenesthetic hallucinations (r=0.10, p=0.77).

Strengths: The PSAS is one of the few scales validated amongst PD patients specifically to evaluate psychotic symptoms. The navigatory instructions provided were clear and comprehensive, and the scale even takes into account the fluctuating nature of hallucinations.

Limitations: The PSAS does not consider passage hallucinations, likely due to its early development prior to the cascade of literature on minor hallucinations, nor does it assess delusions.

3.5.6 The Psychosis and Hallucinations Questionnaire (PsycH-Q)

The PsycH-Q is a 20-item self-reported scale designed to catalogue hallucinatory phenotypes in PD, which has been categorised into five categories : visual misperceptions (including presence and passage hallucinations), sensory misperceptions, disordered thought, attentional dysfunction, and sleep impairment (Shine et al., 2015). If positive answers are obtained on one or more of the first 10 questions of Section I, a series of dichotomous (Yes/No) sub-questions are then administered, that assessed whether: (1) symptoms were experienced before sleep; (2) experiences were perceived as real and/or the patient could be convinced otherwise; (3) experiences were frightening; and (4) symptoms were experienced outside the past month. The scale could apparently be completed within 10 minutes without assistance from caregiver (Muller et al., 2018).

Overall internal consistency and test-retest reliability were excellent (*Table* 3.1). Convergent validity was moderate for hallucinations and low for delusions with the SCOPA-PC, low for hallucinations and moderate for delusions with the NPI-Q, and moderate for hallucinations and low for delusions with the PPQ (*Table* 3.1).

Strengths: The PsycH-Q is one of very few validated self-reported psychosis evaluation instruments amongst a majority of rater-administered scales. There was an informant version

developed later in 2018 (Muller et al., 2018) .It is also one of the few scales developed specifically to measure psychotic features alone in PD.

Limitations: The PsycH-Q does not capture the full continuum of PD psychosis. There was also the addition of a question on "corner vision" hallucination which may be part of the 'passage hallucination' phenomenology in current literature. All three questions on delusions pertained to persecutory delusions only, without consideration of other types of delusions. Interrater reliability has not been tested. There was also low concordance between the informant-based and self-rated versions of the PsycH-Q.

3.5.7 The Ardouin Scale of Behavior in Parkinson's Disease (ASBPD)

Consisting of 21 items, the ASBPD is a rater-administered scale designed to assess three symptom domains over the preceding month:

(i) Part I – 'Hypodopaminergic disorders, including depression, anxiety, irritability, and aggressiveness, hyperemotionality, and apathy.

(ii) Part II – 'Non-motor fluctuations'

(iii) Part III – 'Hyperdopaminergic Behaviours", including psychotic symptoms, hypomania, and impulse control disorders.

On average, the entire scale takes an hour to complete, depending on the extent of the behaviour disorder. Guiding instructions are provided.

Overall internal consistency, interrater, and test-retest reliability were good (*Table* 3.1). Convergent validity ranged from moderate (for delusions) to good (for hallucinations) (*Table* 3.1).

Strengths: The ASBPD has acceptable psychometric properties and includes all the major hallucinations as well as many types of delusions.

Limitations: Despite its comprehensiveness, the ASBPD does not capture minor hallucinations. Medical jargon noted for the suggested questions to elicit delusions (i.e. 'grandiose' behaviour, 'hypochondriasis') may increase patient's confusion. A trained or experienced rater is necessary for administration of this scale.

3.5.8 The Severity of Non-dopaminergic Symptoms in Parkinson's Disease (SENS-PD)

The SENS-PD comprises 18 items - three from each of six related domains: autonomic dysfunction, psychotic symptoms, cognitive impairment, Postural-Instability-and-Gait-Difficulty (PIGD), excessive daytime sleepiness, depression. Half of the items are rater-administered (timeframe of completion: 15 minutes) while the other half are self-reported (timeframe of completion: 5 minutes). Scoring range is 0 – 54.

Internal consistency was moderate for the Psychotic Symptoms domain (*Table* 3.1). Test-retest reliability was largely acceptable, although gleaned from development process of different scales for the items in SENS-PD (Marinus et al., 2002; Marinus et al., 2004; Marinus et al., 2003; Visser et al., 2007). Convergent validity ranged from moderate (for delusions) to good (for hallucinations) (*Table* 3.1) with the MDS-UPDRS (non-motor section).

Strengths: Like the SCOPA-PC, the SENS-PD is a brief and PD-specific measurement. It allows for measurement of change over time. Insight is also accounted for in this scale.

Limitations: The single items for hallucinations and delusions fail to completely depict the phenomenology of PD psychosis. The item on 'Illusions' was also peculiarly worded to include misidentification of persons which may be misinterpreted to include delusions of misidentification common in PD that did not seem to be the developers' intent. Finally, the anchors requested for

multiple condensed questions which may limit the characteristics of the psychotic symptom elicited.

3.5.9 The Parkinson's Disease (PD) Composite Scale (PDCS)

The PDCS was developed for rapid appraisal of disease severity and consists of 17 items categorized into four domains (motor symptoms, non-motor symptoms, treatment complications, and disability), with each item presenting five severity options (Absent, Mild, Moderate, Severe, Very Severe). Non-motor symptoms were evaluated over the preceding two weeks. Absence of symptom is scored 0 for all items, whereas severity levels have a differential scoring scale according to the relative importance and impact of each item on the patient's condition, with some items scoring 0 to 4 and others 0 to 7. A total score can be measured for each domain by summing its component parts, and a total score for the PDCS measured by summing the domain scores.

Hallucinations (Item 12) was denoted as such: 0 - absent; 4 – Mild (Vivid dreaming or Hallucinations); 5 – Moderate ("Benign" hallucinations with retained insight); 6 - Severe (Occasional to frequent hallucinations or delusions, without insight, could interfere with daily activities); 7 – Very Severe (Persistent hallucinations, delusions, or florid psychosis, not able to care for self).

The PDCS has weak internal consistency but excellent test-retest reliability. There was high convergent validity with the corresponding scores of the MDS-UPDRS Part I.

Strengths: The PDCS is a brief and PD-specific measurement. It allows for measurement of change over time and is best suited to a clinical setting where swift decision-making is paramount. Insight is also accounted for in this scale.

Limitations: The single item for psychosis fails to completely depict the phenomenology of PD psychosis. The multiple condensed questions in the response options may limit the characteristics of the psychotic symptom elicited.

3.5.10 The International Parkinson and Movement Disorder Society Non-Motor Rating Scale (MDS-NMS)

Measuring 13 non-motor domains with 52 items, the MDS-NMS is a PD-specific rater-administered instrument assessing within a timeframe of the preceding two weeks. Each item is to be scored twice based on five options, for frequency (0 – never to 4 – majority of the time) and severity (0 – not present to 4 – severe). Each item was phrased as a question regarding the presence of symptom, with specific instructions provided. Item score was calculated by the multiplication of frequency and severity, with total domain scores measured by summing the respective item scores, and a total scale score by summing the domain scores to represent total NMS burden. The total score of the scale ranged from 0 to 832. There is also an option to rate non-motor fluctuations (NMFs), although psychosis was not one of them. The entire scale takes 15-40 minutes to complete, depending on the status of the patient and the number of non-motor symptoms present. Psychosis (Subscale D) consists of 5 items as follows:

1. Sensed things or people in margin of visual field (passage or presence phenomena)?
2. Misinterpreted actual sensations? (Illusions)
3. Seen things that other people did not see (visual hallucinations)?
4. Heard, felt, tasted, or smelled things that other people did not? (auditory, tactile, gustatory, or olfactory hallucinations)
5. Believed things to be true that others did not? (e.g. delusions of persecution, jealousy, or misidentification)

There were negligible floor and ceiling effects for the MDS-NMS. Internal consistency for the Psychosis domain of the MDS-NMS (*Table* 3.1) is good. Interrater reliability was excellent. Test-retest reliability was weak, but the authors explained that the suboptimal results may be explained by the short-term fluctuations in NMSs, therefore reflecting real-world symptoms (Chaudhuri et al., 2020). There was good convergent validity with corresponding items on the MDS-UPDRS as well as NMSS.

Strengths: The MDS-NMS encompasses both minor and major hallucinations, as well as delusions. It considers the frequency and severity (distress level) of both hallucinations and delusions.

Limitations: Although the scale captures the breadth of the spectrum of PD psychosis, the multiple condensed questions within one anchor and the single item referring to delusions may limit the characteristics of the psychotic symptom elicited. There was no separation of the different types of the hallucinations other than minor and visual hallucinations, as well as the various types of delusions when scoring frequency, and degree of distress. Insight was also not assessed. In addition, the low test-retest reliability for this domain may limit its ability to track changes in PD psychosis over time.

3.5.11 The Neuropsychiatric Inventory (NPI)

Originally a 10-item scale (NPI-10) developed mainly for the assessment of neuropsychiatric psychopathology in patients with dementia (Cummings et al., 1994), the NPI was later expanded to the 12-item version (NPI-12) by adding sleep and appetite changes (Cummings, 1997). The 12-item NPI with integrated caregiver distress scale remains the most widely used version (Cummings, 2020). The interview was conducted by a trained rater with a knowledgeable caregiver. Other validated and widely used versions include the Nursing Home NPI (NPI-

NH)(Wood et al., 2000), and the Questionnaire Version (NPI-Q) (Kaufer et al., 2000), but source of information about the patient remains the informant report.

The 12 items of NPI encompass the following domains: delusions; hallucinations; agitation/aggression; depression/dysphoria; anxiety/elation/euphoria; apathy/indifference; disinhibition; irritability; aberrant motor behaviour; nighttime behaviours; and appetite/eating behaviours. A skip-question format is first deployed with screening questions to detect behavioural changes and minimize administration time, followed by more specific questions asked if there is positive endorsement of each of the 12 items. The severity and frequency of the related symptoms are independently rated on a 5-point Likert scale, and then multiplied to produce a composite score ranging from 1-12 for each subdomain, while scores of 5, 7, 10, and 11 are not possible. A separate rating of "distress caused to the caregiver," or the "occupational disruption" at the nursing home, is independently appended (Kaufer et al., 1998). A total composite score for the NPI can be calculated as a measure of general level of psychopathology (maximum of 144 for the 12-item version).

While the NPI has been used in several PD psychosis studies, it is not specific to PD and has never been formally validated in a PD population, other than in a 1999 paper by Aarsland et al (Aarsland, Larsen, Lim, et al., 1999) which reported interrater reliability for NPI-10 amongst 12 PD patients to be high (ICC=0.94) for the Hallucinations domain, as well as for the total NPI-10 score (ICC=0.93). Amongst patients with Alzheimer's disease, the NPI-12 showed adequate internal consistency (*Table 3.1*) . The test-retest reliability over two to three weeks for the 10 constituent scales and the total score of the NPI ranged from 0.51 to 0.97 for frequency of occurrence of symptoms and from 0.51 to 1.00 for ratings of the severity of symptoms. Concurrent validity was established with Behave-AD (*Table 3.1*).

While the NPI may be useful for tracking the incidence and presence of psychosis, some antipsychotic treatment studies suggest that the NPI may not be as sensitive to change in the PD population (Breier et al., 2002; Juncos et al., 2004; Marsh et al., 2001) as the Brief Psychiatric Rating Scale. This may be related to the multiplicative scoring metric, which results in non-continuous scores as symptom frequency and severity increase. In addition, there probably is a non-linear relationship between symptom severity (intensity) and frequency, and these constructs may have differential sensitivity to treatment. Clinimetric testing has been performed on the total score and not the specific subscores related to hallucinations and psychosis.

Strengths: The NPI fulfills criteria as a "Recommended" scale for rating PD psychosis, especially in the cognitively impaired population, according to the MDS Task Force (*Table S1*)(Fernandez et al., 2008). Open-ended questions for each item allow recording of behaviours not listed for a particular domain. Separation of symptom frequency from symptom severity allows tracking of frequency, incidence, prevalence, and the dynamics of psychosis phenomena over time. Ratings of other symptoms, such as agitation, and anxiety, help in the characterization of additional psychiatric phenomena that may occur with psychosis over time.

Limitations: The scale only encompasses the major hallucinations and delusions of PD psychosis and does not capture minor hallucinations in a systematic way. Other than interrater reliability in a very small sample of PD patients (Aarsland, Larsen, Lim, et al., 1999), other psychometric properties were evaluated in non-PD populations. Insight is also not assessed. Its development as an instrument to evaluate patients with dementia potentially limits its application in PD patients who are not demented. Accordingly, if the NPI is to be used in clinical studies of PD patients, the scale needs to be modified so that informant- and patient-derived information is obtained in a standardized fashion. The total score does not provide a specific index of psychosis, because other behaviours are included in the final outcome score.

3.5.12 The Schedule for Assessment of Positive Symptoms (SAPS)

Developed to evaluate the specifics of hallucinations, delusions, behavioural and thought disorders associated with psychosis, the SAPS is a rater-administered structured clinical interview encompassing 35 items in 5 domains: hallucinations (7 items), delusions (13 items), bizarre behaviour (5 items), positive formal thought dsorder (9 items), and inappropriate affect (1 item). Administration should be supplemented with information provided by the nursing-staff or other observers (Andreasen, 1984). The rater is instructed to take detailed notes of the patients' descriptions of their symptoms, and not to rate illusions or hallucinations that occur when the person is falling to or waking from sleep or in the context of an illness or medication exposure that might be associated with the presence of hallucinations. It was not meant to be a tool for measuring change. There are no specific instructions for scoring the SAPS.

The SAPS domain on hallucinations includes one item each on visual hallucinations, olfactory hallucinations, and somatic or tactile hallucinations; three items on auditory hallucinations, of which two rate certain "first rank" symptoms (such as "voices conversing" and "voices commenting," which should be rated independently of the more typical auditory hallucinations); and a global rating. Each hallucination item is assessed on a frequency spectrum (occasional to daily, with the latter rated the most severe). The total score however is based on both the frequency and the extent to which the hallucinations affected functioning.

The section on delusions includes 12 items reflecting various types of delusions (persecutory, grandiose, jealousy, guilt, religious, somatic, referential), relevant first-rank symptoms (mind-reading, thought broadcast, thought insertion, thought withdrawal) and one global delusions score. These items are evaluated by the patient's degree of conviction about the belief, the frequency with which the belief is considered, and whether it is disruptive. The global rating is rated similarly to the independent items.

The final two sections reflect a continuum of phenomena on "bizarre behaviour" and "formal thought disorder" ; the former ranging from social disinhibition to repetitive stereotyped behaviours, the latter characterizing the disruption in how ideas may be linked to one another.

Amongst patients with schizophrenia, internal consistency is weaker for the overall instrument (Cronbach's alpha 0.48) than for the four global domain scores (alpha ranging from 0.66 to 0.79)(Andreasen, 1984). Nevertheless, inter-rater reliability for the SAPS summary score is good (0.84) (Norman et al., 1996). The intra-class coefficient (ICC) is 0.94 (Malla, Norman, & Williamson, 1993). For the global domain, intra-class correlations ranged from 0.50 to 0.91(Norman et al., 1996) Test-retest reliability is weak to moderate (0.54) (Malla, Norman, & Williamson, 1993; Malla, Norman, et al., 1993). Correlations with PANSS and BPRS are consistently high.

Strengths: The SAPS is easy to administer, with a structured interview and clear anchors provided as part of the scale. Its range of assessment of the subtypes of psychosis may provide a tool for cataloguing the range of hallucinatory and delusional phenomena in PD. Studies using the SAPS in clinical trials of PD psychosis (especially the subsection scores on delusions and hallucinations) show that it is sensitive to change in response to effective treatment (Marsh et al., 2001; Parkinson Study, 1999).

Limitations: Like other scales, the SAPS was developed for use in patients with schizophrenia, not PD, so the items do not capture the minor phenomena found specifically in PD in a systematic way, rating many psychotic symptoms not typically experienced by PD patients. No psychometric properties in PD are available. The hallucination items are weighted towards the auditory modality. The scale also does not assess insight and was not designed for use in patients with dementia or cognitive impairment that limits awareness that symptoms are present. Furthermore, the anchors for scoring hallucinations are confusing to apply in PD and may not

reflect the overall severity of the phenomena, due to the dissociation of frequency and severity in the scoring metric. For example, vivid visual hallucinations with insight that occur daily and do not disrupt behaviour would score a "5" (*severe*) in this item, but it is unclear where they would be rated for the global item.

(i) SAPS-PD

This is a 9-item semi-structured clinical interview derived from the SAPS. Items were selected based on retrospective analysis of face validity and symptom frequency across four existing clinical trials amongst PD patients in literature, with a combined sample size of 538 (Voss et al., 2013). Items for which <10% of participants rated with the SAPS as moderate, marked, or severe at baseline were excluded as considered unlikely to represent typical features of PD psychosis, with the remaining item construction based on the results of principal component analyses (PCA) and exploratory factor analyses with orthogonal (varimax) rotation. Only 5 hallucination items (Visual, Somatic/tactile, Auditory, Voices conversing, Global hallucinations) and 4 delusion items (Persecutory, Jealousy, Reference, Global delusions) occurred at a frequency greater than 10%. The SAPS-PD was shown to be sensitive to clinical change (as defined by the Clinical Global Impression-Improvement (CGI-I) scale), like the original SAPS. A 2.33-point change is associated with a 1-unit change in the CGI-I, with an effect size of 0.722. Each item on the SAPS-PD is rated from 0 (no symptoms) to 5 (severe and frequent symptoms), for the highest possible score of 45, with higher scores reflecting greater illness severity. No formal psychometric analyses in PD were available, other than the structural validity and scale responsiveness as described. Aside from being shorter in terms of administration, the other limitations of SAPS as highlighted above apply to SAPS-PD.

(ii) Enhanced SAPS-PD (eSAPS-PD)

This is a 13-item structured clinical interview derived from the SAPS-PD, with additional prompts for delusions as well as olfactory, gustatory, and minor hallucinations. The scale constitutes three domains (Minor Hallucinations, Major Hallucinations, Delusions), with the first domain (Minor Hallucinations) divided into three subtypes (Illusions, Passage Hallucinations, Presence Hallucinations) to be rated independently. In a single-centre cross-sectional study of 199 PD patients (Kulick et al., 2018), the eSAPS-PD detected psychotic symptoms in more subjects (n=55, 28%), inclusive of minor phenomena, than all other assessments combined (clinical visit, UPDRS part 1, and NMS-Quest) (n=22, 11%). The study cohort comprised of primarily highly educated participants, with relatively preserved cognitive function (MoCA across the whole group ranged from 24 to 28). No formal psychometric properties in PD are available. Again, aside from being shorter in terms of administration and more comprehensive in capturing the spectrum of PDP, the other limitations of SAPS as highlighted above apply to the eSAPS-PD.

3.6 Discussion

Evaluation about psychosis has its intrinsic challenges. Foremost is the fact that a proportion of patients will have no insight into their symptoms and who tends to trivialize the matter. Therefore, "hallucinations" and "delusions" are determined by the judgement of the examiner, frequently requiring collaborative input by the family members (Ondo et al., 2015).

While this review looked at the validation studies of the available scales assessing the severity of psychosis in neurodegenerative diseases, this chapter highlights and elaborates on the ones specific to PD. The array of scales that have already been commented upon by earlier

pertinent reviews (Fernandez, 2013; Fernandez et al., 2008) is expanded and appended to this work (*Table* 3.1). To date, NPI and SAPS-PD remained two of the more commonly used instruments in assessing PD psychosis, despite the arsenal of scales now available.

Since 2008, there have been at least nine additional scales developed that could evaluate psychotic features specific to PD. Unfortunately, alongside the increase in our understanding about the unique characteristics of PD psychosis, so does the challenges in identifying or tracking this complex and diverse neuropsychiatric symptom. The literature on PD psychosis is still progressing as this chapter is written. Like what the earlier review has opined, none of the scales evaluating PD psychosis, even the ones referred to in this chapter devised after 2008, was ideal in content or all the necessary essential mechanistic and psychometric requisites. Therefore, selection of scale should depend mainly upon the objectives of assessment (Fernandez et al., 2008). Different scales may be different in certain settings as compared to others.

Among the recent instruments, only the MDS-NMS (Subscale D) has been validated with the necessary clinimetric properties in PD, appears to encompass the breadth of PD psychosis as updated in literature, and can be completed in a short period of time depending on the status of the patient, although the nature of the scale meant that the characteristics of each psychotic symptom may not be adequately elicited. Nonetheless, the **MDS-NMS** would have been listed as **Recommended**, if based on the criterion set out by the Movement Disorders Society (MDS) Task Force on Rating Scales initiatives (Fernandez et al., 2008; Leentjens et al., 2008) where:

1. *Recommended*: a scale that has been applied to PD populations; there are data on its use in clinical studies beyond the group that developed the scale; and it has been studied clinimetrically and considered valid, reliable, and sensitive to the given behaviour being assessed. Ideally this

latter criterion is met for PD psychosis specifically but can be met if strong clinimetric results are available for hallucinations and psychosis in other contexts.

2. *Suggested*: the scale has been applied to PD populations, but only one of the other criteria is fulfilled.

3. *Listed*: the scale has been applied to PD populations, but neither of the other criteria is fulfilled.

***Table* 3.2: Reasons a disease-specific psychosis tool is required in PD:**
• To capture the variable timing and nature of PD psychosis in a holistic and systematic manner.
• No existing disease-specific scale which adequately evaluating PD psychosis spectrum (Refer *Table* 3.1)
• Strong associations of PD psychosis with disease trajectory (Marinus et al., 2004)
• Differential PD psychosis symptom profiles of visual, cortical, and cognitive involvement

3.7 Conclusions

Despite the many scales which have been devised to assess psychosis in PD since the landmark MDS-commissioned review in 2008, there remains no one instrument which can be considered ideal in terms of practicality and comprehensiveness. The lack of an effective and efficient harmonious core screening battery for psychosis limits comparisons across research studies. Such a tool is essential for a holistic assessment of the patient in the delivery of personalised medicine in Parkinson's disease.

Appendix:

(i) Search strategy

Search No.	Search Command	Search No.	Search Command
1.	exp Parkinson's disease/	16.	exp scales
2.	(Parkinson?disease or parkinson?disease or parkinson*disease* or Parkinson*).tw.ot.	17.	exp instruments
3.	exp movement disorder/	18.	exp questionnaire
4.	(movement disorder* or mds).tw.ot	19.	exp inventory
5.	(PD or PD* or pd* or P.D*).tw.ot	20.	(Psychometric*assess*or psychometric*assess* or psychometric?assess* or assess* or scale* or evaluat* or inventor*).tw.ot.
6.	1 or 2 or 3 or 4 or 5	21.	or/15-20
7.	exp psychosis/	22.	6 AND 14 AND 21
8.	(Psychosi* or psychosi* or psycho?disorder or psycho?disord* or psychosi*disorder*).tw.ot.		
9.	(Psychosi* or psychosi* or psycho?disorder or psycho?disord* or psychosi*disorder*)adj5 (disease or disease* or disorder or disorder* or disord*).tw.ot.		
10.	exp hallucinations/		
11.	exp delusions/		
12.	(Hallucin*or hallucin* or hallucin?).tw.ot.		
13.	(Delusio* or delusion* or delusion?disord* or delusion*disord*).tw.ot.		
14.	or/7-13		
15.	exp rating scales/		

(ii) Data Extraction Table

No.	Author (Year)	Instrument	Sample size (n)	Patient Group	Language	Cognitive Assessment Mean (SD or %)	Age (years) Mean (SD of % or Range)	HY Score Mean (SD or %)
1	(Gottlieb et al., 1988)	BPRS	43	AD	English	Unspecified	Low severity dementia: 72.63 (8.7) High severity dementia: 73.37 (5.10)	NA
2	(Bell et al., 1992)	PANSS + BPRS	56	Clinical setting SCZ/Schizoaffecive disorders	English	Unspecified	40.2 (8.6)	NA
3	(Crippa et al., 2001)	BEHAVE-AD BPRS	52	Inpatients 15- Bipolar affective disorder 13- Depressive disorders 12- SCZ 5- Schizoaffective disorders 7- other (not dementia)	English	Unspecified	38.56 (16.44)	NA
4	(Patterson et al., 1990)	BEHAVE-AD	51	Outpatients 32-AD 2- mixed AD 17- Controls	English	MMSE 16.7 (5.81)- AD patients	72.7 (6.13)	NA
5	(Mack & Patterson, 1994)	BEHAVE-AD	81	Outpatients 61- AD 20- healthy controls	English	MMSE 17.57 (5.65) MMSE 29.05 (0.76)- Controls	71.95 (6.73) - AD 69.3 (5.76) - controls	NA

6	(Sclan, 1996)	BEHAVE-AD	18	Outpatients 9- AD 7- Dementia (other) 1- normal aged impairment 1- possible incipient dementia	English	MMSE 18.9 (6.6)	73.9 (7.5)	NA
			20	Nursing-home residents 15- AD 3- Dementia (other) 2- Multi-infarct dementia	French	MMSE 11.4 (7.1)	75.5 (9.2)	NA
7	(Monteiro et al., 1998)	BEHAVE-AD	17	5- MCI 12- AD	English	Unspecified	Unspecified	NA
8	(Monteiro et al., 2001)	BEHAVE-AD-FW	28	5- non-demented with MCI 23- AD	English	MMSE 18.8 (7.8)	73.5 (7.9)	NA
9	(Lam et al., 2001)	BEHAVE-AD	71	Inpatients AD	Chinese	C-MMSE 10.3 (5.8)	80.6 (9.3)	NA
10	(Cohen-Mansfield & Golander, 2011)	BEHAVE-AD	74	NH residents with dementia	Hebrew	MMSE 8.99 (6.76)	85.45 (6.28)	NA

11	(Auer et al., 1996)	E-BEHAVE-AD	49	Clinical setting 5- Normal 5- MCI 27- AD 12- Dementia (other)	English	MMSE : 18.3 (9.7)	72.5 (8.4)	NA
12	(Cummings et al., 1994)	NPI	• 40 (test-retest reliability) • 45 (Interrater reliability) • 40 controls	Caregivers of outpatients with dementia 20- AD 9- VD 11- Dementia (other)	English	MMSE 19.2 (0-29)	75.7 (56-90)	NA
				Caregivers of outpatients with dementia 42- AD 1- VD 2- Dementia (other)		MMSE 17.4 (1-29) MMSE 28.4 (25-30) - controls		
13	(Binetti et al., 1998)	NPI	50	Outpatients AD	Italian	MMSE: 21.8 (20-28) – Mild AD 15.5 (10-19) – Moderate AD 3.1 (0-8) – Severe AD	77.7 (56-88) – Mild AD 74.4 (55-92) – Moderate AD 75.7 (59-85) – Severe AD	NA
14	(Choi et al., 2000)	NPI	141	Dementia group 92- Dementia 43-AD, 32-VD, 11-FTLD, 6 -other dementia 49- Controls	Korean	K-MMSE 17.5 (6.8)	67.5 (9.7)	Unspecified
15	(Leung et al., 2001)	NPI	91	Outpatients 62- Dementia (41- AD, 16- VD, 5- other dementia) 29- Controls	Chinese	C-MMSE 12.7 (5.9)- Dementia Group	76.4 (7)	NA

16	(Fuh et al., 2001)	NPI	95	AD	Chinese	MMSE 12.7 (7.2)	73.9 (7.7)	NA
17	(Politis et al., 2004)	NPI	29	AD outpatients	Hellenic	MMSE 12.4 (6)	71 (5)	NA
18	(Camozzato et al., 2008)	NPI	36	Outpatients AD	Portuguese Brazilian	MMSE 7.1 (6.9)	78.78 (7.48)	NA
19	(Wang et al., 2012)	NPI	219	AD outpatients	Chinese	MMSE 18.6 (8.1)	72 (9)	NA
20	(Kaufer et al., 2000)	NPI-Q	60	Dementia clinic outpatients AD	English	MMSE 18.4 (5.6)	75.9 (6.9)	NA
21	(de Medeiros et al., 2010)	NPI-C	128 dyads (caregiver/patient with dementia)	Community AD	English	MMSE 17.6 (7.0)	75.7 (9)	NA
22	(Stella et al., 2013)	NPI-C	156 dyads (patient/caregiver)	Outpatients 60- Mild dementia 53- Moderate dementia 43- Severe dementia	Brazilian	Mean MMSE 17.2	76.7	NA
23	(Wood et al., 2000)	NPI-NH	69	Nursing-home residents Dementia	English	Mean MMSE 6.7(0-17/30)	87 (7.95)	NA
24	(Iverson et al., 2002)	NPI-NH	52	Geriatric inpatients (Exact diagnosis not provided)	English	Unspecified	Unspecified	NA
25	(Lange et al., 2004)	NPI-NH	204	Inpatients	English	Unspecified	73.4 (10.3)	NA
26	(Selbaek et al., 2008)	NPI-NH	91	Nursing-home residents 71- Dementia (43-AD, 20- VD, 8-other dementia) 20- Depression (unclear)	Norwegian	MMSE 14.3 (9.1)	84.3 (7.38)	NA

27	(Norman et al., 1996)	SAPS	85	Outpatients & Inpatients SCZ	English	Unspecified	36.4 (21-61)	NA
28	(Kulick et al., 2018)	eSAPS-PD	199	PD outpatients 141 PD-controls 30 PDP-minor 28 PDP-major	English	Median MoCA 26 (IQR range 24-28)(PD-controls) median MoCA 25 (IQR 24-27)(PDP-minor) median MoCA 27 (25-28) (IQR 25-28)(PDP-major)	PD-control: 66 (10) PDP-minor: 66 (9) PDP-major: 67 (8)	Median HY 2 (IQR 2–2) across all 3 groups.
29	(Kay et al., 1987)	PANSS	101	Clinical setting SCZ	English	Unspecified	40.2 (8.6)	NA
30	(Molloy et al., 1991)	DBRI	184 dyads (patient/caregiver)	Outpatients 124- AD 38- PD	English	MMSE – unspecified scores	72 (45-90)	Unspecified
31	(Wada-Isoe et al., 2008)	TUHARS	41	PD outpatients 31-PDD 10- PDnD	English	MMSE 23.8 (5.8)- PDD MMSE 27.1 (2.9)- PDnD	PDD: 71.6 (7.7) PDnD: 68.7 (10.1)	PDD: 3.5 (0.9) PDnD: 2.9 (0.8)
32	(Mosimann et al., 2008)	NEVHI	114	80- elderly patients with cognitive impairment or/and eye disease 34- no risk factors for hallucinations - controls	English	Patients: MMSE 26.7 (2.5) Controls: MMSE 28.3 (0.9)	Patients: 79.9 (8.1) Controls: 71.2 (8.7)	NA
33	(Urwyler et al., 2015)	I-NEVHI	59	Outpatients PD	English	MMSE 27.7 (2.4)	71.9 (8.7)	NA
34	(Brandstaedter et al., 2005)	PPQ	50	Outpatients 49- iPD 1- MSA-P 5/50- Mild-Moderate Dementia (MMSE < 23)	German	MMSE (performed in 48/50): 26.6 (2.98)	70.38 (8.12)	3.08 (0.85)
35	(Cargaleiro et al., 2012)	PPQ	36	Outpatients Early Stage PD	Portuguese	MMSE 27.22(2.53)	73.17 (6.54)	Median HY= 2 (IQR=1-3)
36	(Papapetropoulos et al., 2008)	UM-PDHQ	70	Outpatients 31 hallucinators	English	MMSE 25.6 (4.5)	64.3 (10.2)	2.5 (0.7)

				39 non-hallucinators				
37	(Ondo et al., 2015)	Baylor's Hallucination Questionnaire	75	Outpatients 50 PDP 25 PD without psychosis	English	26/75 has dementia – assessment score unspecified	Patients: 70 (10.8)	Unspecified
38	(Goetz et al., 2001)	Rush Hallucination Inventory	89	PD outpatients	English	MMSE 26.9 (11.2)	67.7 (9.5)	Unspecified
39	(Friedberg et al., 1998)	PPRS	29	PD	English	Unspecified	72 (6.9)	Unspecified
40	(Martinez-Martin et al., 2012)	SEND-PD	633	PD outpatients in Spain 109/633- Dementia	English	MMSE 25.81 (4.55)	70.95 (10)	HY1=23% HY2=45% HY3=18% HY4&5=14%
41	(Rodriguez-Violante et al., 2014)	SEND-PD	260	PD outpatients 32/260 had dementia	Spanish	Clinical judgement	62.4 (13.1)	HY1-2= 69.6% HY3= 18.1% HY≥4= 12.3%
42	(Visser et al., 2007)	SCOPA-PC	106	Outpatients PD	Dutch	MMSE 26.4 (3.5)	64.5 (9.7)	HY2= 35% HY3= 35% HY4= 28% HY5= 7%
43	(Chaudhuri et al., 2007)	NMSS	242	Outpatients across 5 countries PD	English/ non-English	Unspecified	67.2 (11.1)	HY1=9.3% HY2=19% HY2.5=17% HY3=32.5% HY5=2.1%
44	(Martinez-Martin et al., 2009)	NMSS	411	Outpatients from 12 centers across 10 countries PD	English/ non-English	Unspecified	64.5 (9.9)	HY1= 15% HY2=40% HY3= 32% HY4=11%

45	(Wang et al., 2009)	NMSS	126	Outpatients PD	Chinese	27.8 (2.98)	65.26 (9.75)	HY1=34 HY2=66 HY3=21 HY4=5
46	(Carod-Artal & Martinez-Martin, 2013)	NMSS	150	Outpatients PD	Brazilian Portuguese	Unspecified	53.1 (11.1)	HY1= 20% HY2= 43.3% HY3= 28% HY4&5=8.7%
47	(Starkstein & Merello, 2007)	UPDRS Part I	168	Outpatients PD	English	24.4 (5.4)	65.9 (9.8)	HY1= 12% HY2= 35% HY3= 36% HY4=15%
48	(Holroyd et al., 2008)	UPDRS MBM Subscale	97	Outpatients PD	English	TICS: 32.1 (4.5)	68 (9)	Unspecified
49	(Gallagher et al., 2012)	MDS-UPDRS 1.2	94	Outpatients PD 5/94- Mild Dementia	English	ACE 89 (10.3) SCOPA-COG 24.9 (7) FAB 15.1 (2.8)	67.5 (9.5)	HY1=1% HY2&3= 91% HY4= 5% HY5=3%
50	(de Chazeron et al., 2015)	PSAS	137	Clinical setting 86- PD 51- SCZ	French	MMSE > 24	53.3 (19.5)	HY1= 7% HY2= 63% HY3= 29%
51	(Shine et al., 2015)	Psych-Q	197	From postal survey - community iPD	English	PDP: 27.2 (3.7) PD without psychosis:28.2 (2.5)	PDP: 70.5 (8.5) PD without psychosis: 68.6 (8.4)	2.2 (0.9)
52	(Rieu et al., 2015)	ASBPD	260	PD outpatients from 13 centers across 4 countries	English/ French/ Spanish	UPDRS part I 2.2 (2)	62.5 (8.5)	Median HY= 2 (IQR=2-2.5)

53	(van der Heeden et al., 2016)	SENS-PD	396	Outpatients PD	English	Unspecified	61.2 (11.5)	HY1= 4% HY2= 48% HY3= 27% HY4= 16%
54	(Stocchi et al., 2018)	PDCS	194	Outpatients from 5 countries PD	English	Unspecified	66.51 (9.34)	HY 1 or 2 (57.2%) HY 3 (36.6%); HY 4 or 5 (6.2%)
55	(Martinez-Martin et al., 2019)	PDCS	776	PD outpatients from 20 centers across 11 countries	English	Unspecified	67.94 (9.96)	Unclear
56	(Chaudhuri et al., 2020)	MDS-NMS (Domain D - Psychosis)	402	PD outpatients from 6 centers across 2 countries	English	MoCA 26.74 (2.48)	67.42 (9.96)	Median HY 2 (IQR 2–3)

PD: Parkinson's disease; iPD: idiopathic Parkinson's disease; AD: Alzheimer's disease; FTLD: Frontotemporal lobar dementia; MCI: Mild cognitive impairment; MSA-P: Mulatisystem Atrophy – Parkinsonian type; SCZ: Schizophrenia; VD: Vascular dementia; NH: Nursing-home; HY: Hoehn & Yahr Staging; IQR: Interquartile range, PDP: PD psychosis; MMSE: Mini-mental state examination; MoCA: Montreal Cognitive Assessment test; PD-D: PD with dementia; PDnD: PD without dementia; NPI: Neuropsychiatric Inventory; NPI-C: Neuropsychiatric Inventory – clinician-rated; NPI-NH:Neuropsychiatric Inventory- Nursing-Home; ACE, Addenbrooke's Cognitive Examination; SCOPA-COG, Scales for Outcome in Parkinson's disease (SCOPA), cognitive scale; FAB, Frontal Assessment Battery; UPDRS-MBM: Unified Parkinson's disease rating scale including mentation, behaviour and mood; TICS: Telephone Interview for Cognitive Status; I-NEVHI: Informant-North East Visual Hallucination Inventory; ASBPD: Ardouin Scale of Behaviour in Parkinson's Disease; BPC: Behaviour Problem Checklist; BPRS: Brief Psychiatric Rating Scale; BEHAVE-AD : Behavioural pathology in Alzheimer's disease rating scale; E-BEHAVE-AD: Empirical Behavioural pathology in Alzheimer's disease rating scale; BEHAVE-AD-FW : Behavioural pathology in Alzheimer's disease rating scale Frequency-Weighted Severity Scale; NEVHI : North-East Visual Hallucinations Interview; I-NEVHI : Informant-based North-East Visual Hallucinations Interview; MDS-UPDRS 1.2: United Parkinson's Disease Rating Scale Part I item 1.2:Hallucinations and Psychosis (Movement Disorder Society sponsored revision); DBRI : Dysfunctional Behaviour Rating Instrument; NMSS : Non-Motor Symptoms Scale; PANSS: Positive and Negative Symptom Scale; PPQ: Parkinson Psychosis Questionnaire; PPRS : Parkinson Psychosis Rating Scale; PSAS : Psycho-Sensory hallucinations Scale; PsycH-Q : Psychosis and Hallucinations Questionnaire; SCOPA-PC : Scales for Outcomes in Parkinson's Disease – Psychiatric Complications; SENS-PD : SEverity of predominantly Nondopaminergic Symptoms in PD; TUHARS : Tottori University Hallucination Rating Scale; UM-PDHQ : University of Miami Parkinson's disease Hallucinations Questionnaire

Chapter 4
Data Acquisition & General Methodology

4.1 UK – Psy-PD Study

4.1.1 Study design

This is a single-center, cross-sectional validation study with retesting done of a newly developed scale over 12 months from April 2018 until April 2019. The initial cognitive pre-testing phase will be followed by a validation study. Cognitive pretesting follows a standard procedure of assessment of value of the proposed scale, with an aim to recruit 30 cases and 20 healthy controls. Test-retest reliability will be tested by having the same healthcare professional administering the scale in 7 to 14 days under standardised conditions.

4.1.2. Study Population

Patients with Parkinson's disease who attended the Parkinson's outpatient clinic at the International Parkinson's Centre of Excellence at King's College Hospital London under the supervision of Professor Ray Chaudhuri. I established this population with the support of the EUROPAR Clinical Research Network (https://parkinsons-london.co.uk/) as well as the Research Support Network of Parkinson's UK (https://www.parkinsons.org.uk/).

4.1.2.1 Inclusion Criteria

Patients:

(a) A confirmed diagnosis of Parkinson's Disease according to internationally accepted UK PD Brain Bank criteria (Hughes et al., 2002).

(b) Both genders and all ages over 18 years of age (encompassing 99% of cases with PD)

(c) Patients from all Hoehn and Yahr stages (a staging of PD expressing severity of condition)

Controls:

(a) Healthy community-dwelling participants

(b) Both genders

(c) Ages 50-90 years

(d) Caregivers accompanying patient for clinic appointments will also be recruited.

4.1.2.2. Exclusion criteria

Patients

(a) Patients with clinically unclassifiable Parkinsonism (CUP) (Mangesius et al., 2018) or with a diagnosis of atypical forms of Parkinsonism (e.g. Multisystem Atrophy, Progressive Supranuclear Palsy, corticobasal degeneration, Lewy Body Dementia)

(b) Those unable to grant signed informed consent

(c) Those unable to communicate effectively in the local language (English for this occasion)

(d) Conditions interfering assessment (e.g. blindness)

Controls or Caregivers

History of dementia or evidence of significant cognitive impairment (<26 points on the Montreal Cognitive Assessment).

4.1.3 Consent and ethical considerations

I developed the study protocol and successfully obtained ethical permission to conduct this study which received full ethical approval from the local Research Ethics Committee (REC) (National Research Ethics Service, London Dulwich) and the research and development (R&D) office at King's College Hospital, London (IRAS project ID number 229095; KCH 18-065)in 2018.

Prior to enrolment in the study, all patients provided informed written consent in the presence of one trained health professional and/or qualified researchers. No reimbursements were given.

All data was sent and stored at the International Parkinson's Centre of Excellence, King's College London in compliance with the National Data Protection Act (United Kingdom Reg: Z6614305) and compliant with General Data Protection Regulation (GDPR) (EU) 2016/679. Patient privacy was always considered and no confidential or identifying patient data was disclosed or transferred. All collected data was anonymized via a well-established coding system (KCH/***). All involved health professional and researchers had valid Good Clinical Practice (GCP) training. I uploaded all recruitment figures from King's with an anonymized number monthly to the clinical research management system (EDGE program: https://www.edge.nhs.uk/).

4.1.4. Work Protocol

The work protocol is summarized in *Figure* 4.1 and will be discussed in detail.

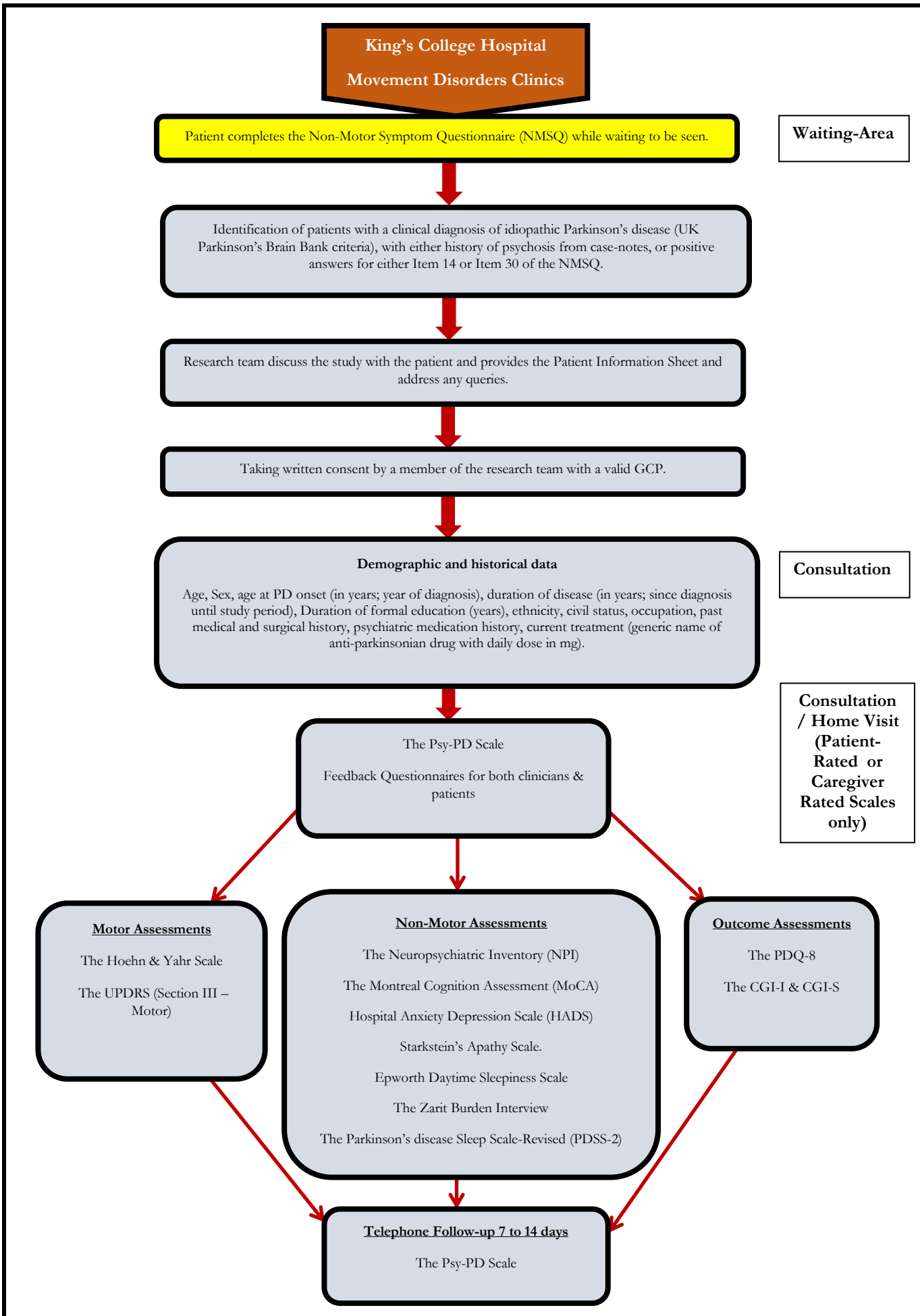


Figure 4.1 Work Protocol of the Psy-PD study (UK)

Abbreviations: UK = United Kingdom; Psy-PD = Psychosis Severity Scale of Parkinson's Disease; UPDRS = Movement Disorder Society-Unified Parkinson's Disease Rating Scale; PDQ-8 = Parkinson's Disease Questionnaire (8 Items); CGI -I = Clinical Global Impression (Improvement) Scale; CGI-S = Clinical Global Impression (Severity) Scale

4.1.4.1 Approaching patients

Patients attending the recruiting Neurology Movement Disorders Clinics at King's College Hospital in London, United Kingdom, were approached during their clinical appointment about this study and provided a detailed patient information sheet. Patients were given time to discuss the study protocol with the health professional or a qualified member of the research team. If patients met the inclusion criteria and agreed to participate, they were asked to sign the written consent form before inclusion into the study.

The patients would routinely be asked to complete the non-motor symptoms questionnaire (NMSQuest) while waiting to be seen. The NMSQuest was originally devised by Prof. K. Ray Chaudhuri and his team, and is now a validated scale recommended for use by Parkinson's UK (http://www.parkinsons.org.uk/) and the International Parkinson and Movement Disorder Society (IPMDS) (https://www.movementdisorders.org/MDS.htm).

In addition, should the patient prefer this option, home study visits were organized and conducted for completion of baseline assessment, to facilitate the ease of patients in completing the patient-rated or caregiver-rated assessments. This is also because of the intrinsic symptoms of Parkinson's disease (PD), including the restricted mobility, hospital anxiety, and fatigue associated with the condition. This option would additionally be beneficial for patients who live at a distance from the study site. This would allow patients to complete the baseline assessment in the comfort of their own homes.

Note: This study was conducted and completed in the UK prior to the year 2020, and therefore the social restrictions pertaining to the COVID-19 pandemic were not applicable at that point in time.

4.1.4.2 Data collection

4.1.4.2.1 Sociodemographic data

Age, sex, age at PD onset (in years; year of diagnosis), duration of disease (in years; since diagnosis until study period), ethnicity (White, Mixed, Asian, Black-African, Chinese, Other), medical history, past surgical history, education level (in years), civil status (single, married, widow, separated/divorced), occupation (previous/current), activity (employee/autonomous, retired/pensioner, housewife, student, unemployed, other) were recorded.

4.1.4.2.2. Parkinson's disease treatment

All therapeutic regimens, including oral and non-oral treatment strategies related to PD, were recorded and recalculated into the levodopa equivalent daily dose (LEDD) according to the method of Tomlinson et al. (Tomlinson et. al., 2020).

4.1.4.2.3. Psychiatric treatment

All forms of psychiatric treatment (antidepressants, antipsychotics, anti-anxiety medication, sedative-hypnotic, cognitive medications) and the total daily doses were recorded.

4.1.4.2.4 Clinical assessments

The tools applied in this research to explore the motor and non-motor profile of the included patients, as well as the associated outcomes such as quality of life and caregiver burden, as well as a global impression are summarized in *Table* 4.1. All instruments, aside from the Psy-PD scale, have been previously validated in Parkinson's disease and have been used successfully in other studies.

***Table* 4.1: The instruments used in the UK research project**

Evaluation Instrument	Administered by Patient or Clinician?	Description	Reference
Motor Assessments			
United Parkinson's Disease Rating Scale (UPDRS) Section III (Motor)	Clinician	The UPDRS III is the subscale of a rating tool developed in 1987 to gauge the severity and progression of Parkinson's disease. It is scored from 0 to 4, with higher scores indicating higher severity.	(Martinez-Martin et al., 1994)
Hoehn & Yahr Scale (HY) - Original	Clinician	Categorised into 5 stages, the HY scale measures disease progression: Stage 1 (unilateral involvement); Stage 2 (bilateral involvement without balance impairment); Stage 3 (bilateral involvement with balance impairment; physically independent); Stage 4 (unable to walk or stand unassisted); Stage 5 (bedbound or wheelchair-bound).	(Hoehn & Yahr, 1967)
Outcomes (Quality of life and Caregiver Burden)			
Parkinson's disease Questionnaire-8 (PDQ-8)	Patient	The PDQ-8 is an abbreviated form of the PDQ-39 and addresses the frequency of 8 items (score 0-4) related to quality of life in patients with Parkinson's disease (mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication, bodily discomfort). The PDQ-8 Summary Index is expressed to present the data as a percentage of the sum of item scores on the maximum possible scale score, with the maximum or worst score being 100.	(Jenkinson et al., 1997)
Zarit Burden Interview (ZBI)	Caregiver or Proxy	The ZBI consists of 22 items with five ordered frequency-related response options, ranging from 0 (never) to 4 (nearly always), except for the final item which has fiver ordered intensity-related response options ranging from 0 (not at all) to 4(extremely). The total score ranged from 0 to 88 (88=more burden), with 21 as the burden cut-point.	(Hagell et al., 2017)
Non-Motor Assessments			
Non-Motor Symptom Questionnaire (NMSQuest)	Clinician	Complementary to the NMSS, the NMSQuest is an internationally validated patient completed tool assessing 30 different NMS covering the domains of gastrointestinal tract (7 items), urinary function (2 items), depression/anxiety (2 items), sleep disorders (5 items), miscellaneous (pain, weight change, swelling, sweating, diplopia) (5 items), with 'yes or 'no' response options. The NMSQuest total score ranges from 0 to 30. The higher the score, the higher the non-motor symptom load.	(Chaudhuri, Martinez-Martin, et al., 2006; Chaudhuri, Sauerbier, et al., 2015)

Non-Motor Symptoms Scale (NMSS)	Clinician	The NMSS comprised 30 items grouped into nine domains (cardiovascular (2 items), sleep/fatigue (4 items), mood/apathy (6 items), perceptual problems/hallucinations (3 items), attention/memory (3 items), gastrointestinal tract (3 items), urinary function (3 items), sexual function (2 items), and miscellaneous (4 items). Each item is scored twice on severity (0 to 3) and frequency (1 to 4). The NMSS total score ranges from 0 to 360.	(Chaudhuri et al., 2007)
Hospital Anxiety Depression Scale (HADS)	Patient	The Hospital Anxiety and Depression Scale (HADS) scale is a simple patient completed scale including 14 different items (7 for depression and 7 for anxiety). The HADS total score ranges from 0 to 42. Clinical depression (as denoted by the even-numbered questions) is represented by a score of 11 or higher, while correspondingly clinical anxiety (as denoted by the odd-numbered questions) is also represented by a score of 11 or higher.	(Zigmond & Snaith, 1983)
Parkinson's disease sleep scale – revised version (PDSS-2)	Patient	The Parkinson's disease sleep scale (revised version) is a 15-item frequency measure to characterise and quantify various aspects of nocturnal sleep problems in Parkinson's disease. It is rated using one of five categories, from 9(never) to 4 (very frequent). The PDSS-2 total score ranges from 0 (no disturbance) to 60 (maximum nocturnal disturbance).	(Trenkwalder, Kohnen, et al., 2011)
Epworth Sleepiness Scale (ESS)	Patient	The Epworth sleepiness scale (ESS) is a screening instrument for evaluation of daytime sleepiness in Parkinson's disease. It involves a 4-point scale (0-3). Total score ranges from 0 to 24. The higher the score, the worse the daytime sleepiness.	(Johns, 1991)
Neuropsychiatric Inventory (NPI)	Clinician	The NPI is a copyrighted 12-item scale to assess for psychopathology in patients with dementia. It is usually conducted by a trained rater with a knowledgeable caregiver as informant. There are screening questions about presence of the symptom or behaviour associated with each of the 12 items, with more specific questions on frequency and severity asked only if a positive screening response is endorsed. Frequency and severity ratings are then multiplied to obtain the domain score.	(Cummings et al., 1994)

Starkstein's Apathy Scale (SAS)	Patient	The SAS is a 14-item scale to evaluate cognitive, behavioural, and emotional symptoms of apathy in PD patients. An optimal cut-off score ≥14, with sensitivity of 66% and specificity of 100%.	(Starkstein et al., 1992)
Montreal Cognitive Test (MoCA)	Clinician	The MoCA is a 30-item test that assesses different cognitive domains including orientation, delayed recall, visuospatial ability/executive function, language, abstraction, semantic fluency, attention, clock-drawing test. The cut-off threshold for PD-MCI is a score less than 26/30.	(Gill et al., 2008)
Global Assessment			
Clinical Global Impressions Scale (CGI): Severity of Illness (CGI-S) and Global-Improvement (CGI-I)	Clinician	The CGI was devised in 1976 for a brief one-stop assessment of the patient's global functioning prior to and after initiating an intervention. CGI-S generally tracks with CGI-I such that improvement in one follows the other.	(Busner et al., 2009)

PD-MCI: Mild cognitive impairment in Parkinson's disease

***Table* 4.2: Study Schedule – overview.**

	Screening	**Baseline**	**Phone call**
Visit No	**-24h**	**0d**	**(+7-14d)**
Eligibility criteria	X		
Informed Consent	X		
Sociodemographic & PD-related data		X	
Psy-PD		X	
Validated questionnaires and scales (as detailed above)		X	X

Abbreviations: h = hours; d = day; PD= Parkinson's disease; Psy-PD: Psychosis Rating Scale in Parkinson's disease

4.1.4.2.4.1. Grading of non-motor symptoms

The NMSS (*Table* 4.2) can be used to measure the NMS burden experienced by the patient which is a holistic approach towards the patients' health (Chaudhuri et al., 2013).

***Table* 4.3: Non-motor burden according to NMSS**

Burden Level	0 (None)	1 (Mild)	2 (Moderate)	3 (Severe)	4 (Very Severe)
NMSS total score	0	1 – 20	21 – 40	41 – 70	>70

4.1.5 Patient and Public Involvement

Patients and carers have been and are actively involved in all stages of this study as below:

1. The Community for Research Involvement and Support for People with Parkinson's (CRISP) (see http://parkinsonslondon. co.uk/europar/crisp/) is an established Public and Patient Involvement (PPI) as well as a National Institute for Health and Care Research (NIHR)- accredited expert patient group at the Parkinson's Centre of Excellence at King's College Hospital (KCH). This study has been supported and approved by CRISP and interface via the "group consultation evening clinics and meetings" held at Kings cited by The National Institute for Health and Care Excellence (NICE) as a good practice guide.

2. Patients and carers will be actively involved also in managing the research project by regular update meetings and feedback re questionnaires and scales used. The study itself also incorporates a patient and control feedback questionnaire (refer Chapter 6).

4.2 Singapore – Apathy and Genetics Study

4.2.1 Study design

This is a single-center longitudinal study called "A Longitudinal View of Apathy and Its Impact in Parkinson's Disease ("Apathy Study")". The study is still ongoing and the presented baseline data was extracted for one-point analysis in November 2020.

4.2.2 Study Population

Patients with Parkinson's disease who attended the specialist Movement Disorder clinics at the Singapore General Hospital (SGH) under the supervision of Professor Eng-King Tan. I established this population with the support of the Department of Neurology, as well as the Department of Psychiatry, at the Singapore General Hospital.

4.2.2.1 Inclusion Criteria

Patients:

(a) A confirmed diagnosis of Parkinson's Disease according to internationally accepted UK PD Brain Bank criteria (Hughes et al., 2002)

(b) Both genders and all ages over 21 years of age (encompassing 99% of cases with PD)

(c) Not on antidepressants for at least 4 weeks prior to study initiation

(d) Sufficiently proficient in English to comprehend and complete the questionnaires

(c) Patients from all Hoehn and Yahr stages (a staging of PD expressing severity of condition)

Caregivers:

(a) Healthy community-dwelling participants

(b) Both genders

(c) Ages 50-90 years

4.2.2.2. Exclusion criteria

Patients

(a) Patients with clinically unclassifiable Parkinsonism (CUP) (Mangesius et al., 2018) or with a diagnosis of atypical forms of Parkinsonism (e.g. Multisystem Atrophy, Progressive Supranuclear Palsy, corticobasal degeneration, Lewy Body Dementia)

(b) Those unable to grant informed consent

(c) Those unable to communicate effectively in English

(d) Conditions interfering with assessment (e.g. blindness, delirium)

(e) Active alcohol or illicit substance use

Caregivers

History of dementia or evidence of significant cognitive impairment (<26 points on the Montreal Cognitive Assessment).

4.2.3 Consent and ethical considerations

I developed the study protocol and successfully obtained ethical permission to conduct this study which received full ethical approval from the local institutional research board (CIRB 2012/759/A).

Prior to enrolment in the study, informed consent was provided by all patients in the presence of one trained health professionals and/or qualified researchers. No reimbursements were given.

All data will be recorded in an online document with an encrypted password known only to the research team at the Singapore General Hospital according to local regulations. Patient privacy was always considered and no confidential or identifying patient data was disclosed or transferred. All collected data was anonymized via a coding system. All involved health professionals and researchers had completed the relevant Collaborative Institutional Training Initiative (CITI) training (see https://www.citiprogram.org/), that included Good Clinical Practice (GCP) certification. I uploaded all recruitment figures from SGH with an anonymized number to the computer system at SGH.

4.2.4. Work Protocol

The work protocol is summarized in *Figure* 4.2 and will be discussed in detail.

4.2.4.1 Approaching Patients

Patients attending the Neurology Movement Disorders Clinics at Singapore General Hospital, Singapore, were approached during their clinical appointment about this project and were given the study information sheet. Patients were given time to discuss the study protocol with the healthcare professional or a qualified member of the research team. Eligible patients who provided consent were then enrolled into the study.

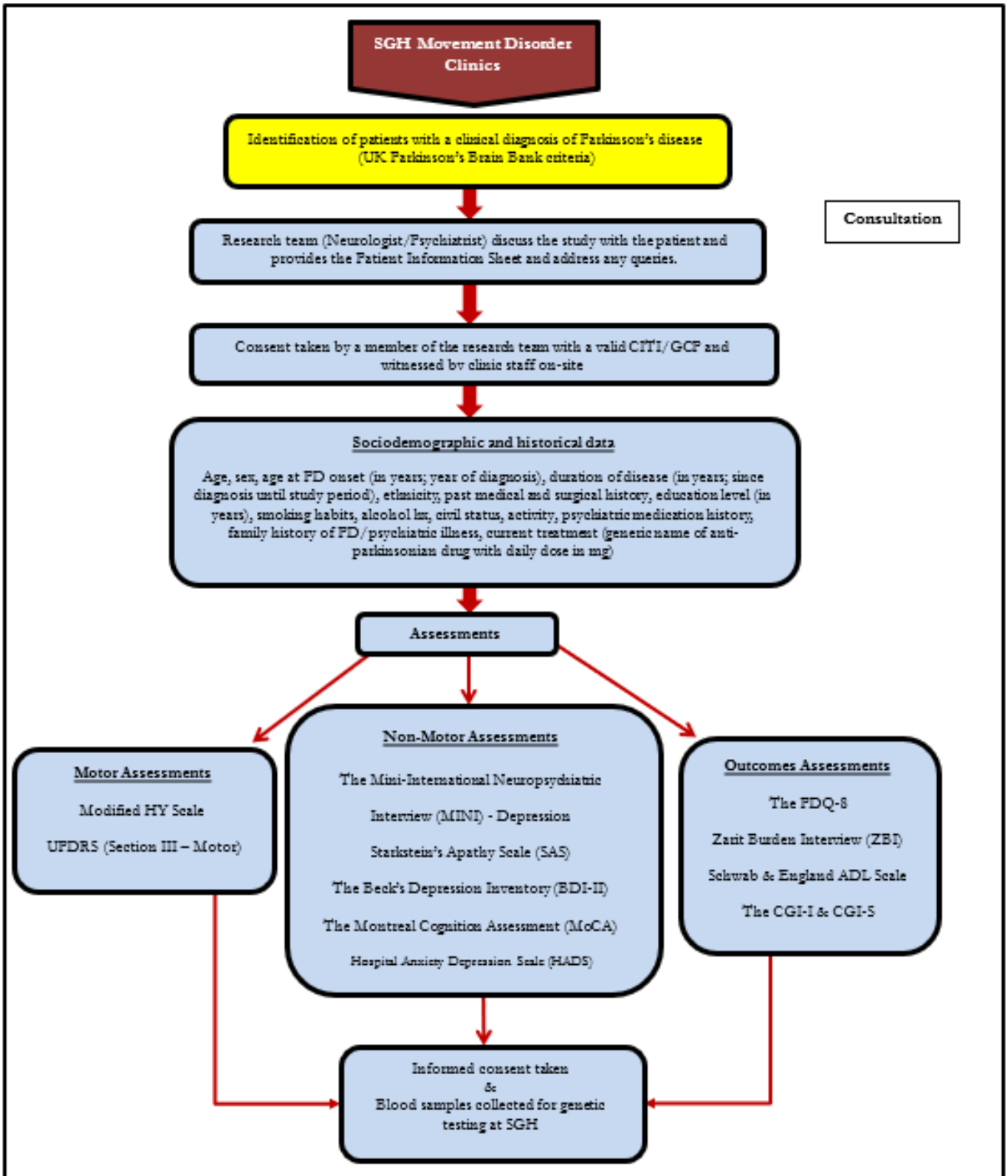


Figure 4.2 Work Protocol of the Apathy & the Genetic Analysis Study (Singapore)

Abbreviations: SGH=Singapore General Hospital; UK=United Kingdom; CITI/GCP=Collaborative Insitutional Training Initiative/Good Clinical Practice; HY=Hoehn&Yahr; UPDRS=Unified Parkinson's Disease Rating Scale; FDQ-8 = Parkinson's Disease Questionnaire (8 Items); ADL=Activities of Daily Living; CGI -I = Clinical Global Impression (Improvement) Scale; CGI-S = Clinical Global Impression (Severity) Scale

4.2.4.2 Data collection

4.2.4.2.1 Sociodemographic data

Age, sex, age at PD onset (in years; year of diagnosis), duration of disease (in months; since diagnosis until study period), family history of PD, ethnicity (Chinese, Malay, Indian, Eurasian/Mixed, Other), medical history, past surgical history, education level (in years), civil status (single, married, separated/divorced, widowed, in a relationship), occupation (previous/current), activity (employee/autonomous, retired/pensioner, housewife, student, unemployed, other) were recorded.

4.2.4.2.2. Parkinson's disease treatment

All therapeutic regimen including oral and non-oral treatment strategies related to PD were recorded and recalculated into the levodopa equivalent daily dose (LEDD) according to the method of Tomlinson et al. (Tomlinson et al., 2010).

4.2.4.2.3. Psychiatric treatment

All forms of psychiatric treatment (antidepressants, antipsychotics, anti-anxiety medication, sedative-hypnotic, cognitive medications) and the total daily doses were recorded.

4.1.4.2.4 Clinical assessments

The tools applied in this research to explore the motor and non-motor profile of the included patients, as well as the associated outcomes such as quality of life and caregiver burden, as well as a global impression are summarized in *Table* 4.3, similar to *Table* 4.1. All instruments have been validated in Parkinson's disease and have been widely used in other studies. The English versions of all questionnaires were used in this study in Singapore.

***Table* 4.4: The instruments used in the research project in Singapore**

Evaluation Instrument	Administered by Patient or Clinician?	Description	Reference
Motor Assessments			
United Parkinson's Disease Rating Scale (UPDRS) Section III (Motor)	Clinician	The UPDRS III is the subscale of a rating tool developed in 1987 to gauge the severity and progression of Parkinson's disease. It is scored from 0 to 4, with higher scores indicating higher severity.	(Martinez-Martin et al., 1994)
Hoehn & Yahr Scale (HY) - Modified	Clinician	Originally categorised into 5 stages, the modified HY scale adds two additional 'intermediate' stages to measure disease progression : Stage 1 (unilateral involvement); Stage 1.5 (unilateral and axial involvement); Stage 2 (bilateral involvement without balance impairment); Stage 2.5 (mild bilateral disease with recovery on pull test); Stage 3 (bilateral involvement with balance impairment; physically independent); Stage 4 (unable to walk or stand unassisted); Stage 5 (bedbound or wheelchair-bound).	(Larsen et al., 1984)
Outcomes (Quality of life and Caregiver Burden)			
Parkinson's disease Questionnaire-8 (PDQ-8)	Patient	The PDQ-8 is an abbreviated form of the PDQ-39 and addresses the frequency of 8 items (score 0-4) related to quality of life in patients with Parkinson's disease (mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication, bodily discomfort). The PDQ-8 Summary Index is expressed to present the data as a percentage of the sum of item scores on the maximum possible scale score, with the maximum or worst score being 100.	(Jenkinson et al., 1997; Tan et al., 2004)
Zarit Burden Interview (ZBI)	Caregiver or Proxy	The ZBI consists of 22 items with five ordered frequency-related response options, ranging from 0 (never) to 4 (nearly always), except for the final item which has fiver ordered intensity-related response options ranging from 0 (not at all) to 4(extremely). The total score ranged from 0 to 88 (88=more burden), with 21 as the burden cut-point.	(Hagell et al., 2017)
Schwab and England Activities of Daily Living Scale (SEADL)	Rater	The Schwab and England Activities of Daily Living (ADL) Scale estimates the ability of the PwP to perform their daily activities in terms of speed and independence. The rating can be determined by the professional or by the person being tested, with the scores ranging from 0% indicating a state of complete dependence to 100%	(Schwab & England, 1969)

		indicating total independence. Each 10-point increment is accompanied by a description of function.	
Non-Motor Assessments			
The Mini-International Neuropsychiatric Interview (MINI) Depression	Clinician	The MINI is a structured diagnostic interview that comprises modules for assessment of 17 psychiatric diagnoses according to the DSM-IV and ICD-10 criteria, including for depression. Questions are phrased to allow only "yes" or "no" answers.	(Sheehan et al., 1998)
Hospital Anxiety Depression Scale (HADS)	Patient	The Hospital Anxiety and Depression Scale (HADS) scale is a simple patient completed scale including 14 different items (7 for depression and 7 for anxiety). The HADS total score ranges from 0 to 42. Clinical depression (as denoted by the even-numbered questions) is represented by a score of 11 or higher, while correspondingly clinical anxiety (as denoted by the odd-numbered questions) is represented by a score of 11 or higher.	(Zigmond & Snaith, 1983)
The Beck's Depression Inventory-second edition (BDI-II)	Patient	The BDI-II is a widely used 21-item self-reported measure that screens for symptoms of major depressive disorder according to diagnostic criteria listed in the Diagnostic and Statistical Manual for Mental Disorders-fifth revision (DSM-5). Total score is obtained by summing up the item scores, with higher scores indicating higher levels of depression. (Minimal: 0-13; Mild:14-19; Moderate:20-28; Severe: 29-63. Compared to the original version, the BDI-II added loss of energy and concentration difficulties.	(Beck & Beamesderfer, 1974; Beck et al., 1996)
Starkstein's Apathy Scale (SAS)	Patient	The SAS is a 14-item scale to evaluate cognitive, behavioural, and emotional symptoms of apathy in PD patients. An optimal cut-off score $\geq$14, with sensitivity of 66% and specificity of 100%	(Starkstein et al., 1992)
Montreal Cognitive Test (MoCA)	Clinician	The MoCA is a 30-item test that assesses different cognitive domains including orientation, delayed recall, visuospatial ability/executive function, language, abstraction, semantic fluency, attention, clock-drawing test. The cut-off threshold for PD-MCI is a score less than 26/30.	(Gill et al., 2008)

Global Assessment			
Clinical Global Impressions Scale (CGI): Severity of Illness (CGI-S) and Global-Improvement (CGI-I)	Clinician	The CGI was devised in 1976 for a brief one-stop assessment of the patient's global functioning prior to and after initiating an intervention. CGI-S generally tracks with CGI-I such that improvement in one follows the other.	(Busner et al., 2009)

PD-MCI: Mild cognitive impairment in Parkinson's disease

4.3 Risk

We do not anticipate any distress or lifestyle changes to occur apart from what is expected as part of good clinical care. I devised both the UK and Singapore studies to investigate the phenomenology of two debilitating neuropsychiatric symptoms and their connections with each other, with the aim of ultimately leading to better clinical management of both psychosis and apathy in Parkinson's disease. No undue distress or danger to healthcare staff was anticipated either. Any incidental findings of significance that can impact patient care will be informed to patients as part of the requirements stipulated by the institutional review board upon approval of the research.

4.4 Data Management

The collected data was anonymized, and each patient assigned an anonymised code. All the UK data was entered into a cloud-based clinical research management system (EDGE)(see https://www.edge.nhs.uk/), as per King's College Hospital (KCH) protocol, a system which was embedded into the clinical research infrastructure across UK. The Singapore data was stored online and password-protected, with the password known only to the research team. For the purpose of statistical analysis, all data were analysed in the form of Microsoft Excel 2010, using the Statistical Package for Social Science (version 28.0 for Windows; SPSS).

4.5. Statistical Analysis

I conducted the statistical analysis, with guidance from the statistical support team of Prof. P. Martinez-Martin from the National Center of Epidemiology and CIBERNED, Carlos III Institute of Health in Madrid, Spain, and statistician Dr. S. Vitoratou as part of the King's College London Institute of Psychiatry, Psychology, and Neuroscience biostatistics advisory service. The statistical

analysis was conducted, and graphs created using Statistical Package for Social Science (version 28.0 for Windows, Microsoft Excel 2010, Microsoft PowerPoint 2010, and R software (Version 3.4.0; R Foundation for Statistical Computing, Vienna, Austria). The general statistical methods applied across this thesis are characterized in this chapter, with more specific strategies described in each corresponding chapter.

4.5.1 Missing Data

In terms of handling missing data, imputation techniques were not applied. As this is a real-life clinical study, missing data for both UK and Singapore projects were mostly due to time issues if the patient had to leave the clinic before the instruments could be completed, the patient missed out a question or two on the self-rated tools, or the healthcare professionals were unable to thoroughly check for completeness of responses before the patient left. Therefore, the data can be considered missing completely at random (MCAR)(Bhaskaran & Smeeth, 2014). Moreover, less than 5% of data were missing in both datasets for the variables examined. Therefore, the cases with missing data were omitted for the affected variable, and the analyses run using the remainder, which is an approach associated with unbiased item estimates (Allison, 2009).

4.5.2 Descriptive Statistics

Descriptive statistics for central tendency measures and dispersion (e.g. median, mean, percentages, standard deviation) were explored for each variable to characterise the clinical profile of interest. Sociodemographic data are expressed as mean ±standard deviation, and median (interquartile range), unless otherwise specified. Categorical data is presented as a percentage.

4.5.3 Genetic Testing

In a subset of patients in Singapore, genetic testing was performed as part of a research study (CIRB Ref. 2019/2330, Protocol No. 2002/008/A) supervised by Prof. Eng-King Tan at the Singapore General Hospital. Further details will be applied in Chapter 5.

Chapter 5

Exploring Potential Risk Factors in the phenotypic expression of Neuropsychiatric Symptoms (Psychosis, Apathy) in Parkinson's disease

An interplay of environmental and genetic factors underlies the complex and heterogenous aetiology of Parkinson's disease (PD)(Berg et al., 2021). Environmental factors such as pesticide exposure (van der Mark et al., 2012), head injury, and well-water consumption have been linked to an increased risk for PD, while some factors such as coffee and tobacco use are well-recognized to be associated with decreased risk of developing PD (Liu et al., 2012; Noyce et al., 2012).

Among the variable non-motor symptoms of PD, neuropsychiatric features remain the more debilitating, associated with poorer quality of life, disability, increased institutionalisation, accelerated cognitive decline, and increased caregiver burden (Eichel et al., 2022). While most of the neuropsychiatric symptoms in PD share some commonalities with that of primary psychiatric disorders, the neurobiology and pathophysiology have been shown to be different, complex, and still inadequately understood (F*igures* 5.1 and 5.2) (Taddei et al., 2017; Weintraub et al., 2022). Identifying and predicting risks of developing neuropsychiatric symptoms in PD are therefore major unmet needs.

Figure 5.1 A conceptual model of potential risk factors for PD Psychosis

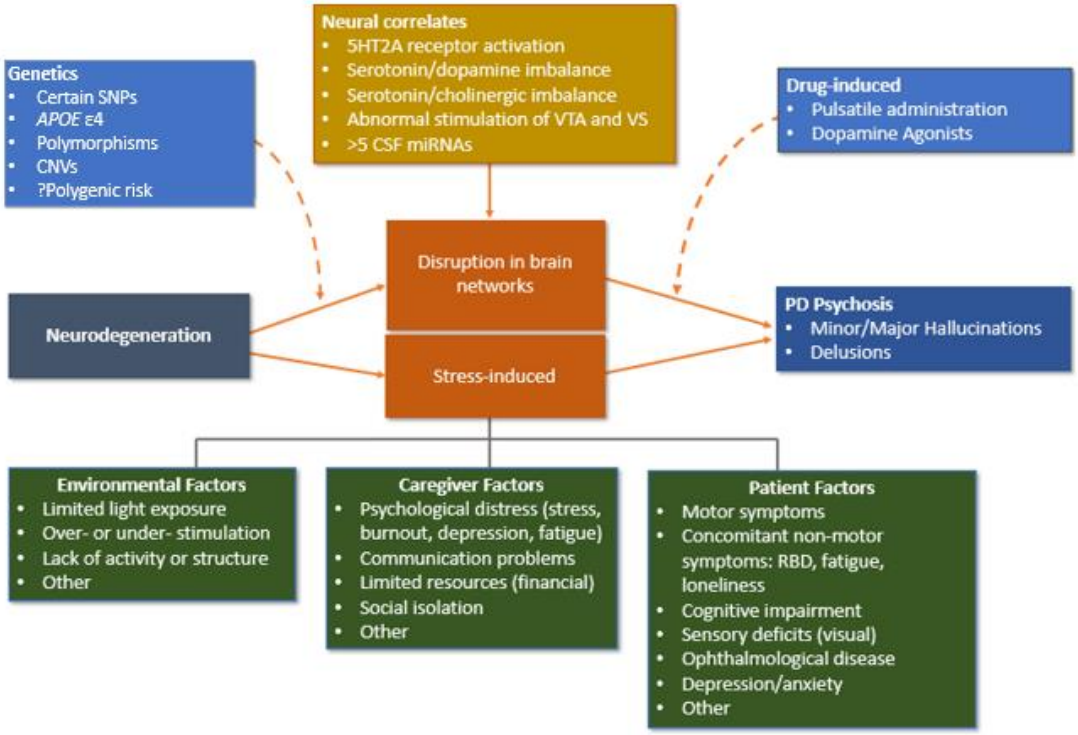
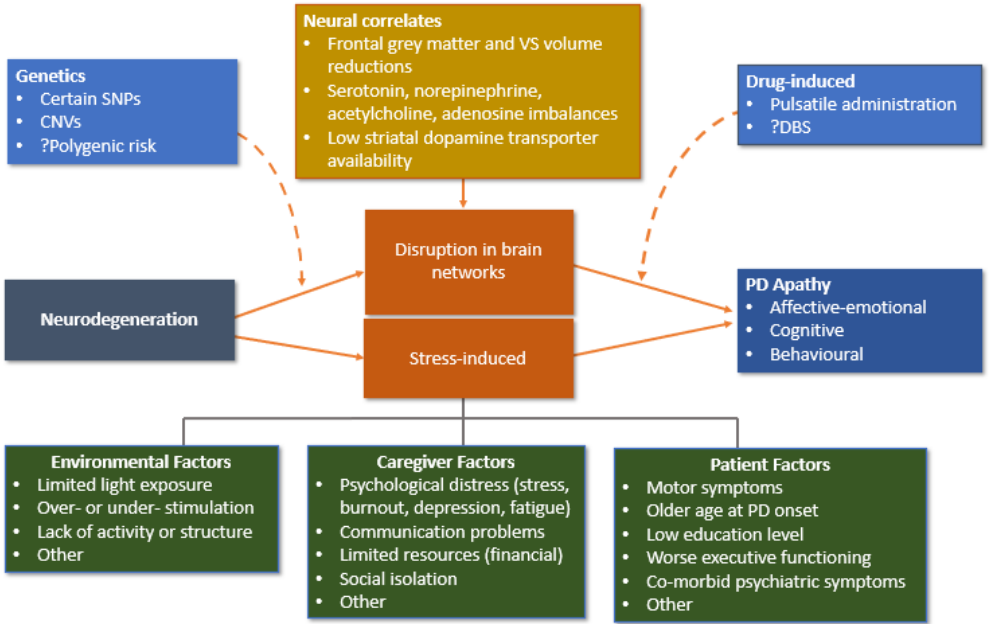


Figure 5.2 A conceptual model of potential risk factors for PD Apathy.



SNPs, single nucleotide polymorphism; CNVs, Copy Normal Variants; CSF, cerebrovascular fluid; VS, Ventral Striatum; RBD, Rapid Eye Movement Sleep Behaviour Disorder; DBS, Deep Brain Stimulation.

***Figures* 5.1 and 5.2 were adapted from Figure 1 of (Ballard et al., 2020), with the summarized content of Chapters 1 and 2, as well as from (Angelopoulou et al., 2022; Kelly et al., 2019; Taddei et al., 2017; Weintraub et al., 2022).**

In this chapter, I will focus on research into:

- Potentially shared genetic architecture between PD and primary psychotic disorders (schizophrenia) as well as mood disorders (bipolar disorder) – Section 5.1.
- The role of geographical and ethnic disparities on apathy in PD in an exploratory analysis – Section 5.2.

5.1 Genetic Analysis of Shared Risk Loci for Schizophrenia and Bipolar disorder with Parkinson's disease in Singapore

5.1.1 Introduction

Though associated with differential involvement of the dopamine system, PD and schizophrenia have overlapping phenotypical features (de Jong et al., 2014; Winter et al., 2006), where iatrogenic parkinsonism in schizophrenia and psychotic symptoms in PD are common. Despite putatively opposing dopaminergic disease mechanisms, schizophrenia is reportedly associated with increased risk of PD (Kuusimaki et al., 2021). This may be related to the chronic risk-altering effects of dopamine receptor antagonists (Erro et al., 2015; Foubert-Samier et al., 2012) or to the increased vulnerability of the dopaminergic system induced by illness phase-dependent dopamine dysregulation (Brisch et al., 2014) in schizophrenia spectrum disorder.

Notwithstanding uncertain aetiology and pathophysiology, bipolar disorder (BD) is known as a multifactorial disorder with presumptive involvement of the dopaminergic network, as levodopa has been shown to induce hypomania or mania in BD patients (Murphy et al., 1971), and because dopamine receptor antagonists can improve manic symptoms. There is robust evidence that people suffering from BD have a significantly increased likelihood of developing PD (Bellou et al., 2016; Faustino et al., 2020) . The dopamine dysregulation hypothesis (Berk et al., 2007) states that the cyclical disease process of BD involves a downregulation of dopamine receptor sensitivity

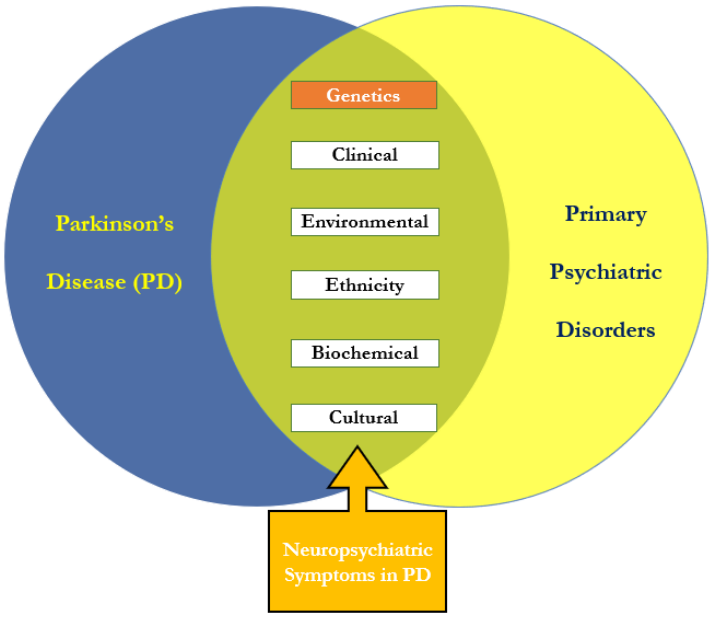
(depression), which is subsequently compensated by augmentation (mania), leading eventually to an overall reduction of dopaminergic activity, the prototypical PD condition. As earlier mentioned in Chapter 2, mood fluctuations are related to the on/off phenomena in PD. Manic symptoms occurred more frequently in the 'on' phase, in contrast to depressive symptoms which are more common in the 'off' phase (Nissenbaum et al., 1987). However, it is important to highlight that the pathophysiological processes underpinning the on/off mood states in PD differ from that of the sustained abnormal mood fluctuations in BD, including involvement of other neurochemical systems besides dopamine.

The role of genetic factors underpinning the risk of patients with schizophrenia or bipolar disease in developing PD remained unclear. Recent genome-wide association studies (GWAS) have revealed shared risk loci between PD (OMIM entry: 168600) and schizophrenia spectrum disorders (Kuusimaki et al., 2021; Smeland et al., 2021) as well as bipolar disorder (Faustino et al., 2020), but only in European ancestry populations. Investigating the extent of cross-phenotype genetic architecture across diverse ancestral groups may simplify the functional characterization of pleiotropic loci that differentiate from disorder-specific loci. Identification of genetic risk variants specific to certain populations will help identify and develop precision medicine-based genetic targets for diagnostic and therapeutic purposes.

We hypothesise that overlapping genetic risk factors between PD and complex psychiatric disorders may help further classify subsets of PD patients at risk of developing neuropsychiatric symptoms such as psychosis and apathy. To address this gap in knowledge, we investigate if selected genetic risk variants that are associated with major psychiatric disorders comprising prominent psychosis within their clinical manifestation, such as schizophrenia and bipolar disorder, modulate the risk of PD in a Southeast Asian population. The outcome of this study will inform future research into the association between the identified genetic risk variants and PD patients who develop psychosis or apathy. The primary aim of this study is to identify the types

and frequencies of genetic variation in the 4 single nucleotide polymorphisms (SNP) between PD and healthy control populations.

***Figure* 5.3 A conceptual model of potential aetiological factors shared between Parkinson's & primary psychiatric disorders in the phenotypic expression of neuropsychiatric symptoms.**



5.1.2 Contributions and Collaborations

The genetic angle of the study was part of the collaboration between UK and Singapore for this academic project. I assisted in participant recruitment and conducted the statistical analysis. Blood samples were collected by the research staff of Prof. Eng-King Tan's team at the Singapore General Hospital (SGH) (refer Chapter 4), and genomic DNA extraction was carried out. The samples were then analysed at the SGH Movement Disorders laboratory.

5.1.3 Methods

From recent meta-analyses of GWAS identifying novel risk loci for both schizophrenia and bipolar disorders (Faustino et al., 2020; Kuusimaki et al., 2021; Li et al., 2021; Smeland et al., 2021),

we selected 2 SNPs for each disease with the largest effect size in terms of genetic risk – specifically rs302714 *RERE*, rs62333164 *CLCN3*, rs7969091 *RHEBL1*, rs41335055 *VRK2*.

We analysed these 4 SNPs at the novel risk loci using a case control methodology comprising a total of 1291 subjects. Patients and ethnically matched controls were recruited in tertiary movement disorder centres in Singapore. Patients were diagnosed with PD using the UK Parkinson's Disease Society Brain Bank criteria. The control group consists of subjects who did not have PD or other neurological and psychiatric diseases.

Written informed consent was obtained according to the Declaration of Helsinki. This study was approved by the institutional ethics committee (Singhealth Centralized Institutional Review Board (CIRB), 2002/008/A).

5.1.3.1 Genotyping

Peripheral blood samples were obtained from 821 PD patients and 470 controls. A total of 10ml of peripheral blood was collected and genomic DNA extracted from venous blood using standard methods. Genotyping of the 4 SNPs of interest (rs302714, rs7969091, rs41335055, and rs62333164) was performed using a Real Time 7500 PCR platform (Life Technologies) and 10% were verified using Sanger sequencing.

5.1.3.2 Statistical analyses

Power analysis suggests that the current sample size of 821 PDs and 470 controls will achieve 80% power to detect a difference between the SNPs proportions of more than 5%. The prevalence of the 4 SNPs varies from 12% to 30%. The test statistic used for the power calculation is the two-sided z-test with unpooled variance. Type I error was adjusted for multiple testing and set at 1.25%

(5% corrected for 4 SNP using Bonferroni correction). Sample size calculation is conducted via PASS software (2022 Power Analysis and Sample Size Software (2022). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass.).

Descriptive statistics were used to characterize demographic profiles of patients. Categorical data are presented as n (%). Differences in genotype distributions between the two groups were analysed using Pearson's Chi-squared test. The Chi-squared test was two-sided, with $p < 0.05$ considered statistically significant. Data analyses were performed using the software *STATA* version 16 (StataCorp, College Station, TX, USA).

The mean age of the PD and control groups were 66.8 (range: 34–92) and 52.3 (range: 30–83) respectively. To adjust for the significant difference in mean age between the two groups, we ran a secondary analysis for a subset of the sample that is age 65 or below. The sample sizes of these age-adjusted subsets were n=342 and n=426 for the PD and control groups respectively, with the mean age for the former at 57.3 years, and for the latter at 50.3 years.

5.1.4 Results

The demographic data of our sample population (as presented in *Table* 5.1) are comparable across both groups, with the exception of age. Frequencies of the 4 investigated genetic polymorphisms in the genes *RERE*, *CLCN3*, *RHEBL1*, and *VRK2* are provided in *Table* 5.2. The distributions of the 4 SNPs did not deviate significantly from Hardy-Weinberg equilibrium in both PD and control groups.

There were no significant statistical differences in genotype distributions of rs302714 *RERE*, rs62333164 *CLCN3*, rs7969091 *RHEBL1*, and rs41335055 *VRK2* genes when comparing PD patients and healthy controls (p=0.67, p=0.11, p=0.77, p=0.78, respectively) in the full sample (*Table* 5.2). There was a trend in the directional effects of allele A, with a higher percentage of the

AC heterozygotes of rs302714 (*RERE*; +1.8%), as well as lower frequency of the AG heterozygotes of rs62333164 (*CLCN3*; -1.6%), observed among the PD patients.

In the secondary analysis of the age-adjusted sample, the outcomes were largely similar although there was a trend towards significance in the frequency differences of rs62333164 *CLCN3* between the PD patients and healthy controls (p=0.11, *Table* 5.2; p=0.06, *Table* 5.3).

***Table* 5.1: Demographics data of the PD patients and controls in the sample population.**

Variable	PD patients, n=821	Controls, n=470	*p*
Sex: male/female	479 (58.3)/342 (41.7)	265(56.4)/205(43.6)	NS
Age, years	66.8 ± 10.1	52.3 ± 9.3	<0.001
Age at PD onset, years	63.8 ± 10.8	NA	NA
Positive family hx of PD	70 (8.5)	30 (6.4)	NS

Values are number of patients with frequencies (%) and mean ± standard deviation. NA, not applicable; NS, not significant. PD, Parkinson's disease; y, years; hx, history.

***Table* 5.2: Genotype frequencies of selected risk loci of schizophrenia and bipolar disorder among PD patients and healthy controls of Asian ancestry, full sample (n=1291).**

Candidate Psychiatric disease	Gene	Lead SNP	Genotypes	PD patients n (%)	Controls n (%)	*p*
Schizophrenia	Chr 1, *RERE*	rs302714	AA(WT)	691 (84.2)	404 (86.0)	0.67
			AC	125 (15.2)	63 (13.4)	
			CC	5 (0.6)	3 (0.6)	
	Chr 4, *CLCN3*	rs62333164	AA	2 (0.2)	5 (1.1)	0.11
			AG	97 (11.8)	63 (13.4)	
			GG(WT)	722 (87.9)	402 (85.5)	
Bipolar disorder	*RHEBL1*	rs7969091	AA(WT)	228 (27.8)	139 (29.6)	0.77
			AG	412 (50.2)	232 (49.4)	
			GG	181 (22.0)	99 (21.1)	

	VRK2	rs41335055	CC (WT)	714 (87.0)	412 (87.7)	0.78
			CT	101 (12.3)	56 (11.9)	
			TT	6 (0.7)	2 (0.4)	

Values are number of patients with frequencies (%). PD, Parkinson's disease; SNP, single nucleotide polymorphism; *RERE*, arginine-glutamic acid dipeptide repeats; *CLCN3*, chloride voltage-gated channel 3; *RHEBL1*, Ras Homolog Enriched in Brain-Like Protein 1; *VRK2*, Vaccinia-Related Kinase 2.

***Table* 5.3: Genotype frequencies of selected risk loci of schizophrenia and bipolar disorder among PD patients and healthy controls of Asian ancestry, age-adjusted sample (age ≤ 65; n=768).**

Candidate Psychiatric disease	Gene	Lead SNP	Genotypes	PD patients n (%)	Controls n (%)	*p*
Schizophrenia	Chr 1, *RERE*	rs302714	AA(WT)	284 (83.0)	365 (85.7)	0.53
			AC	55 (16.1)	59 (13.8)	
			CC	3 (0.88)	2 (0.47)	
	Chr 4, *CLCN3*	rs62333164	AA	1 (0.3)	4 (0.94)	0.06
			AG	30 (8.8)	58 (13.6)	
			GG(WT)	311 (90.9)	364 (85.4)	
Bipolar disorder	*RHEBL1*	rs7969091	AA(WT)	101 (29.5)	123 (28.9)	0.54
			AG	158 (46.2)	212 (49.8)	
			GG	83 (24.3)	91 (21.4)	
	VRK2	rs41335055	CC (WT)	303 (88.6)	374 (87.8)	0.89
			CT	38 (11.1)	50 (11.7)	
			TT	1 (0.3)	2 (0.5)	

Values are number of patients with frequencies (%). PD, Parkinson's disease; SNP, single nucleotide polymorphism; *RERE*, arginine-glutamic acid dipeptide repeats; *CLCN3*, chloride voltage-gated channel 3; *RHEBL1*, Ras Homolog Enriched in Brain-Like Protein 1; *VRK2*, Vaccinia-Related Kinase 2; WT, Wild Type

5.1.5 Discussion

The gene *CLCN3* encodes a brain-expressed voltage-sensitive chloride channel that directly modulates fast excitatory glutamatergic synapses modulating plasticity in the hippocampus (Guzman et al., 2014), and has been linked to neurodegenerative disorders (Perrone et al., 2021). The gene *RERE* mediates a nuclear receptor coregulator that coordinates retinoic acid signalling in key tissues during neurodevelopment, with its variants implicated in schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics, 2014), neurodevelopmental disease (Jordan et al., 2018) and depression (Wray et al., 2018).

In a previous meta-analysis of all available GWAS of PD risk loci (Nalls et al., 2019) among patients of European ancestry, rs62333164 *CLCN3* was identified as a novel risk locus for PD, and was also linked to higher susceptibility in schizophrenia in another, more recent, study (Smeland et al., 2021), whereas the schizophrenia risk allele at the *RERE* locus has been linked to lower PD risk (Smeland et al., 2021). This is consistent with the lower frequency of AG genotype of the former gene, and the higher frequency of the AC genotype of the latter found among PD patients in this study.

To our knowledge, this is the first genetic association study of these 4 SNPs for both schizophrenia and bipolar disorder as risk loci for PD in an Asian population. We found a trend indicating an association for rs62333164 *CLCN3* in our PD patients.

Limitations to this study include that of crucial pleiotropic associations being omitted due to external factors, or rare genetic variations. Another major limitation includes the lack of information about important potential confounders such as family history of psychiatric illness. While our sample size of 1291 subjects was relatively large, it is possible that the actual effect size of the tested SNPs may be smaller in our Asian population compared to that of previously tested Western populations.

In accordance with the overall theme of this thesis, I would have preferred to also investigate for shared genetic markers for apathy or apathetic syndromes in this sample population, but no such data existed at the point this study was conceptualised and initiated.

5.1.6 Conclusions

In a case control study, we found a borderline association between rs62333164 *CLCN3* and PD in our Asian population, suggesting a potential overlap of genetic risk factors between PD and psychiatric disorders. Further validation in independent cohorts and meta-analyses involving larger samples are warranted, as identification of shared genetic factors can help facilitate stratification of PD patients at risk of neuropsychiatric complications for the development of targeted therapeutic strategies as part of personalized medicine.

5.2 Exploring the roles and impact of geographical & ethnic disparities on apathy in Parkinson's disease

5.2.1 Introduction

Research underlying PD apathy has been largely hampered not only by inconsistent diagnostic frameworks, but also by its considerable overlap with depression and anxiety, as well as the inherent symptoms of PD itself (e.g facial impassivity, functional disability)(Ineichen & Baumann-Vogel, 2021). The nature and degree to which the problem of apathy exists in PD may also be influenced by exogenous factors such as the role of ethnicity, sociocultural heterogeneity, geographical position, altitude, and climate (Ben-Joseph et al., 2020; Rana et al., 2016; Sauerbier et al., 2021).

While some contended that apathy in PD is merely an epiphenomenon of low mood (Bogart 2011) and not a clinically meaningful syndrome, most studies now agreed that both apathy and

depression can exist independent of each other. Nevertheless, many did not consider the presence of anxiety which often overlapped with apathy (Aarsland et al., 2007; Aarsland & Karlsen, 1999; Kulisevsky et al., 2008; Maillet et al., 2016; Starkstein & Brockman, 2011) in PD, reflecting not only shared clinical features, but also possibly the intersecting dysfunction of dopaminergic and serotonergic neurotransmitter networks (Maillet et al., 2016). As such, some have re-defined "true" apathy as not only a syndrome independent of depression, but also of anxiety (Foley & Cipolotti, 2021),the characteristics of which remained unknown.

So far, apathy profiles in PD have not yet been explored and compared in detail between the various ethnic groups in diverse geographical locations.

Here, we aim to evaluate frequency and phenomenology of apathy in PwP and assess whether the nature of PD apathy transcends not only ethnic disparities, but also geographical boundaries. The primary aims of the current study were to characterise the apathy burden in PD patients across two different geographical locations spanning the globe from East to West, and the differential impact on quality of life, measured through the PDQ-8. Other outcomes consisted of determining the differential patient profiles between patients with apathy and without depression/anxiety, patients with apathy and depression/anxiety, and patients without apathy and depression/anxiety.

5.2.2 Contributions and Collaborations

I wrote the entirety of this manuscript, did the data analysis, as well as contributed all the tables. My research colleague helped to check that the appropriate statistical analysis methods have been used.

5.2.3 Methods

For the purposes of the current analysis, information was extracted (in November 2019) from patients whose data were collected as part of clinical research at King's College Hospital London (United Kingdom), as well as from the Singapore General Hospital (Singapore), for whom

an assessment of apathy with the Starkstein's Apathy Scale (SAS) was available. Prior to each study procedure, all patients in both cohorts gave written consent in accordance with the Declaration of Helsinki respectively. Data included consisted of sex, disease duration, and the Levodopa equivalent daily dose (LEDD). Clinician-based evaluations included the Hoehn and Yahr (HY) staging (Hoehn & Yahr, 1967), while patient-reported outcomes included the SAS (Starkstein et al., 1992), the Hospital Anxiety and Depression Scale (HADS)(Mondolo et al., 2006; Zigmond & Snaith, 1983), and the PD Questionnaire-8 item (PDQ-8)(Martinez-Martin et al., 2004) for assessment of quality of life.

For both cohorts, clinical apathy was defined as a score of 14 or higher on the SAS (Starkstein et al., 1992). Clinical depression was defined as a score of 11 or higher on the depression subscale of the HADS, while clinical anxiety was reported as a cutoff score of 7 and higher on the corresponding anxiety subscale (Mondolo et al., 2006, 2007; Schrag et al., 2007).

5.2.3.1 London, United Kingdom

Cross-sectional data for analysis were obtained from the multi-center longitudinal observational real-life "ethnicity study", adopted by the National Institute of Health Research (NIHR) in the UK (UKCRN No: 18278) and authorised by the local Research Ethics Committee (REC) (National Research Ethics Service, London Bromley) and the research and development (R&D) office at King's College Hospital, London as part of the Non-motor Longitudinal International cohort study (NILS; UKCRN 10084). The main inclusion criterion was a diagnosis of idiopathic PD according to the UK Brain Bank criteria and those who belonged to the ethnic groups categorised according to the Office for National Statistics criteria from the Census 2011 in England and Wales (Office for National Statistics, 2018) used in the National Health System (NHS). Exclusion criteria were (1) diagnosis of atypical Parkinsonism; (2) dementia (as per internationally accepted criteria) (Zadikoff et al., 2008); (3) inability to give informed consent. (4) Conditions interfering with assessment (e.g. blindness) (5) Patients from mixed ethnic groups.

5.2.3.2 Singapore

Cross-sectional data for analysis were extracted from an ongoing multi-center prospective, longitudinal study of apathy in PD approved by the local ethics committee since 2012 (CIRB 2012/759/A). Ethnic groups were categorised according to the decennial population census provided by the Singapore government at the portal: https://data.gov.sg – comprising 74.3% Chinese, 13.3% Malays, 9% Indians, and 3.2% classified as Others, updated as of 2015. The main inclusion criteria were a diagnosis of idiopathic PD according to the UK Brain Bank criteria, and that patients were not on any antidepressants for at least four weeks prior to study initiation. Exclusion criteria were (1) diagnosis of atypical Parkinsonism; (2) concurrent neurodegenerative disorders (as per internationally accepted criteria) (Zadikoff et al., 2008); (3) inability to give informed consent. (4) Conditions interfering with assessment (e.g. blindness) (5) Active alcohol or illicit substance use.

5.2.4 Statistical Analyses

Sample size calculation is not required for retrospective studies, and power calculation will not add much information. A significant *p*-value would mean the study having enough statistical power, while the study would be under-powered for non-significant *p*-value findings. Hence *post-hoc* power calculation is not recommended.

As the scores of the different scale data were not normally distributed (determined through Kolmogorov-Smirnov test), we used the Mann-Whitney-U-test to evaluate the differences between groups. For categorical data, we used the Chi-Square test. To correct for statistically significant differences in disease duration and LEDD between the London and Singapore cohorts, Quade's rank procedure was applied. To determine statistically significant associations between SAS scores, demographic data, and non-motor outcomes, we performed univariate analyses (Spearman's test) between the different assessments, as mentioned above, and SAS scores.

The significance threshold was set at ≤0.05 and where relevant, a Benjamini-Hochberg procedure (Benjamini & Hochberg, 1995) was used for multiple comparisons. We used Benjamini-Hochberg approach as a powerful and conservative method to account for multiple comparisons to avoid inflation in type I error and to control false discovery rate. *Post-hoc* analyses were performed for outcomes that remained significant after correction for multiple testing. All data were analysed using SPSS Version 27 (IBM SPSS Statistics for Windows (Version 27.0. Armonk, NY: IBM Corp.). Data are represented as mean ± standard deviation, number (percentage), median (25^{th}-75^{th} percentile), or *r* -values, unless otherwise specified.

5.2.5 Results

A total of 202 PD patients, comprising of 75 and 127 patients from UK and Singapore were included in the analysis.

Demographics and outcome measures for these groups are summarized in *Table* 8.1. As compared to the London PD cohort, the Singapore cohort had a shorter disease duration and charted lower mean LEDD scores and reduced PDQ-8 scores. After correction for multiple testing and accounting for the statistically significant differences in disease duration and LEDD, the main difference between both groups was in disease severity, with the UK cohort at a median HY stage of 3 and that of Singapore cohort at a median HY stage of 2.5 (p<0.001). There were no significant differences between the two cohorts in terms of apathy prevalence, occurrence with depression, or apathy burden (SAS total scores), although both cohorts posted mean SAS scores indicating a collective presence of clinical apathy.

5.2.5.1 Distribution of apathy across the two cohorts

In 75 PD patients from London, SAS scores ranged from 10 to 21, with an overall mean of 15.5 (SD=8.1). A total of 42 (56%) suffered from clinical apathy (SAS≥14), with 19(25.3%) indicating depression and 18 (24%) experiencing anxiety. For 127 PD patients from Singapore, SAS

scores ranged from 10 to 19 with a mean of 14.6 (SD=6.4), with 74 (58.3%) suffering clinical apathy, 31 (24.4%) depression, and 47 (37%) endorsing anxiety.

There was a significant overlap between apathy, depression, and anxiety. In the London cohort, of the 42 PD patients afflicted with clinical apathy, 1 (2.4%) had associated depression only, 17 (40.5%) had comorbid anxiety only, and 14 (33.3%) had concurrent depression and anxiety. Amongst the 74 similarly affected patients in Singapore, about 5 (6.8%) had associated low mood only, 19(25.7%) had comorbid anxiety only, and 18(24.3%) experienced both concurrently. Consistent with existing literature, apathy was significantly associated with both depression (London: r=0.540, p<0.001; Singapore: r=0.306, p<0.001), and anxiety (London: r=0.445, p<0.001; Singapore: r=0.270, p<0.01). *Post hoc* analyses revealed depression remained the primary predictor of apathy scores across both cohorts (*Table* 5.8).

5.2.5.2 Impact of ethnicity

As the next step, we determined whether ethnicity impacted the apathy scale scores by analysing for differences across the different ethnic groups for both PD cohorts. We also compared the apathy scores between Asian PD patients (n=17) in London and those in Singapore (n=121). In the Singapore cohort, 6 patients of unknown ethnicity were excluded from further analysis accordingly, with the remaining 121 patients of Chinese, Malay, and Indian backgrounds available for analysis.

5.2.5.2.1 London cohort

There were no significant differences observed in terms of apathy burden and quality of life between the top three ethnicity groups in our London PD sample (*Table* 5.10). Approximately 10.9% of the White PwPs, 17.6% of the Asians, and 18.2% of the Black PwPs demonstrated 'pure' clinical apathy independent of both depression and anxiety. Anxiety and depression occurred at similar rates across all three ethnicity groups (*Table* 5.11).

5.2.5.2.2 Singapore cohort

Our findings revealed that there were no significant differences found across the top three ethnicity groups in the Singapore sample in terms of apathy burden and quality of life (*Table* 5.9). Isolated apathy occurred across ethnic background with a prevalence of 26.5% in Chinese PwP, 30.0% in Malay PwP, and 15.4% of the Indian PwP (*Table* 5.13). Like the London cohort, there were no significant differences in the prevalence of anxiety or depression across all three ethnicity groups (*Table* 5.10).

5.2.5.2.3 Asians in London v. Asians in Singapore

When comparing the demographics of Asian patients in both PD cohorts, there were significant differences noted in terms of disease duration, HY, as well as LEDD. Generally, both populations charted mean SAS scores indicating clinical apathy (SAS≥14). Prevalence of depression (HADS depression ≥ 11) and anxiety (HADS anxiety ≥7) were comparable across both groups (*Table* 5.9).

***Table* 5.4: Demographics and non-motor outcomes in two cohorts of PD patients (London, Singapore)**

	London (n=75)	**Singapore (n=127)**	***p***	***p****
Age, years	66.2±10.9	64.6±11.1	0.318	0.445
Sex (M/F)	48/27	92/35	0.209	0.366
Disease duration, years	9.7±5.6	5.9±5.7	<0.001	NA
HY	3.0 (2.0-3.0)	2.5 (2.0-3.0)	<0.001	**<0.001**
LEDD, mg	875.9±655.6	402.7±317.0	<0.001	NA
HADS				
Anxiety	7.9±4.5	5.6±10.7	0.013	**0.030**
Depression	7.2±4.3	7.1±4.3	0.895	0.895
PDQ-8	12.3±7.0	8.6±6.8	<0.001	**<0.001**
SAS	15.5±8.1	14.6±6.4	0.525	0.613

*p**: corrected for statistically significant differences in disease duration and LEDD using Quade's rank procedure and corrected for multiple testing using Benjamini-Hochberg procedure.

***Table* 5.5: Distribution of apathy, anxiety, and depression across the two cohorts of PD patients (London, Singapore)**

	London (n=75)	**Singapore (n=127)**
Apathy without depression & without anxiety	10 (13.3%)	32 (25.2%)
Apathy and depression without anxiety	1 (1.3%)	5 (3.9%)
Apathy and anxiety without depression	17 (22.7%)	19 (15%)
Apathy + depression + anxiety	14 (18.7%)	18 (14.2%)
Depression and anxiety without apathy	2 (2.7%)	5 (3.9%)

Depression without apathy & without anxiety	2 (2.7%)	3 (2.4%)
Anxiety without apathy & without depression	2 (2.7%)	5 (3.9%)
Neither apathy nor depression nor anxiety	23 (30.7%)	40 (31.5%)
Group difference: p=0.322 (Chi Square test)		

Apathy: SAS 14 or higher ; Depression: HADS depression subscore 11 or higher;
Anxiety: HADS anxiety subscore 7 or higher

***Table* 5.6: Association of apathy (SAS) scores with demographics and other symptoms of Parkinson's disease.**

	London (n=75)	**Singapore (n=127)**	**Entire cohort (n=202)**
Age	0.179	0.230**	0.211**
Disease duration	0.102	0.157	0.148*
LEDD	0.249*	0.172	0.183**
HADS			
Anxiety	0.445***	0.295**	0.348***
Depression	0.540***	0.439***	0.480***
PDQ-8	0.503***	0.299**	0.392***

Values expressed as r. *: 0.01<p≤0.05; **: 0.001<p≤0.01; ***: p<0.001

***Table* 5.7: Regression analyses with predictors of apathy (SAS) scores.**

	London (n=75) R^2**=0.318**	**Singapore (n=127)** R^2**=0.285**	**Entire cohort (n=202)** R^2**=0.291**
Age	NA	0.214**	0.177**
Disease duration	NA	NA	0.031
LEDD	0.133	NA	0.067
HADS			
Anxiety	0.136	-0.186*	-0.113
Depression	0.464**	0.522***	0.528**

Values expressed as standardised β. *: 0.01<p≤0.05; **: 0.001<p≤0.01; ***: p<0.001; NA: not applicable.

***Table* 5.8: Regression analyses with predictors of quality of life (PDQ-8) scores.**

	London (n=75) R^2**=0.530**	**Singapore (n=127)** R^2**=0.525**	**Entire cohort (n=202)** R^2**=0.519**
Disease duration	NA	0.184*	0.100
LEDD	0.198*	0.033	0.196**
HADS			
Anxiety	0.256*	-0.017	0.038
Depression	0.360**	0.625***	0.537***
SAS	0.177	0.054	0.131*

Values expressed as standardised β. *: 0.01<p≤0.05; **: 0.001<p≤0.01; ***: p<0.001; NA: not applicable.

***Table* 5.9: Comparing apathy scores between Asian patients with Parkinson's disease across both London and Singapore respectively.**

	London (n=17)	**Singapore (n=121)**	***p***	***p****
Age, years	67.5±11.6	64.9±10.9	0.203	0.305
Sex (M/F)	11/6	90/31	0.432	0.486
Disease duration, years	10.1±4.8	5.9±5.8	0.001	**0.003**
HY	3.0 (2.5-4.0)	2.5 (2.0-3.0)	<0.001	**<0.001**
LEDD, mg	885.7±528.3	390.1±298.7	<0.001	**<0.001**

HADS Anxiety Depression	 8.5±4.8 7.9±4.0	 5.7±10.9 7.1±4.4	 0.107 0.411	 0.193 0.486
SAS	16.2±7.8	14.7±6.5	0.516	0.516
PDQ-8	12.8±7.3	8.7±6.8	0.019	**0.043**

Ethnicity: **Asian** (for KCH Asian other + Indian; for Singapore Chinese, Malay, and Indian only);
*p**: corrected for multiple testing using Benjamini-Hochberg procedure.

***Table* 5.10: Apathy scores in patients with Parkinson's disease across different ethnic backgrounds in London.**

	White (n=46)	Asian (n=17)	Black (n=11)	*p*	*p**
Age, years	65.4±10.6	67.5±11.6	63.8±11.8	0.653	0.888
Sex (M/F)	29/17	11/6	8/3	0.833	0.888
Disease duration, years	10.4±6.0	10.1±4.8	7.0±3.7	0.228	0.888
HY	2.0 (2.0-3.0)	3.0 (2.5-4.0	3.0 (2.0-3.0)	0.365	0.888
LEDD, mg	958.8±747.1	885.7±528.3	546.0±243.1	0.190	0.888
HADS Anxiety Depression	 7.9±4.7 6.9±4.7	 8.5±4.8 7.9±4.0	 6.8±4.0 6.7±3.3	 0.888 0.597	 0.888 0.888
SAS	16.0±8.0	16.2±7.8	13.1±10.0	0.735	0.888
Presence of Apathy (SAS≥14)	26 (56.5%)	11 (64.7%)	5 (45.5%)	0.603	0.888
PDQ-8	12.5±7.3	12.8±7.3	10.7±5.4	0.700	0.888

*p**: corrected for multiple testing using Benjamini-Hochberg procedure.

***Table* 5.11: Distribution of apathy, anxiety, and depression in PD patients across different ethnic backgrounds in London**

	White (n=46)	Asian (n=17)	Black (n=11)
Apathy without depression & without anxiety	5 (10.9%)	3 (17.6%)	2 (18.2%)
Apathy and depression without anxiety	1 (2.2%)	0 (0.0%)	0 (0.0%)
Apathy and anxiety without depression	11 (23.9%)	5 (29.4%)	1 (9.1%)
Apathy + depression + anxiety	9 (19.6%)	3 (17.6%)	2 (18.2%)
Depression and anxiety without apathy	0 (0.0%)	1 (5.9%)	0 (0.0%)
Depression without apathy & without anxiety	1 (2.2%)	1 (5.9%)	0 (0.0%)
Anxiety without apathy & without depression	3 (6.5%)	1 (5.9%)	1 (9.1%)
Neither apathy nor depression nor anxiety	16 (34.8%)	3 (17.6%)	4 (36.4%)
Group differences: *p*=0.780(Chi-Square test)			

***Table* 5.12: Apathy scores in patients with Parkinson's disease across different ethnic backgrounds in Singapore.**

	Chinese (n=98)	Malay (n=10)	Indian (n=13)	*p*	*p**
Age, years	64.5±11.4	65.1±8.6	66.6±7.9	0.916	0.916
Sex (M/F)	76/22	5/5	9.4	0.266	0.892
Disease duration, years	5.5±5.5	10.7±8.2	5.5±4.7	0.100	0.892
HY	2.5 (2.0-3.0)	2.5 (1.5-3.0)	2.5 (2.0-2.75)	0.738	0.892
LEDD, mg	380.0±306.0	340.0±173.3	334.8±334.3	0.371	0.892
HADS Anxiety Depression	 5.3±11.7 7.3±4.4	 8.3±8.1 7.0±5.8	 7.1±5.3 6.1±3.2	 0.617 0.803	 0.892 0.892
SAStotal	14.8±6.6	16.2±7.6	13.4±4.8	0.586	0.892
Presence of Apathy (SAS≥14)	60.2%	60.0%	46.2%	0.773	0.892
PDQ-8	8.3±6.3	11.1±9.8	9.7±7.9	0.783	0.892

*p**: corrected for multiple testing using Benjamini-Hochberg procedure

***Table* 5.13: Distribution of apathy, anxiety, and depression in PD patients across different ethnic backgrounds in Singapore.**

	Chinese (n=98)	**Malay (n=10)**	**Indian (n=13)**
Apathy without depression & without anxiety	26 (26.5%)	3 (30%)	2 (15.4%)
Apathy and depression without anxiety	4 (4.1%)	0 (0.0%)	0 (0.0%)
Apathy and anxiety without depression	14 (14.3%)	1 (10.0%)	3 (23.1%)
Apathy + depression + anxiety	15 (15.3%)	2 (20%)	1 (7.7%)
Depression and anxiety without apathy	4 (4.1%)	1 (10.0%)	0 (0.0%)
Depression without apathy & without anxiety	2 (2%)	0 (0.0%)	1 (7.7%)
Anxiety without apathy & without depression	4 (4.1%)	0 (0.0%)	1 (7.7%)
Neither apathy nor depression nor anxiety	29 (26.2%)	3 (30%)	5 (38.5%)
Group differences: p=0.926 (Chi-Square test)			

5.2.6 Discussion

A recent literature survey of non-motor symptoms in Asian regions found that a high prevalence of non-motor symptoms (NMS) was noticed across all ethnic groups (Sauerbier, Jitkritsadakul, et al., 2017). Although 90-100% of patient report at least one NMS, irrespective of ethnic background, there seems to be a difference in the distribution of specific NMS (van Wamelen, Sauerbier, et al., 2021). Current data on the impact of geographical and ethnic differences on the trajectory of apathy in PD has been lacking. Comparing individual epidemiological studies is a challenging feat, not least due the wide heterogeneity between studies in terms of case ascertainment, applied instrument, sample sizes, and methodology, as well as possible confounding factors such as seasonal and sociocultural differences.

A recent large cross-sectional study noted that there was a universal presence of non-motor symptoms in PD across the different geographical locations, with an overall severe non-motor burden. The mood/apathy domain of the Non-Motor Symptom Scale (NMSS) represented one of the highest NMS burden, with a clear negative impact on the quality of life amongst PD patients (van Wamelen, Sauerbier, et al., 2021).

To our knowledge, the current study represents the first in comparing and contrasting the clinical profile of apathy and its associations with depression and anxiety in a multi-national cohort

of non-demented PD patients, in a real-life observational design, with characterisation across the different ethnicities in each distinct geographical site, utilising a standardised recommended and validated measurement scale for clinical apathy.

The key primary findings were:

(a) A universal presence of isolated clinical apathy in Parkinson's disease transcending age, sex, geographical boundaries, and ethnicity discrepancies, and which can occur independent of depression and anxiety.
(b) Depression, which frequently co-occurs with apathy in PwP, appears to be a significant contributor to a decline in quality of life.

Other findings include:

(a) Clinical apathy is likely intrinsic to PD and seems to occur at similar prevalence across different ethnicities.
(b) Prevalence of clinical apathy in PD was more than 50% in both London and Singapore populations, which is consistent with previous estimates in the literature.
(c) Clinical apathy exists despite high average LEDD in PD, particularly in the London cohort, suggesting the involvement of non-dopaminergic neurotransmitter networks in its underlying pathophysiology.

Different prevalence rates of apathy have been shown to vary across PD populations of disparate ethnicities; 31.5% amongst Korean patients (Chung et al., 2016), 17% - 47% amongst patients in Japan (Oguro, 2014; Oguru et al., 2010), 18.6% -28.8% (17.29% apathy without depression) amongst patients in China (Liu et al., 2017; Ou et al., 2020). Nosological difficulties, different population groups, diverse measuring instruments, and overlap with depression as well as anxiety hampered comparisons (Refer Chapter 1)(Bogart, 2011; den Brok et al., 2015).

The prevalence of apathy amongst PD populations of more than 50% across both London and Singapore in this study is consistent with the range (12% - 62.3%) elucidated in recent meta-

analyses on this matter (den Brok et al., 2015; Mele et al., 2019). When considering only those experiencing "true" apathy, with no depression or anxiety (Foley & Cipolotti, 2021), in a non-demented population, the prevalence in our study dropped to 13.3% in London and 25.2% in Singapore (*Table* 5.2). These rates however, were dissimilar to that reported by the only other study on the prevalence of apathy without overlapping depression and anxiety (14.7%) in PD (Foley & Cipolotti, 2021). This was likely due to their different in diagnosing depression and anxiety (HADS subscale 8 or higher) as compared to our study (Depression: HADS corresponding subscale of 11 or higher; Anxiety: HADS corresponding subscale of 7 or higher); however the HADS cut-off points we used have been recommended to diagnose probable cases of clinical depression or anxiety in Parkinson's disease (Mondolo et al., 2006, 2007; Schrag et al., 2007).

Our study also showed that apathy (without depression or anxiety) is prevalent across the top three ethnic groups at similar rates in each study location respectively (*Table* 5.8 - London: 10.9%-18.2%; *Table* 5.10 - Singapore: 15.4% - 26.5%). This further confirms that apathy is a distinct neuropsychiatric phenomenon from depression and anxiety that is likely intrinsic to Parkinson's disease, irrespective of ethnic and geographical boundaries.

Although apathy in PD has long been thought of as primarily hypodopaminergic in origin (Pagonabarraga et al., 2015; Thobois et al., 2010; Thobois et al., 2013), emerging lines of evidence support the roles of non-dopaminergic disruptions of the mesolimbic and mesostriatal networks for its pathogenesis (Maillet et al., 2016). Noradrenergic alterations in several key parts of the limbic system has been shown to result in increased apathy amongst PD patients (Remy et al., 2005). A neuroimaging study found that there were more disturbances found with the serotonergic circuits for PD apathy than dopaminergic, affecting the bilateral caudate nuclei, putamen, thalami, and pallidum, with a specific focus within the insula, orbitofrontal, and subgenual anterior cingulate cortices in early PD (Maillet et al., 2016). Cholinergic system dysfunction may also play a significant role in pathogenesis, as reflected by pharmacological studies which demonstrated improvement in apathy after Rivastigmine intake (Devos et al., 2014). Certainly, our study

demonstrating that apathy exists even despite the high average LEDD across both our study cohorts supports the notion of intersecting non-dopaminergic involvement (*Table* 5.1).

In terms of impact on quality of life, our study did not find significant differences among the diverse ethnic groups either in London or in Singapore. However, it appears that depression played more of a key role in the decline of quality of life (*Table* 5.5), consistent with existing evidence (Prakash et al., 2016; van Wamelen, Sauerbier, et al., 2021), while apathy may have exerted some influence as part of frequently co-occurring with depression in PD (Bogart, 2011; Gallagher & Schrag, 2012).

There are several important limitations to the current analyses, with the main ones being the cross-sectional design with all the restrictions associated with it, as well as the low sample sizes. There was also a marked lack of a control group of healthy subjects to compare our apathy burden against in both geographical sites, as apathy can also occur in healthy people. In addition, we focused almost exclusively on the self-rated Starkstein's apathy scale, without concurrent proxy-rated measures, which may introduce bias in apathy estimates. Our subgroup sizes were also unequal, with a considerably smaller Asian group in London as compared to the Asian group in Singapore. Nonetheless, we feel that our findings remain clinically useful, and that the two cohorts represent real-world sample populations which provide a good starting point for future research into apathy in PwP.

5.2.7 Conclusion

In summary, the findings of our study demonstrated that clinical apathy is common in PD, and exists independent of depression and anxiety, irrespective of geographical or ethnicity disparities. These data can serve as a platform for future longitudinal research looking at the specific progression of this complex neuropsychiatric symptom in PD, with implications on management and quality of life.

Chapter 6
Developing A Comprehensive Disease-Specific Psychosis Severity Scale in Parkinson's disease (Psy-PD)

6.1 Introduction

As has been outlined in earlier chapters, psychosis is a common and debilitating neuropsychiatric non-motor symptom intrinsic to Parkinson's disease (PD) which is a challenge in terms of identification and treatment. Assessment of PD psychosis is usually carried out by the clinical mental state examination, with information from a carer acquired in later stages of the disease. The stigma of psychosis as a sign of mental illness may mean patients are reluctant to admit the symptoms in early stages (Chaudhuri et al., 2010) so that direct and sensitive questioning is required.

A range of quantitative assessment tools are used in research settings, but none covered the whole range of symptoms encountered in PD psychosis (PDP). Most are derived from existing scales evaluating psychosis in symptoms such as schizophrenia. In addition, few of the psychosis scales in PD assess for delusions (refer Chapter 3).

In 2008, the Movement Disorder Society (MDS) Task Force recommended the Schedule for the Assessment of Positive Symptoms (SAPS), the Neuropsychiatric Inventory (NPI), the Brief Psychiatric Rating Scale (BPRS), as well as the Positive and Negative Syndrome Scale (PANSS) evaluate PDP (Fernandez et al., 2008), although they acknowledged that no existing scale was ideal. As stated in Chapter 3, the definition of "**Recommended**" meant that the scale that has been applied to PD populations; there are data on its use in clinical studies beyond the group that developed the scale; and it has been studied clinimetrically and considered valid, reliable, and sensitive to the given behaviour being assessed (Fernandez et al., 2008). Among these, the SAPS

remained the most popular and widely used in PD, although the MDS cautioned against its utilization in populations with neurocognitive disorders.

The SAPS, however, was originally developed to assess the positive psychotic symptoms in schizophrenia, and therefore had questions not pertinent to PD. It was also not developed to track symptom change. Subsequently, it was shortened and adapted into the SAPS-PD (Voss et al., 2013), through *post-hoc* analyses based on data from earlier failed drug trials of Pimavanserin, excluding questions with low symptom frequency (arbitrarily defined as fewer than 10% of participants rating an item moderate, marked, or severe). Indeed, SAPS-PD was later used in a pivotal phase 3 randomized controlled drug trial in 2014 (Cummings et al., 2014), leading to that same drug Pimavanserin to be successfully licensed in 2016 (Andalo, 2016) in the United States for the specific purpose of treating PDP. However, the main critique of this seminal study (Schubmehl & Sussman, 2018) included the lack of a rigorous clinimetric testing of the SAPS-PD as well as the lack of evidence that it can assess change in PDP. There was also no data on interrater reliability of the scale. This introduced significant concerns about the efficacy and safety of the drug Pimavanserin that is used in a particularly vulnerable PD population.

Two years later, another instrument derived from SAPS-PD, the enhanced SAPS-PD (eSAPS-PD) was introduced (Kulick et al., 2018) that could detect minor hallucinations, unusual subtypes of major hallucinations, and unusual delusions, which the original version could not do. However, the sample population was again a highly educated one with relatively preserved cognitive function, and neither was there proper clinimetric testing nor any data on interrater reliability in PD.

Therefore, there is a clear demand for a comprehensive, reliable, and valid one-stop disease-specific scale to assess psychosis in PD, incorporating the multiple dimensions of hallucinations and delusions. This scale can be used for a more homogenous outline in research, especially in the context of new clinical trials as the identification and management of psychosis continues to be a major "unmet need" in the field of PD.

Considering the above, the main aim of this chapter was to focus on developing a comprehensive tool assessing PD psychosis in a clinical setting, that can allow movement disorder specialists to better address the patients' specific needs and provide a robust evidence base for the holistic management of psychosis in PD. As previously mentioned in Chapter 3, there is a sore lack of studies examining a PD-specific scale in evaluating the severity of the full spectrum of PDP.

The proposed tool investigates the clinical features of two core aspects of PD psychosis, specifically that of hallucinations and delusions. This new scale is derived from existing literature which incorporates semi-quantitative and qualitative information, differentiating patients with different symptoms and psychopathology severity. Its development will also take into account the weaknesses of existing instruments, as characterized in Chapter 3.

I hope that this new instrument would:

1. Provide a truly comprehensive "one stop" assessment of the burden of psychosis in PD
2. Provide an assessment of both disease-related and drug-induced psychosis in PD.
3. Provide assessment of psychosis in relation to non-motor fluctuations (NMFs).
4. Enable psychosis to be quantified as an endpoint in clinical trials related to PD (therapeutic and possibly neuroprotection-related).

The current research is part of a 4-phase study which will aim to validate (using standardised and accepted methods) the use of the Psy-PD in people with Parkinson's and normal healthy controls (required for any scale validation) to international and subsequent worldwide use.

6.2 Contributions and Collaborations

This work is based on several successful international scale validation projects that have been performed at the Parkinson's Centre at King's College Hospital, where this study was conducted. Such scales have now become quality standards for good clinical practice in many countries, such as the UK. Relevant examples include the validation of the King's Parkinson's disease Pain scale

(Chaudhuri, Rizos, et al., 2015), as well as the Parkinson's disease Sleep Scale (Trenkwalder, Kohnen, et al., 2011) and the Non-Motor Scale (Chaudhuri et al., 2007), which have been successfully completed at this centre. Using a well-established network, results have been disseminated worldwide, leading to global adoption of such scales.

As outlined in chapter 4, I developed, designed, and obtained ethical approval of this study. I led the data collection with support from the clinical research network (CRN) staff at King's College Hospital London. I performed the data upload to the clinical research management system (EDGE program) at King's College Hospital. I also carried out the data analysis with guidance and statistical support from the statistical team of Prof. P. Martinez-Martin from the National Center of Epidemiology and CIBERNED, Carlos III Institute of Health in Madrid, Spain, and from Dr S. Vitoratou as part of the King's College London Institute of Psychiatry, Psychology and Neuroscience biostatistics advisory service.

6.3 Methods

6.3.1 Developing and Validating a Scale: Considerations

A complex task, the first step in designing a scale (Martinez-Martin et al., 2014) is by applying the preliminary version to a small number of individuals from the target population in a pilot study to identify flaws and uncertainties, from which preliminary data on acceptability and reliability can be obtained. The definitive version of the scale must then be validated in a representative sample of the target population to determine scale quality. The underlying principles for rating scales validation were derived from the Classical Test Theory, Item Response Theory, and Rasch analysis (Andrich, 2011; DeVellis, 2006; Hays et al., 2000; Nunnally & Bernstein, 1994)

Properties determining scale quality (*Table* 6.1) should be analysed using standard statistical methods. Before applying any instrument in clinical practice or research, most of these criteria must be verified (Martinez-Martin et al., 2014).

***Table* 6.1: Standard values for basic attributes of scales**

Attribute	Criteria	Reference
Feasibility		
Missing data	<5%	(Smith et al., 2005)
Acceptability		
F/C effects	<15%	(McHorney & Tarlov, 1995)
Skewness	-1 to +1	(van der Linden et al., 2005)
Internal consistency		
Cronbach's alpha	α>0.70 (group); 0.90-0.95 (individual)	(Aaronson et al., 2002)
Inter-item correlation	*r*>0.20 and *r*>0.75	(Smith et al., 2005)
Item-total correlation	*r*>0.20 – *r*>0.40	(Streiner & Norman, 2008; Ware & Gandek, 1998)
Homogeneity coefficient	*r*>0.30	(Eisen et al., 1979)
Reliability		
Inter-rater – nominal or ordinal	*Kappa r*>0.60 or *r*>0.70	(Landis & Koch, 1977)
Continuous data	Intraclass correlation coefficient *r*>0.70	(Terwee et al., 2007)
Test-retest – nominal or ordinal	*Kappa r*>0.60 or *r*>0.70	
Continuous data	Intraclass correlation coefficient *r*>0.70	
Construct validity (Hypotheses-testing)		(Chassany et al., 2002; Fitzpatrick et al., 1998)
Convergent validity	*r*>0.40 – *r*>0.60	
Divergent validity	*r*<0.30	(Hobart et al., 2001)
Internal validity	*r*=0.30-0.70	(Fayers & Machin, 2000)
Known-groups validity	Significant difference between groups	

Source: (Martinez-Martin et al., 2014)

6.3.2 Phase I – Scale development

We drafted a disease-specific psychosis severity assessment scale in PD, comprising of both hallucination and delusion subscales. We named it the "Psychosis Severity Scale of Parkinson's Disease (Psy-PD)".

The content of the scale was formulated using deductive methods (Hinkin, 1995) based on a comprehensive literature review on the most frequent types of hallucinations and delusions in Parkinson's disease (Aarsland & Kramberger, 2015; Aarsland, Larsen, Cummins, & Laake, 1999; Ffytche et al., 2017), the phenomenology of both hallucinations and delusions (Chou et al., 2005; Phillips et al., 2013; Phillips et al., 2014), the dimensions of existing psychosis scales (Allardyce,

McCreadie, et al., 2007; Allardyce, Suppes, & Van Os, 2007; Llorca et al., 2016; Ondo et al., 2015; Papapetropoulos, 2006; Papapetropoulos et al., 2008) used in PD, including those outlined in the earlier chapter 3, as well as on expert consensus. The Psy-PD was configured as a form of clinical interview and was meant to be administered by trained healthcare professionals (therefore, rater-administered). It was also designed so that it can be both administered to patients or to their caregivers/proxies in the interview, with the navigatory questions worded accordingly. Time of administration was noted to be between 15 to 30 minutes, depending on quantity of psychotic symptoms and the experience of the administrator in eliciting a history of psychotic symptoms. Subsequently, the Psy-PD scale underwent extensive internal and external reviews in the following manner:

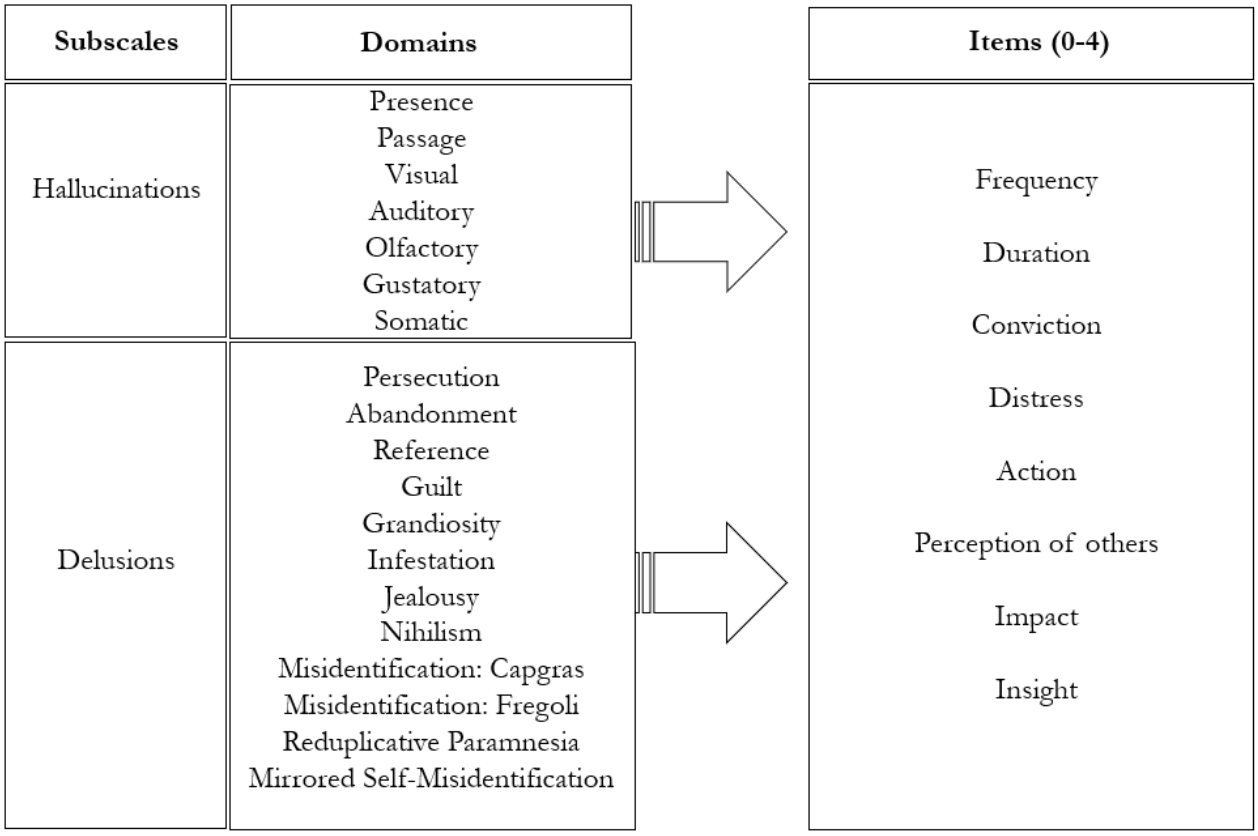
1. By the Kings Neuroscience Research Advisory Group (internal) – comprising of Parkinson's disease (PD) specialists including movement disorder specialists and PD specialist nurses, and other healthcare professionals such as geriatricians with special interest in PD, neuropsychiatrists, occupational therapists, as well as speech therapists.

2. By an expert group of EUROPAR, a non-profit Parkinson's non motor research group. Led by Prof K Ray Chaudhuri, EUROPAR is a multidisciplinary group that was formed to perform "real life" non-motor based clinical studies across a wide range of people with Parkinson's throughout Europe. The main aim of EUROPAR is to pursue studies as they happen in real life and described as a "holistic" natural history study in Parkinson's (refer to the website link: http://parkinsons-london.co.uk/europar/). Presentation and review of my project was done on 22 November 2017.

3. By independent external peer review by the CRISP (Community for Research Involvement and Support by PwPs) group. As stated earlier, CRISP is the expert patient group formed to promote PPI (public and patient involvement). The purpose of CRISP is to raise awareness of research, highlight the importance of participation of people (specifically with Parkinson's) in clinical research, and encourage patients and their carers to ask about clinical

research when with their consultant. Presentation of my project was completed on 21 November 2017 with positive feedback received.

***Figure* 6.0: Preliminary configuration of the Psy-PD Scale**



The preliminary template of the Psy-PD is rater-administered on a semi-structured scale to assess a broad range of psychotic symptoms. Originally, it was configured with seven main domains to evaluate the core subscale of hallucinations and twelve to assess that of delusions specific to PD. However, after reviewing the content validity of the scale with various key stakeholders such as a multidisciplinary panel of movement disorder specialists (comprising neurologists, psychiatrists, geriatricians, research staff, and specialist nurses), and the CRISP expert patient group in Europe, there was mutual agreement to remove the domain of olfactory hallucinations as it would have been difficult to differentiate from the established prodromal olfactory constellation of PD comprising anosmia, phantosmia, and parosmia (Haehner, Boesveldt, et al., 2009; Haehner, Hummel, & Reichmann, 2009; Haehner et al., 2019; Hirsch, 2009; Huisman et al., 2008; Landis & Burkhard, 2008; Ponsen et al., 2004). The domain of gustatory hallucination was removed as

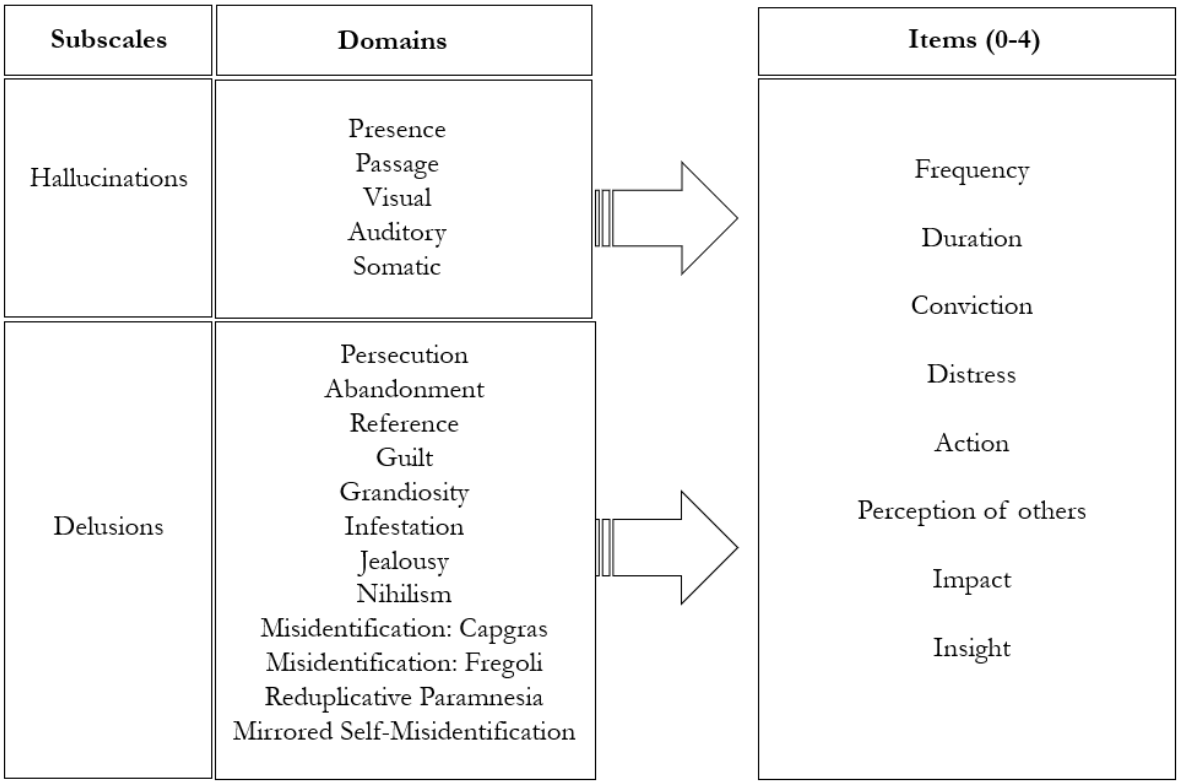
well, due to its close association with the olfactory symptoms (Solla et al., 2021). While the phenomenon of reduplicative paramnesia and mirrored self-misidentification rarely occur in PD (Moro et al., 2013), it was decided upon mutual discussion that these should be kept in the scale as part of the misidentification delusion syndromes which could be underdiagnosed.

Following some revision and refinement, the hallucinations subscale now comprises five domains, and the delusions subscale remained at twelve. Each domain has 8 specific items comprising severity. Responses will be quantified by using a 5-point Likert scale s ranging from 0 (least pathological) to 4 (most pathological). The items are standardised across the board of domains for ease of applicability (*Figure* 6.1). Item ratings represent an average score over a time frame of the preceding 4 weeks. A longer time frame may pose a challenge for accurate recall and introduce bias to the responses.

Probing queries or "probes" are provided to help steer the interview, but the Psy-PD is overall formatted to be adapted at the discretion of the examiner, to maximise analysis of all potential psychotic symptoms. Guiding probes into eliciting relevant responses from the caregiver or proxy are also provided, thus allowing the scale to be potentially used in a PD population with cognitive dysfunction. An example of a guiding probe is the following, assessing the item of Distress: "How much does this experience bother you?". As expert input from both patients and movement disorder specialists criticized the absence of screening questions in the scale, I decided to add two further screening questions prior to the scale itself in agreement with them.

Assignment of different score levels were done according to expert opinion and not based on empirical data. Points are accumulated according to the total severity score as defined by both subscales. The maximum total score for each domain is 32. The maximum grand total for the subscale of hallucinations is 160, and the corresponding one for delusions is 384. The overall maximum total for the scale is 544 (Refer *Appendix*).

***Figure* 6.1: Final configuration of the Psy-PD Scale**



Severity items of the Psy-PD address the following:

- **Item 1:** Frequency of the hallucination/delusion
- **Item 2 :** Duration of symptom
- **Item 3 :** Degree of conviction with which the patients regard their symptom
- **Item 4 :** Extent of emotional distress caused by the symptom
- **Item 5 :** Extent of reaction to the symptom
- **Item 6 :** Perception of others' response to the symptom
- **Item 7 :** Impact of the symptom on the patient's socio-occupational functioning
- **Item 8 :** Level of insight about the symptom being related to PD or its treatment

6.3.3 Phase II – Cognitive Pre-testing

A cross-sectional pilot study was performed on a sample of raters (movement disorder specialists) within the target population of PD patients with psychotic symptoms and healthy controls.

There were three categories of participants: (1) Movement disorder specialists (comprising a panel of neurologists, psychiatrists, geriatricians, PD specialist nurses, research staff experienced in PD), attending to $\geq$ 300 PD patients per year; (2) patients with idiopathic PD diagnosed based on UK Brain Bank criteria and without significant cognitive impairment based on the judgement of the attending neurologist; (3) healthy 50- to 80-year-old community-dwelling controls without PD, dementia, neurological, or psychiatric disorders. Exclusion criteria included neurologists/psychiatrists/geriatricians/research staff inexperienced in PD, patients with parkinsonism other than idiopathic PD, controls with comorbid disease at a moderate or severe level, institutionalized persons, or patients/controls who were unable to consent or are not literate in English or are unable to complete questionnaires accurately.

Feedback questionnaires about the Psy-PD were provided for the participating movement disorder specialists (n=10), patients (n=34), and controls (n=25), involving questions about wording, length, relevance, suitability, comprehensiveness, issues with response options, as well as an additional section for further comments or suggestions.

All study participants were informed about the objective of the study. Each movement disorder specialist completed the Psy-PD for one patient and the feedback questionnaire. Correspondingly, each patient or control also completed the Psy-PD and the feedback questionnaire about the instrument. All data were then analysed to create the definitive version of the Psy-PD to be used in the subsequent validation study.

Prior to study procedures, all patients provided written consent in accordance with the Declaration of Helsinki. The study was authorised by a local ethics committee (NRES London-Dulwich REC, IRAS 229095, 18/LO/0383, KCH 18-065).

6.3.3.1 Statistical Analysis

Descriptive statistics (mean, standard deviation, percentage) were used to describe the baseline characteristics of the sample. The two-sample t-test or Mann-Whitney U test (depending on normality assumption) was used for continuous variables; Chi-square test was used for analysis of the Gender variable. As both cases and controls are not matched for age and gender, linear regression analysis was used to adjust the results for the applied measures for age and gender, with the normality assumption assessed via QQ plot. Gamma or Log-Normal distributions were used when normality assumption was not satisfied under Gaussian distribution.

Total daily levodopa equivalent dose (LEDD) was calculated according to Tomlinson et al., 2010 (Tomlinson et al., 2010). Data collected did not follow a normal distribution (as determined by the Shapiro-Francia test) (Shapiro & Francia, 1972).

The feedback questionnaires from the movement disorder specialists, patients, and controls were analysed qualitatively to evaluate the critique about the instrument. Based on the results, potential changes in the number of items, wording of the questions or response options, and other amendments will be discussed and considered, to obtain the definitive version of the Psy-PD.

Criterion applied for the Psy-PD scale were as follows: data quality (standard values: missing data <10% with full computable scores >90%), F/C effects (value $\leq$15%), and skewness (standard, from -1 to +1) were determined in both PD patients and healthy controls.

Preliminary outcomes of reliability (Cronbach's alpha >0.70; inter-item correlation of 0.20-0.75; item homogeneity coefficient of >0.30; and corrected item-total correlation $\geq$0.20) were explored only in patients.

6.3.3.2 Results

Overall, ten movement disorder specialists and 34 PD patients with psychosis (64.7% male) were included in the study. The mean age of the patient cohort was 67.2 ± 9.6 (range: 45-81) years, with an average of 15.2 ± 4.9 (range: 8-30) years of education. Most of the patients were either married (76.5%) or separated/divorced (14.7%). Mean age at PD onset was 57.1 ± 9.3 (range 38-73) years, and disease duration was 10.1 ± 7.0 (range 0-31) years. Mean LEDD was 1058.3 ± 710.9mg (90-3280). Majority of patients were at HY stage 2 (35.3%) or 3 (32.4%).

We recruited 25 healthy controls (80% female) who were primarily hospital employees and relatives, with mean age of 61.2 ± 9.9 years (range 43-81) who had an average of 14.4 ± 4.3 (range 10-30) years of education. Most were married (96%) and retired (52%).

Table 6.2: Description of the Psy-PD patient sample

Demographics	**PD (n=34) Mean ± SD; Median (Q1-Q3)**	**Controls (n=25) Mean ± SD; Median (Q1-Q3)**	***p*-value**	***Adj p*-value**
Age (years)	67.2 ± 9.6 68.5 (51-74)	61.16 ± 9.87 63 (52-68)	0.0219	-
Male gender	22 (64.71%)	5 (20%)	0.001	-
Education (years)	15.2 ± 4.9 26 (11-18)	14.44 ± 4.25 13 (12-16)	0.546	-
Disease duration	10.1 ± 7.0 9 (5-15)	NA	NA	NA
LEDD (mg/day)	1058.3 ± 710.9 957 (560-1409.8)	NA	NA	NA
Hoehn & Yahr Stage 1 Stage 2 Stage 3 Stage 4 Stage 5	 1 (2.9%) 12 (35.3%) 11 (32.4%) 7 (20.6%) 3 (8.8%)	NA	NA	NA

PD, Parkinson's disease; LEDD, Levodopa equivalent daily dose (mg)

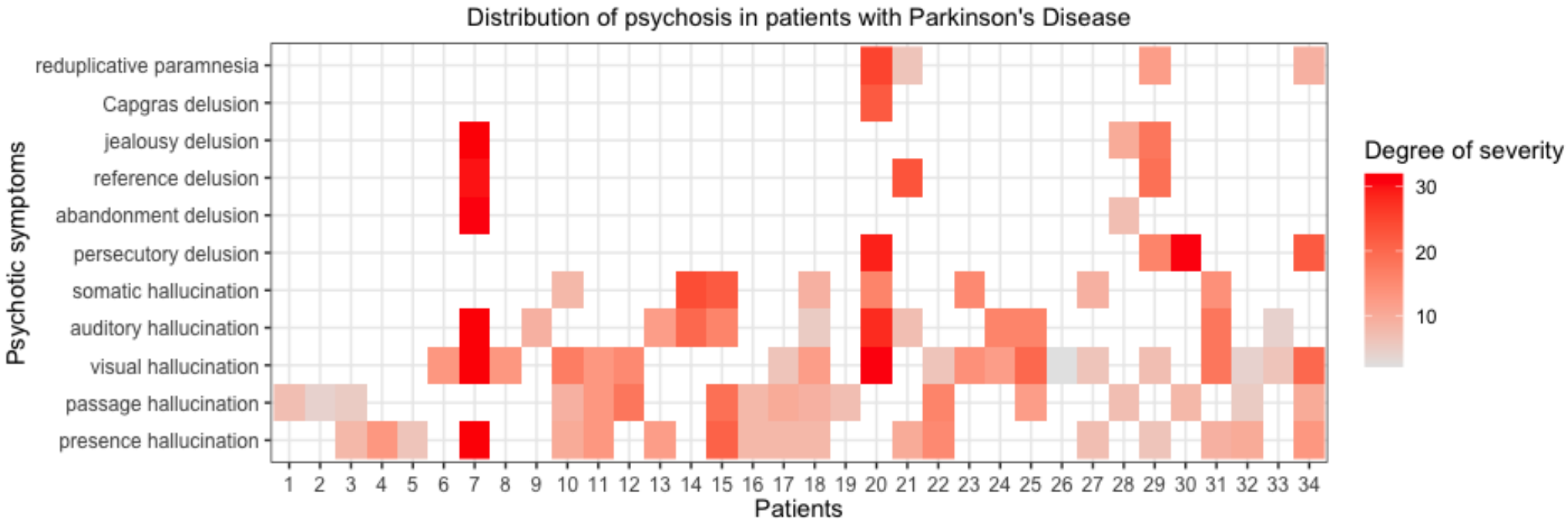
Table 6.3: Descriptive statistics of applied measures in the Psy-PD patient sample

Applied measures	PD (n=34) Mean ± SD; Median (Q1-Q3)	Controls (n=25) Mean ± SD; Median (Q1-Q3)	*p*-value	*Adj p*-value
MoCA	22.74 ± 4.50 24 (19-26)	27.92 ± 1.4 28 (27-29)	<0.001	<0.001
UPDRS(III) Motor	31.06 ± 12.62 30.5 (23-39)	NA	NA	NA
NMSS	87.21 ± 47.51 94.5 (56-122)	0 (0)	<0.001	<0.001
HADS (Anxiety)	9 ± 4.34 9 (6-13)	4.88 ± 3.85 5 (2-7)	<0.001	<0.001
HADS (Depression)	7.79 ± 4.37 2 (0-4)	2.96 ± 3.21 2 (0-4)	<0.001	<0.001
ESS	13.56 ± 6.30 16 (9-18)	4.48 ± 4.25 4 (2-6)	<0.001	<0.001
PDSS-2	23.65 ± 10.87 23 (15-28)	0	<0.001	<0.001
PDQ-8	47.90 ± 18.43 46.9 (37.5-59.4)	NA	NA	NA
Psy-PD (hallucination score)	27.74 ± 23.07 20.5 (10.8-42)	2.24 ± 6.46 0(0-0)	<0.001	<0.001
Psy-PD (delusion score)	10.06 ± 23.52 0(0-0)	0 ± 0 0 (0-0)	0.017	0.005*
Total Psy-PD score	37.79 ± 39.77 26 (13-44)	2.24 ± 6.46 0 (0-0)	<0.001	<0.001

MoCA, Montreal Cognitive Assessment; UPDRS, United Parkinson's Disease Rating Scale; NMSS, Non-Motor Symptom Scale; HADS, Hospital Anxiety Depression Scale; ESS, Epworth Sleepiness Scale; PDSS-2, Parkinson's Disease Sleep Scale – second revision; PDQ-8, Parkinson's Disease Questionnaire-8.

* distribution is too skewed, so the adjusted p-value is based on binary version of Psy-PD (delusion) as 0 vs >0

***Figure* 6.2: Description of the distribution of psychotic symptoms in the Psy-PD study sample**



Psy-PD, Psychosis Severity Scale of Parkinson's disease

***Table* 6.4: Description of the fluctuating nature of psychotic symptoms in the Psy-PD study sample**

Psychotic symptoms	Rarely: Approximately once or twice in the last 4 weeks	Sometimes: Approximately once a week in the last 4 weeks	Often: Several times a week but not everyday	Always: Daily or virtually all the time	Total n (%)
Hallucinations					
Presence	5 (27.8)	1 (5.6)	8 (44.4)	4 (22.2)	18 (52.9)
Passage	5 (29.4)	4 (23.5)	5 (29.4)	3 (17.7)	17 (50.0)
Visual	5 (25)	3 (15)	6 (30)	6 (30)	20 (58.8)
Auditory	6 (50)	3 (25)	2 (16.7)	1 (8.3)	12 (35.3)
Somatic	5 (62.5)	1 (12.5)	2 (25)	0	8 (23.5)
Delusions					
Persecution	0	1 (25)	2 (50)	1 (25)	4 (11.8)
Abandonment	1 (50)	0	0	1 (50)	2 (5.9)
Reference	1 (2.9)	0	0	4 (5.9)	3 (8.8)
Jealousy	2 (66.7)	0	0	1 (33.3)	3 (8.8)
Capgras	1 (100)	0	0	0	1 (2.9)
Reduplicative paramnesia	3 (75)	1 (25)	0	0	4 (11.8)

***Table* 6.5: Description of the duration of psychotic symptoms in the Psy-PD study sample**

Psychotic symptoms	Fleeting: Seconds to minutes	Minutes to Hours	Hours to Days	Continuously	Total n (% sample population)
Hallucinations					
Presence	16 (88.9)	1 (5.6)	0	1 (5.6)	18 (52.9)
Passage	17 (100)	0	0	0	17 (50.0)
Visual	12 (60)	4 (20)	2 (10)	2 (10)	20 (58.8)
Auditory	9 (75)	2 (16.7)	0	1 (8.3)	12 (35.3)
Somatic	6 (75)	1 (12.5)	1 (12.5)	0	8 (23.5)
Delusions					
Persecution	0	1 (25)	2 (50)	1 (25)	4 (11.8)
Abandonment	1 (50)	0	0	1 (50)	2 (5.9)
Reference	0	1 (2.9)	0	2 (5.9)	3 (8.8)
Jealousy	1 (33.3)	1 (33.3)	0	1 (33.3)	3 (8.8)
Capgras	1 (100)	0	0	0	1 (2.9)
Reduplicative paramnesia	1 (25)	3 (75)	0	0	4 (11.8)

6.3.3.3 Psy-PD basic sample characteristics

From *Figure* 5.2, all 34 PD patients suffered from hallucinations, with those suffering from delusions charting higher Psy-PD psychotic severity scores compared to those without. In terms of occurrence, minor hallucinations were the commonest, with almost equal proportions experiencing either *presence* or *passage* hallucinations (*Table* 6.4 and *Table* 6.5). Most of those with *presence* hallucinations experienced it often, though not daily (*Table* 6.4). Among those with well-formed major hallucinations, visual hallucinations were the commonest, consistent with previous literature (refer Chapter 1). On the other hand, delusions were mostly experienced either intermittently (rarely, fleeting) or continuously (*Table* 6.5).

6.3.3.4 Psy-PD scores

The Psy-PD scores were fully computable for all patients with no missing data (*Table* 6.6). Total Psy-PD mean score was 37.8±39.77 (range 2-189). All domains showed floor effects >15% (41.2-100%), but none had relevant ceiling effects. Cronbach's alpha was satisfactory ($\alpha \geq 0.70$) for all 5 domains of the Hallucinations subscale and for 6/12 domains (Persecution, Abandonment, Reference, Jealousy, Capgras, Reduplicative Paramnesia) of the Delusions subscale. For the remaining 6 (Guilt, Grandiosity, Infestation, Nihilism, Misidentification (Fregoli), Mirrored Self-Identification) of the Delusions subscale, none of the patients experienced any symptoms (*Table* 6.6). Differences in floor effects between patients and controls were statistically significant for across all domains (*Table* 6.6, $p < 0.001$) except for the 6 in the Delusions subscale stated earlier (Guilt, Grandiosity, Infestation, Nihilism, Misidentification (Fregoli), Mirrored Self-Identification).

Inter-item and Item-total correlations (standard, $r>0.20$) were satisfactory across all domains except for Passage Hallucinations and Somatic Hallucinations (*Table* 6.6). The item homogeneity index (mean of inter-item correlation; $r>0.30$) was globally satisfactory. In controls, there were no missing values, with total Psy-PD score (mean±SD) of 2.24±6.46 (range: 0-26

Skewness summarizes the extent to which a distribution of scores is non-normal. A positive value indicates that scores cluster to the left of the mean. A negative value indicates that scores cluster to the right of the mean. Skewness statistics usually are evaluated informally; values < -1 or > +1 signal substantially non-normal distributions potentially in need of additional evaluation (Holmes et al., 1996). In this instrument, a positive skewness that was higher than standard was present in all scores of patients except in Passage Hallucinations (*Table* 6.6, Skewness 0.88), mirroring the floor effect. In controls, a moderate skewness was present only in the domains of Passage (Skewness 2.41) and Auditory Hallucinations (Skewness 4.69).

6.3.3.5 Qualitative Responses Regarding the Psy-PD

Over 90% of the movement disorder specialists' opinions were positive regarding the relevance, usefulness, and comprehensiveness of the scale, with less than 50% reporting wording issues. More than half expressed a negative opinion about the length of the scale which precludes it from being appropriate for use in daily clinical practice, and more suitable in a research setting. For patients, 11.8% reported wording issues, and 20.6% felt that the scale was too long. One recommended for the scale to be done at home, rather than at a clinic setting. However, more than 60% of the patients felt that the scale was relevant, useful, and very comprehensive.

After a thorough consideration of the comments regarding the scale, and the results of acceptability as well as internal consistency, the following amendments were made: (i) Instructions for navigating across the scale were reworded (with the addition of definitions to frequencies in

particular), (ii) Two screening questions were added to the beginning of the scale to determine presence and absence of distressing psychotic symptoms, and (iii) The layout was made simpler, with removal of unnecessary gridlines.

Table 6.6: Data quality and acceptability of the Psy-PD

Psy-PD	Missing	Mean	Median	SD	Skewness	Observed Range	Floor (%)	Ceiling (%)	Inter-item correlation	Item-total correlation (corrected)	Cronbach's Alpha	Test-retest (n=34)		Inter-rater (n=34)	
												$Kappa_w$	ICC	$Kappa_w$	ICC
Hallucinations															
Presence	0	6.15	6	7.41	1.43	0 - 32	47.1**	0	0.50 – 0.58	0.25 – 0.59	0.77	0.58 – 0.93	0.89	0.85 – 1.0*	0.96
Passage	0	4.91	2	5.87	0.88	0 - 19	50.0**	0	0.40 – 0.48	0.04 – 0.2	0.79	0.11 – 0.88	0.68	0.42 – 1.0*	0.88
Visual	0	7.85	6	8.93	1.06	0 - 32	41.2**	0	0.61 – 0.65	0.36 – 0.78	0.74	0.69 – 0.94	0.90	0.84 – 0.98	0.99
Auditory	0	5.38	0	9.10	1.06	0 - 32	64.7**	0	0.70 – 0.73	0.52 – 0.80	0.73	0.72 – 0.97	0.93	0.96 – 1.0*	1.0*
Somatic	0	3.44	0	6.88	1.81	0 - 24	76.5**	0	0.60 – 0.70	0.11 – 0.50	0.79	0.26 – 0.97	0.89	0.83 – 1.0*	0.99
Total Hallucinations	0	27.74	20.5	23.07	1.25	2 - 96	0**	0	--	--	--	--	--	--	--
Delusions															
Persecution	0	2.88	0	8.28	2.64	0 - 31	88.2**	0	0.89 – 0.94	0.34 – 0.46	0.77	0.95 – 1.0*	1.0*	0.90 – 1.0*	1.0*
Abandonment	0	1.12	0	5.42	5.20	0 - 31	94.1**	0	0.99 – 1.0	0.63 – 0.65	0.74	0.80 – 1.0*	1.0*	0.80 – 1.0*	1.0*
Reference	0	2.12	0	7.04	3.11	0 - 30	91.2**	0	0.79 – 0.87	0.52 – 0.61	0.74	0.77 – 1.0*	0.99	0.54 – 0.94	0.79
Guilt	0	0	0	0	-	-	100	0	--	--	--	--	--	--	--
Grandiosity	0	0	0	0	-	-	100	0	--	--	--	--	--	--	--
Infestation	0	0	0	0	-	-	100	0	--	--	--	--	--	--	--
Jealousy	0	1.76	0	6.38	3.83	0 - 32	91.2**	0	0.92 – 1.0	0.60 -0.67	0.74	0.90 – 1.0*	1.0*	0.91 – 1.0*	1.0*
Nihilism	0	0	0	0	-	-	100	0	--	--	--	--	--	--	--
Capgras	0	0.65	0	3.77	5.57	0 - 22	97.1**	0	1.0	0.55	0.75	0.79 – 1.0*	1.0*	0.79 – 1.0*	0.98
Fregoli	0	0	0	0	-	-	100	0	--	--	--	--	--	--	--
Reduplicative Paramnesia	0	1.53	0	4.94	3.69	0 - 25	88.2**	0	0.74 – 0.83	0.39 – 0.60	0.74	0.51 – 0.96	0.95	0.78 – 1.0*	0.96
Mirrored Self-Identification	0	0	0	0	-	-	100	0	--	--	--	--	--	--	--
Total Delusions	0	10.06	0	23.52	2.41	0 - 93	79.4**	0	--	--	--	--	--	--	--
Total Psy-PD Score	**0**	**37.80**	**26**	**39.77**	**2.34**	**2 - 189**	**0**	**0**	--	--	**0.77**	--	**0.97**	--	**0.98**

Statistically significant difference between patients and controls for floor effects: ** $p < 0.001$. The rest of differences was not significant.

Psy-PD, Psychosis Severity Scale of Parkinson's disease; SD, standard deviation
$Kappa_w$: weighted (quadratic) kappa coefficient; ICC : Intraclass correlation coefficient.
* Rounded figures when weighted kappa value was >0.99

***Table* 6.7: Response synthesis of movement disorder specialists and patients about the Psy-PD**

	Movement disorder specialists (n=10)			Patients (n=34)		
		N	%		N	%
1. Do you find the scale relevant?	No	1	10	No	2	5.9
	Yes	9	90	Yes	22	64.7
	NR	0	0	NR	10	29.4
2. Does this scale help you better understand your patient's/ your current health state?	No	0	0	No	3	8.8
	Yes	10	100	Yes	21	61.8
	NR	0	0	NR	10	29.4
3. Do you think this scale is comprehensive?	No	0	0	No	3	8.8
	Yes	10	100	Yes	21	61.8
	NR	0	0	NR	10	29.4
4. Do you think this scale is too long?	No	4	40	No	17	50
	Yes	6	60	Yes	7	20.6
	NR	0	0	NR	10	29.4
5. Do you find the questions easy to understand?	No	4	40	No	4	11.8
	Yes	6	60	Yes	19	55.9
	NR	0	0	NR	11	32.4
6. Did you find any questions embarrassing?	No	10	100	No	23	67.6
	Yes	0	0	Yes	0	0
	NR	0	0	NR	11	32.4
7. Did you find any particular question(s) difficult to answer?	No	7	70	No	17	50
	Yes	3	30	Yes	6	17.6
	NR	0	0	NR	11	32.4

NR: no response

6.3.4 Phase III – Reliability Checking

6.3.4.1 Test-retest and Inter-rater reliability of the Psy-PD

34 patients with Parkinson's disease psychosis completed the Psy-PD on two separate occasions within one to two weeks' interval, under standardised conditions, with the same healthcare professional administering the scale on each occasion. All 34 patients underwent interrater evaluation by 2 raters.

6.3.4.1.1 Statistical Analysis

Test-retest (baseline and 7-14 days later) and interrater (2 raters) reliability were analysed using percentage of agreement and weighted kappa ($kappa_w$) with quadratic weights for items and the intraclass correlation coefficient (ICC, 1-, and 2-way, random effect) for each item and total scores.

In test–retest, the ICC is the most frequently used for numerical or continuous measurements (Koo & Li, 2016). The Kappa coefficient indicates the extent of agreement (categorical/ordinal) between frequencies of two sets of data collected on two different occasions.

With inter-rater reliability, ratings can be made at a categorical (yes/no), ordinal (Likert-type scale), or continuous level depending upon the process of evaluation. The number of ratings taken, and the number of independent raters, also plays a significant role in choosing the correct test. The kappa statistic is a very conservative measure and is utilized to generate this estimate of reliability between two independent raters on a categorical or ordinal outcome. Significant Kappa statistics are harder to find as the number of ratings, number of raters, and number of potential responses increases. Similar for the test-retest, the ICC is used to assess interrater reliability when the outcome is measured at a continuous level. Raters should be independent but should also be trained in the operational identification of the construct.

Overall, Kappa values >0.60 (substantial agreement) and ICC $\geq$0.70 were deemed reasonable (Table 6.1).

6.3.4.1.2 Results

The analysis findings are summarised in *Table* 6.6.

For test-retest reliability, weighted kappa index ranged from 0.11 to 0.97 for all the domains across the Hallucinations subscale, and from 0.51 to 1.00 (*Table* 6.6) for the domains of the Delusions subscale. The ICC was 0.97 for the total Psy-PD score, which is high.

For inter-rater reliability, weighted kappa index ranged from 0.42 to 1.00, and ICC ranged from 0.79 to 1.00 (*Table* 6.6).

6.3.4.2 Convergent Validity and Known-Groups Validity

For convergent validity, we hypothesized that Psy-PD domains would be highly associated (Spearman rank correlation coefficient value, $r_s > 0.50$) with corresponding features of the NMSS Domain 4 as well as the NPI (both commonly used scales in assessing psychosis in PD, refer Chapter 3). The known-groups validity of the Psy-PD was assessed by comparing total scores in terms of subgroups based on sex, age, HY, age at PD onset, and LEDD, with the latter three groups stratified by tertiles.

6.3.4.2.1 Results

Psy-PD domains correlated 0.45-0.79 with the NMSS Domain 4 items on psychotic symptoms in PD (*Table* 6.8). The correlation between Psy-PD total score and the NMSS Domain 4 Psychosis score was 0.36, and with NPI Psychosis Score as 0.55. Correlation coefficients of the Psy-PD domains with the corresponding domains of the NPI ranged between 0.59-0.63.
There were no significant differences between the total Psy-PD score and all the subgroups analysed.

***Table* 6.8: Convergent Validity of the Psy-PD**

Psy-PD	NMSS	Spearman R	*p*-value
Hallucinations	Domain 4 Question 13 (Hallucinations)	0.45	<0.01
Delusions	Domain 4 Question 14 (Delusions)	0.79	<0.001
Total Psy-PD Score	Total NMSS Psychosis Score: (Q13 +Q14)	0.36	0.038
Psy-PD	**NPI**	**Spearman R**	***p*-value**
Hallucinations	NPI Domain B: Hallucinations	0.59	<0.001
Delusions	NPI Domain A: Delusions	0.63	<0.001
Total Psy-PD Score	Total NPI Psychosis Score: Domain A + Domain B	0.55	<0.001

NMSS, Non-Motor Symptom Scale; NPI, Neuropsychiatric Inventory

***Table* 6.9: Known-groups validity of the Psy-PD**

	Stratification	Psy-PD Total Score	Significance
Sex	Males Females	39.95 ± 46.77 33.83 ± 23.30	A
Age (years)	<65 65 – 75 >75	35.62 ± 25.80 32.79 ± 36.52 51.86 ± 64.64	B
Hoehn and Yahr staging	1 2 3 4 5	6 ± 0.00 37.75 ± 21.86 27.55 ± 24.28 43.71 ± 49.29 72.33 ± 101.16	B
Age at PD diagnosis (years)	<65 65-70 >70	37 ± 33.25 25.3 ± 16.24 61.25 ± 86.20	B
Levodopa-equivalent daily dose (mg)	<430 430 – 800 >800	40.86 ± 27.37 20.33 ± 23.11 41.76 ± 46.26	B

Significance:

A – Mann-Whitney test – Not significant (p>0.05)

B – Kruskal-Wallis test – Not significant (p>0.05)

• Bonferroni adjustment for multiple comparisons (n=14): $p<0.0036$

6.4 Discussion

Psychosis in PD has a debilitating effect on quality of life and leads to poor outcomes for both patients and their caregivers; yet remains one of the most undeclared and under-recognized non-motor symptoms (Chaudhuri et al., 2010). The results presented here represent the preliminary clinimetric validation of the comprehensive Psy-PD scale from a pilot single-center study. The data indicate that this preliminary version of the Psy-PD has reasonably acceptable clinimetric properties to encompass the severity parameters of the spectrum of psychosis specific to PD in a single instrument.

Data quality was considered excellent, with no missing data. All the domain scores were fully computable, with no statistical imputation needed. Correspondingly, there was also no missing data in the control group.

The critique from cognitive pretesting that was gathered from relevant stakeholders were reviewed, with come critical comments related to scale length, item content and wording leading to further revisions of the scale. Comments that contradicted each other, or arose from a lack of training regarding the description spectrum of PD psychosis (e.g. how to describe passage hallucinations properly to patients?) were not considered when making amendments to the Psy-PD. In general, the scale is relatively easy to administer, taking about ~15 to 30 minutes to administer, depending on the number of psychotic features that the patient has. Raters should be trained personnel however, who are experienced in eliciting history on PD psychosis.

The high floor effect and skewness values observed in both groups are likely due to there being a high proportion of the psychotic symptoms not experienced by this patient population. As the Psy-PD was designed to be a thorough scale to holistically capture the broad range of PD psychosis as updated in literature, it was expected that a considerable proportion of patients would not experience all the symptoms simultaneously in this cross-sectional study. Certain psychotic features, particularly minor hallucinations, are expected to be present in an otherwise healthy population, but with lower prevalence and distress than in PD. Consistent with this

rationale, the floor effect was higher in the control group throughout both subscales of the Psy-PD. This result was also reflected in the high skewness values observed in the domain scores. Crucially, for the total Psy-PD score, the floor effect was negligible, as was the ceiling effect for domains and total score in both groups.

Overall, there was adequate internal consistency, with most of the domains showing α-coefficients higher than or close to the standard 0.70. Most items showed suitable inter-item relationships and with the corrected total score, although some domains overall showed subpar performance (e.g. passage and somatic hallucinations). However, given that the definitions of these recently updated psychotic symptoms were ambiguous at best (e.g. passage hallucinations), and their rising importance in the canon of PD psychosis, these domains were kept with their wording reviewed.

In relation to the test-retest reliability, most of the Psy-PD domains showed adequate results. Only one in the Hallucinations subscale (the passage hallucination domain) reached ICC values under the standard 0.70, but only marginally ($r = 0.68$). These suboptimal results may be because minor phenomena like passage hallucinations rarely occurred in isolation (*Figure* 6.2) and are usually experienced alongside other well-formed hallucinations which may confound recall. Its fluctuating frequency trajectory, as described in earlier chapters, may further add to the confusion.

The findings of interrater reliability analyses were excellent, with all ICC values higher than 0.96 across the board, except for that of passage hallucinations (ICC=0.88), and delusions of reference (ICC=0.79) for similar reasons as stated for test-retest, although still higher than the accepted standard of 0.70, reflecting the stability of the measure.

In terms of convergent validity, the Psy-PD subscales and total score correlated better with the corresponding features of the NPI rather than with the NMSS. This is likely due to the NMSS assessing hallucinations based on a single question alone, the fact that NMSS does not evaluate for minor hallucinations, as well as NMSS having only two questions addressing the

complex phenomena of psychosis in the entire scale. The strong correlation between the Psy-PD and the NMSS single query on the presence of delusions may be due to the nature of the psychotic symptom, depicting a false fixed belief that is unshakeable despite evidence to the contrary, which often occurred in the late stages of disease progression, and which caused much distress.

There were no significant differences in the total Psy-PD score when stratified into categories of age or gender. There were also no observed differences with LEDD, HY staging, and age of PD onset, which may be due to an inadequate sample size.

There were several important limitations. First, the participants were patients with predominant mild-to-moderate disease severity. In addition, the healthy controls comprised of primarily of females, which may have influenced the differences observed between the groups. The Psy-PD has also not been assessed with regards to its sensitivity to change, an issue with many currently existing measurements. Another limitation was the small size of the sample for test-retest.

6.5 Conclusion

Overall, the Psy-PD appears robust, reproducible and has satisfactory basic clinimetric attributes although some domains performed poorly. Many raters deemed the scale too lengthy to administer in daily clinical practice and may be more suitable for use in research settings. However, patients in general found the scale length acceptable. Future studies may be performed to improve its metric properties. Until then, the Psy-PD may be considered a feasible and reliable instrument for the comprehensive evaluation of psychosis severity in PD.

6.6 Publications (international abstracts) related to this chapter

Y.M Wan, E.K Tan, D. Aarsland, T.S Lee, Y.L Lo, SKS. Ting, P., K.R Chaudhuri. Developing A Novel Disease-Specific Psychosis Severity Scale in Parkinson's disease (Psy-PD): A Pilot Study [abstract]. *Mov Disord.* 2020; 35 (suppl 1). https://www.mdsabstracts.org/abstract/developing-a-novel-disease-specific-psychosis-severity-scale-in-parkinsons-disease-psy-pd-a-pilot-study/.

Appendix:

(i) Psy-PD Scale

Psychosis Severity Scale of Parkinson's disease

(Psy-PD)

Screening Questions

In administering the scale, prior use of other instruments [such as the Structured Clinical Interview for DSM-IV (or SCID-I) to identify the psychotic experience, the Hallucinations/Delusions sections of the Neuropsychiatric Inventory (NPI), or the Non-Motor Symptom Questionnaire (NMSQuest) item 14 and/or item 30] can be helpful in screening for such hallucinatory or delusional experiences. The following questions can be used to generate a list of the patient's psychotic experience:

1. **Are there certain experiences that you have that are deemed to be unusual by others?**

[If caregiver/proxy: Has your relative/ loved one ever reported experiences which are deemed uncharacteristic or abnormal? Have they experienced any hallucinations or delusions?]

_____

_____

_____

_____

2. **Which one would you rate to be the most distressing to you?**

[If caregiver/proxy: Which uncharacteristic/abnormal experience(s) are considered the most distressing to him/her, or to you?]

_____

_____

_____

_____

Psy-PD

General Instructions:
The following structured interview is designed to elicit specific details regarding the severity of different hallucinations and delusions. When asking questions, the interview is designed to rate the patient's experiences over **the last 4 weeks**. Sources of information can be from the caregiver or the patient. This is a clinician-administered scale with the instructions appended at the end of the scale.

Description: *Tick in the boxes as relevant and circle the severity score for each item.*

Hallucinations								
Domain		*If present, please tick*	*Severity (Circle only if present)*					
1.	**Presence** *the experience that somebody is present nearby, in the absence of actual sensory clues revealing a presence*		Frequency	0	1	2	3	4
			Duration	0	1	2	3	4
			Conviction	0	1	2	3	4
			Distress	0	1	2	3	4
			Action	0	1	2	3	4
			Perception of others	0	1	2	3	4
			Impact	0	1	2	3	4
			Insight	0	1	2	3	4
2.	**Passage** *the perception that an animal, person, or indefinite object is passing through the peripheral visual field, in the absence of actual external stimuli*		Frequency	0	1	2	3	4
			Duration	0	1	2	3	4
			Conviction	0	1	2	3	4
			Distress	0	1	2	3	4
			Action	0	1	2	3	4
			Perception of others	0	1	2	3	4
			Impact	0	1	2	3	4
			Insight	0	1	2	3	4
3.	**Visual** *the visual perception of an object or event in the absence of actual external stimuli*		Frequency	0	1	2	3	4
			Duration	0	1	2	3	4
			Conviction	0	1	2	3	4
			Distress	0	1	2	3	4
			Action	0	1	2	3	4
			Perception of others	0	1	2	3	4
			Impact	0	1	2	3	4
			Insight	0	1	2	3	4
4.	**Auditory** *the auditory perception of an object or event in the absence of actual external stimuli*		Frequency	0	1	2	3	4
			Duration	0	1	2	3	4
			Conviction	0	1	2	3	4
			Distress	0	1	2	3	4
			Action	0	1	2	3	4
			Perception of others	0	1	2	3	4
			Impact	0	1	2	3	4
			Insight	0	1	2	3	4
5.	**Somatic** *the tactile perception of an object or event in the absence of actual external stimuli*		Frequency	0	1	2	3	4
			Duration	0	1	2	3	4
			Conviction	0	1	2	3	4
			Distress	0	1	2	3	4
			Action	0	1	2	3	4
			Perception of others	0	1	2	3	4
			Impact	0	1	2	3	4
			Insight	0	1	2	3	4
Total (Hallucinations)								

Delusions								
Domain		*If present, please tick*	*Severity (Circle only if present)*					
1	**Persecution** *a fixed false belief that others are intent on harming the patient despite evidence to the contrary and which is not in keeping with local culture*		Frequency	0	1	2	3	4
			Duration	0	1	2	3	4
			Conviction	0	1	2	3	4
			Distress	0	1	2	3	4
			Action	0	1	2	3	4
			Perception of others	0	1	2	3	4
			Impact	0	1	2	3	4
			Insight	0	1	2	3	4
2.	**Abandonment** *a fixed false belief that others are intent on abandoning the patient despite evidence to the contrary and which is not in keeping with local culture*		Frequency	0	1	2	3	4
			Duration	0	1	2	3	4
			Conviction	0	1	2	3	4
			Distress	0	1	2	3	4
			Action	0	1	2	3	4
			Perception of others	0	1	2	3	4
			Impact	0	1	2	3	4
			Insight	0	1	2	3	4
3.	**Reference** *a fixed false belief that everything is related to, or referencing, the patient despite evidence to the contrary and which is not in keeping with local culture*		Frequency	0	1	2	3	4
			Duration	0	1	2	3	4
			Conviction	0	1	2	3	4
			Distress	0	1	2	3	4
			Action	0	1	2	3	4
			Perception of others	0	1	2	3	4
			Impact	0	1	2	3	4
			Insight	0	1	2	3	4
4.	**Guilt** *a fixed false belief that the patient has committed an unforgiveable crime, or expressed disproportionate guilt, despite evidence to the contrary and which is not in keeping with local culture*		Frequency	0	1	2	3	4
			Duration	0	1	2	3	4
			Conviction	0	1	2	3	4
			Distress	0	1	2	3	4
			Action	0	1	2	3	4
			Perception of others	0	1	2	3	4
			Impact	0	1	2	3	4
			Insight	0	1	2	3	4
5.	**Grandiosity** *a fixed false belief that the patient special powers or superhuman abilities despite evidence to the contrary and which is not in keeping with local culture*		Frequency	0	1	2	3	4
			Duration	0	1	2	3	4
			Conviction	0	1	2	3	4
			Distress	0	1	2	3	4
			Action	0	1	2	3	4
			Perception of others	0	1	2	3	4
			Impact	0	1	2	3	4
			Insight	0	1	2	3	4
6.	**Infestation** *a fixed false belief that the patient has been infested by insects or animals, despite evidence to the contrary and which is not in keeping with local culture*		Frequency	0	1	2	3	4
			Duration	0	1	2	3	4
			Conviction	0	1	2	3	4
			Distress	0	1	2	3	4
			Action	0	1	2	3	4
			Perception of others	0	1	2	3	4
			Impact	0	1	2	3	4
			Insight	0	1	2	3	4

	Domain	If present, please tick	Severity (Circle only if present)					
7	**Jealousy** *a fixed false belief that the spouse or partner of the patient has been unfaithful, despite evidence to the contrary and which is not in keeping with local culture*		Frequency	0	1	2	3	4
			Duration	0	1	2	3	4
			Conviction	0	1	2	3	4
			Distress	0	1	2	3	4
			Action	0	1	2	3	4
			Perception of others	0	1	2	3	4
			Impact	0	1	2	3	4
			Insight	0	1	2	3	4
8.	**Nihilism** *a fixed false belief that everything (including the patient's self) doe not exist, or is dead/diseased/ missing, despite evidence to the contrary and which is not in keeping with local culture*		Frequency	0	1	2	3	4
			Duration	0	1	2	3	4
			Conviction	0	1	2	3	4
			Distress	0	1	2	3	4
			Action	0	1	2	3	4
			Perception of others	0	1	2	3	4
			Impact	0	1	2	3	4
			Insight	0	1	2	3	4
9.	**Misidentification: Capgras** *a fixed false belief that familiar person(s) have been replaced, or that they are actually somebody else in disguise, despite evidence to the contrary and which is not in keeping with local culture*		Frequency	0	1	2	3	4
			Duration	0	1	2	3	4
			Conviction	0	1	2	3	4
			Distress	0	1	2	3	4
			Action	0	1	2	3	4
			Perception of others	0	1	2	3	4
			Impact	0	1	2	3	4
			Insight	0	1	2	3	4
10.	**Misidentification: Fregoli** *a fixed false belief that everyone around is actually the same person in disguise, or is a familiar person, despite evidence to the contrary and which is not in keeping with local culture*		Frequency	0	1	2	3	4
			Duration	0	1	2	3	4
			Conviction	0	1	2	3	4
			Distress	0	1	2	3	4
			Action	0	1	2	3	4
			Perception of others	0	1	2	3	4
			Impact	0	1	2	3	4
			Insight	0	1	2	3	4
11.	**Reduplicative Paramnesia** *a fixed false belief that the patient is in an unfamiliar place, despite evidence to the contrary and which is not in keeping with local culture*		Frequency	0	1	2	3	4
			Duration	0	1	2	3	4
			Conviction	0	1	2	3	4
			Distress	0	1	2	3	4
			Action	0	1	2	3	4
			Perception of others	0	1	2	3	4
			Impact	0	1	2	3	4
			Insight	0	1	2	3	4
12.	**Mirrored-Self Misidentification** *a fixed false belief that the patient's reflection in the mirror is actually somebody else, despite evidence to the contrary and which is not in keeping with local culture*		Frequency	0	1	2	3	4
			Duration	0	1	2	3	4
			Conviction	0	1	2	3	4
			Distress	0	1	2	3	4
			Action	0	1	2	3	4
			Perception of others	0	1	2	3	4
			Impact	0	1	2	3	4
			Insight	0	1	2	3	4
Total (Delusions)								
Total Psychosis Severity Score								

Psychosis Severity Scale of Parkinson's disease (Psy-PD)

Guidance on the appropriate questions to elicit responses to each category:
(Please do not say the words "hallucinations" or "delusions" in your questions)

Hallucinations

1. Presence

Have you ever sensed as if there is someone or something nearby, but you don't see or hear them otherwise?

[If caregiver/proxy: Has your relative ever reported that he/she sensed as if there is someone or something near by, but there is actually nobody or nothing there?]

2. Passage

Have you ever seen, briefly, someone or something passing by in your peripheral vision, but there is actually nobody or nothing there?

[If caregiver/proxy: Has your relative ever reported that he/she saw someone or something passing by at the edge of his or her vision, but there is actually nobody or nothing there?]

3. Visual

Have you ever seen someone or something that other people could not see?
(Visions might be of something miniature)

[If caregiver/proxy: Has your relative ever reported that, or behaved as if, he/she saw someone or something, but there is actually nobody or nothing there?]

4. Auditory

Have you ever heard any voices/ noises/music that other people could not hear?
(Have you heard any voices/ noise/music around you, but there is nobody/nothing there?)

[If caregiver/proxy: Has your relative ever reported that, or behaved as if, he/she heard somebody or something, which nobody else can hear?]

5. Somatic

Have you ever had unusual or uncomfortable physical sensations for which there is no clear explanation? (For instance, the feeling of being touched)

[If caregiver/proxy: Has your relative ever reported that, or behaved as if, he/she physically felt an unusual sensation, of which origin cannot be explained or about which he/she has abnormal beliefs?]

Delusions

1. Persecution

(i) Does it seem that people are intent on hurting you in any way? (For instance, by spying on you, monitoring you, or following you)

[If caregiver/proxy: Has your relative ever reported, or behaved as if, other people is plotting against him/her, or intend to hurt him/her, even though this is not true?]

(ii) Does it seem that people are stealing from you?

[If caregiver/proxy : Has your relative ever reported, or behaved as if, his/her belongings have been stolen, even though this is not true?]

2. Abandonment

Does it seem that your relatives or loved ones will abandon or leave you, even if they told you they would not?

[If caregiver/proxy: Has your relative ever reported that, or behaved as if, he/she believed that you, or his/her loved ones, will abandon him/her?]

3. Reference

Does it seem that you receive special messages that other people do not? (For instance, from the television or radio)

[If caregiver/proxy: Has your relative ever reported, or behaved as if, he/she receives special messages from the media, such as the TV or radio?]

4. Guilt

Does it seem that you have committed an unforgiveable sin or unspeakable crime, even when people tell you that you have not?

[If caregiver/proxy: Has your relative ever reported that, or behaved as if, he/she is guilty of doing something which is unforgiveable?]

5. Grandiosity

Does it seem that you have any special powers or abilities?

[If caregiver/proxy: Has your relative ever reported that, or behaved as if, he/she has any special powers or abilities?]

6. Infestation

Does it seem that you are infested by insects/animals?

[If caregiver/proxy: Has your relative ever reported, or behaved as if, he/she was infested by insects/animals even though it is not true?]

7. Jealousy

Does it seem that your partner may be unfaithful to you?

[If caregiver/proxy: Has your relative ever reported that, or behaved as if, he/she is suspicious of his/her partner's fidelity?]

8. Nihilism

Do you believe yourself to be dead?
(Does it seem that your body is diseased, abnormal, or changed in any way?)

[If caregiver/proxy: Has your relative ever reported that, or behaved as if, he/she not alive, or that his/her organs (or body) are diseased/abnormal/missing in any way?]

9. Misidentification: Capgras

Does it seem as if someone that you know has been replaced, or that he/she is actually somebody else in disguise?

[If caregiver/proxy: Has your relative ever reported that, or behaved as if, he/she believes that people he/she knows have been replaced by others, or are other people in disguise?]

10. Misidentification: Fregoli

Does it seem that everyone around you is actually the same person in disguise?

[If caregiver/proxy: Has your relative ever reported that, or behaved as if, he/she believes that everyone around him/her is actually the same person in disguise?]

11. Reduplicative Paramnesia

Does it seem as if you are not in your own house or in a location you are familiar with, and that you are in an unfamiliar place, even if other people tell you otherwise?

[If caregiver/proxy: Has your relative ever reported that, or behaved as if, he/she is not in his/her own house or in a place he/she is familiar with, but is in a strange place instead which appears similar to his/her own house or a familiar place?]

12. Mirrored-Self Misidentification

Have you ever looked in the mirror and seen someone unfamiliar?

[If caregiver/proxy: Has your relative ever reported that he/she looked into a mirror and saw somebody else?]

Instructions on Severity Scoring

Frequency
How often do you experience this?

[If caregiver/proxy: how often does he/she experience this?]

0 Not at all
1 Rarely: approximately once or twice in the last 4 weeks
2 Sometimes: approximately once a week in the last 4 weeks
3 Often: several times a week but not every day
4 Always: every day or virtually all the time.

Duration
How long does this experience usually last?

[If caregiver/proxy: how long does the experience usually last for him/her?]

0 None
1 Fleeting: Seconds to Minutes
2 Minutes to Hours
3 Hours to Days
4 Continuously

Conviction
How convinced are you that this experience is real?

[If caregiver/proxy: how convinced is he/she that the experience is real?]

0 Completely certain it is not real/false
1 Fairly certain that it is likely false, but still has some doubts
2 Believes that it may or may not be true; they can't decide
3 Fairly certain that it is likely real/true, but still has some doubts
4 Completely certain it is real/ true

Distress
How much does this experience bother you?

[If caregiver/proxy: how much does this experience bother or distress him/her?]

0 Completely undisturbed emotionally by the experience
1 Uncertain if emotionally disturbed by the experience
2 Rarely emotionally disturbed by the experience
3 Fairly emotionally disturbed by the experience
4 Completely disturbed emotionally by the experience

Action
Over the past 4 weeks, how often have you reacted or responded to the experience?

[If caregiver/proxy: has he/she behaved as if he/she is reacting or responding to the experience?]

0 No reaction to the experience because the patient believes the experience as not true or unrealistic
1 Rarely responding to the experience
2 Sometimes reacting to the experience
3 Often behaved in such a way as a response to the experience
4 Consistently or always behaved in such a way as a response to the experience

Perception of others
How realistic do you think most people (would) think of this experience?

[If caregiver/proxy: how certain is he/she that most people would think this experience makes sense?]

0 Completely certain that most people would think this experience unrealistic.
1 Fairly certain that most people think this experience unrealistic.
2 Others may or may not think this experience as unrealistic; cannot decide
3 Fairly certain that most people would think this experience as realistic.
4 Completely certain that most people would think this experience as realistic

Impact
How does this experience affect your functioning or social relationships in everyday life?

[If caregiver/proxy: how did this experience affect his/her daily functioning or relationships with others?]

0 This has not affected the patient's functioning or his/her social relationships at all
1 This has rarely affected the patient's functioning or his/her social relationships
2 This has sometimes affected the patient's functioning or his/her social relationships
3 This has often affected the patient's functioning or his/her social relationships.
4 This has completely interfered with the patient's functioning or his/her social relationships

Insight
If I am to tell you that this experience is likely due to Parkinson's disease or its treatment, do you believe me?

[If caregiver/proxy: how certain is he/she that this experience is likely due to Parkinson's disease or its treatment?]

0 The cause is definitely Parkinson's disease or its treatment.
1 The cause is probably Parkinson's disease or its treatment.
2 The cause is possibly Parkinson's disease or its treatment.
3 The cause is probably not Parkinson's disease or its treatment.
4 The cause is definitely not Parkinson's disease or its treatment.

SCORING

Psy-PD has two subscales – one scoring the severity of hallucinations, and the other scoring the severity of delusions. The hallucinations subscale has 5 domains, and the delusions subscale has 12. Each domain has 8 items comprising severity. Each item is rated on a 5-point scale ranging from 0 to 4 based on the extent of its effect. The maximum total score for each domain is 32. The maximum grand total for the subscale of hallucinations is 160, and that for the subscale of delusions is 384. The overall maximum total for the scale is 544.

Calculation :

Domain total = Sum of all items for that domain
Subscale total = Sum of all domains for that subscale
Psy-PD total score = total score of both subscale totals

Raw Scores	Psychosis Severity
0-8	Minimal
9-16	Mild
17-24	Moderate
>25	High

Questionnaire Related to Psy-PD for the PD Specialist/ Healthcare Professional

This is a questionnaire to be completed by the PD specialist using the first version of the Psychosis Severity Scale (Psy-PD) for Parkinson's Disease patients.

The developers of this new scale request your opinion about this assessment as this is a crucial step in its development. Your response is very much appreciated.

Please respond to the following questions after application of the Psy-PD to your patients:

1. **Do you find the scale relevant?**

   YES **NO**

2. **Does this scale help you to better understand the current health state of your PD patients?**

   YES **NO**

3. **Do you think this scale is comprehensive?**

   YES **NO**

If "NO", please provide information about the gaps in its content:

_____

_____

4. **As many components comprise the concept of severity in the context of psychosis in Parkinson's disease, the scale includes a long list of questions to capture all relevant information. Do you think this scale is too long?**

   YES **NO**

5. **Do you find the questions easy to understand?**

   YES **NO**

If "NO", please provide comments about how to simplify:

_____

_____

6. **Did you find any question(s) embarrassing?**

   YES **NO**

If "YES", please provide information about the question(s) which were embarrassing:

_____

_____

7. Did you find any particular question(s) difficult to answer?

YES NO

If "YES", please provide information about the question(s) which were difficult to answer:

_____

_____

8. Do you have any additional comments or ideas for improving the current version of this scale?

_____

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Questionnaire Related to Psy-PD

This is a questionnaire to be completed in relation to a rating-scale to be used by professionals for the evaluation of psychosis in Parkinson's disease. These psychotic symptoms can be variable in nature, and are known to affect the health state and quality of life of patients and their caregivers. Psychosis is frequently more troublesome than the motor disability associated with the Parkinson's disease.

Some of these symptoms are also be present in people without Parkinson's and in Parkinson's patients who have not yet been not diagnosed.

It may be possible that you may not have any, or only a few, of the psychotic symptoms listed. However, Parkinson's can vary from person to person, and for some patients many of these symptoms are important, thus the scale includes as many psychotic symptoms as possible.

Doctors are now evaluating a new psychosis severity scale, your opinion about this evaluation is crucially important and we appreciate your response.

Please, respond to the following questions after the psychosis severity scale has been completed:

	YES	NO
1. **Do you find the scale relevant?**	☐	☐
2. **Does this scale help you to better understand your current health state ?**	☐	☐
3. **As many components comprise the concept of severity in the context of psychosis in Parkinson's disease, the scale includes a long list of questions to capture all relevant information. Do you think this scale is too long?.....**	☐	☐
4. **Were the questions easy to understand?.....**	☐	☐

If "NO", please provide comments about how to simplify:

_____

_____

5. **Did you find any question(s) embarrassing?.....** ☐ ☐

If "YES", please provide information about the question(s) which were embarrassing.

_____

_____

King's College Hospital NHS
NHS Foundation Trust

6. **Did you find any particular question(s) difficult to answer?.....** ☐ ☐

If "YES", please provide information about the question(s) which were difficult to answer:

_____

_____

7. **Do you have any additional comments or ideas for improving the current version of this scale?**

_____

_____

Chapter 7
Overlapping Psychosis and Apathy in Parkinson's Disease

7.1 Introduction

Emergent evidence is showing Parkinson's disease (PD) to be a complex neuropsychiatric disorder that includes the clinical features of apathy and psychosis, two key biomarkers of cognitive outcome (Barone et al., 2009; Han et al., 2018; Isella et al., 2002) and quality of life (Laatu et al., 2013; van Reekum et al., 2005). Currently these symptoms are often under-recognised and considered challenging to treat. Although both are common non-motor features of PD, and despite the reported co-occurrence of these symptoms (Omoto et al., 2021; Santangelo et al., 2007) , their relationship remains largely unclear. Further clarification of the latter, as well as the underlying pathophysiology, holds importance for a personalised approach to both neuropsychiatric features in people with PD (PwP) as treatments might need to be tailored to underlying neurotransmitter changes(Titova & Chaudhuri, 2017c).

PD psychosis has been described in literature as a continuum of "*positive*" or "surplus of brain function" symptoms spanning a spectrum from minor phenomena of illusions, presence and passage hallucinations to well-formed major hallucinations and delusions (Ffytche et al., 2017), clinically distinct from the manifestations of primary psychotic disorders or psychotic features occurring in other degenerative disorders. On the other hand, clinical apathy, the "*negative*" or "brain function deficit" constellation of symptoms (Winograd-Gurvich et al., 2006), has been shown to exist independently from depression in PwPs with growing research interest into its pathophysiology, progression, and management (Benoit, 2015; Martin et al., 2020; Mele et al., 2019; Oguro H, 2014; Prange et al., 2019). While much progress has been achieved in characterising the nature and impact of psychosis and apathy, respectively, studies into their interactions with *each other* have been lacking. Analysing the in-depth connections between

psychosis and apathy among PwP, or lack thereof, may be of tremendous value in furthering our understanding of the phenomenology of both *positive* and *negative* neuropsychiatric symptoms. The clinical associations of these separate dimensions can then be further explored in order to provide clues to aetiology or outcomes.

For the current analysis, we hypothesized that apathy and psychosis in PwP represent clinically distinct symptoms that, although often present concurrently in PwP, have a differential impact on quality of life.

7.2 Contributions and Collaborations

I wrote the entirety of this chapter, did the analyses, and drew up the tables. My research colleague (DvW) helped to check that the appropriate statistical analyses were done.

7.3 Methods

The primary aims of the current study were to evaluate apathy burden, measured through the Starkstein Apathy Scale (SAS) in PwP with and without psychosis, and the differential impact on quality of life, measured through the 8-item Parkinson's Disease Quality of Life instrument (PDQ-8).

Data for analysis were extracted from the prospective, longitudinal Non-motor International Longitudinal Study (NILS), adopted by the National Institute of Health Research in the UK (UKCRN No: 10084) and authorised by a local ethics committee (NRES SouthEast London REC3, 10084, 10/H0808/141). This initiative includes over 30 centres worldwide and contains non-motor data for over 1,600 PwP (van Wamelen, Sauerbier, et al., 2021). Prior to study procedures, all patients gave written consent in accordance with the Declaration of Helsinki. The main inclusion criterion for NILS was a diagnosis of idiopathic PD according to the UK Brain Bank criteria and exclusion criteria were (1) diagnosis of atypical Parkinsonism;

(2) dementia (as per internationally accepted criteria) (Zadikoff et al., 2008); and (3) inability to give informed consent. In addition, we recruited a group of healthy controls for whom the same exclusion criteria were used as above with the addition of idiopathic Parkinson's disease as an exclusion criterion.

For the current analysis, we used data from patients whose data were collected at King's College Hospital London (United Kingdom) and for whom assessment with SAS was available. Data included consisted of sex, age, disease duration, and Levodopa equivalent daily dose (LEDD). Information on antidepressant and antipsychotic use was also collected, with the antidepressants further specified as being of the selective serotonin reuptake inhibitor (SSRI) class or otherwise. Patient-reported outcomes included Hospital Anxiety and Depression Scale (HADS)(Mondolo et al., 2006; Zigmond & Snaith, 1983), PD Questionnaire-8 item (PDQ-8) for quality of life (Martinez-Martin et al., 2004), and clinician-based evaluations included Hoehn and Yahr (HY) staging (Hoehn & Yahr, 1967), and Non-Motor Symptom Scale (NMSS) scores (van Wamelen, Martinez-Martin, et al., 2021).

Psychosis was defined as a score of one or higher on the domain 4 (perceptual problems/hallucinations) score of the NMSS. This cut-off was arbitrarily chosen as a consensus among the authors of the current manuscript as no validated cut-off scores for this symptom were available for this scale. Apathy was defined as a score of 14 or higher on the SAS (Starkstein et al., 1992), and depression defined as a score of 11 or higher on the depression subscale of the HADS (Mondolo et al., 2006).

To address the primary aims of the analysis, SAS scores and PDQ-8 scores were compared between PwP and healthy controls. Secondary outcomes consisted of differences in specific non-motor symptoms, measured through the domains of the NMSS, and determining the potentially different patient profiles between patients with apathy and without depression, patients with apathy and depression, and patients without apathy and depression.

In addition, we classified 58 PD patients from this cohort who did not have clinical depression (HADS-depression subscore less than 11), into one of the following four groups: (1) a *positive*-symptom group for PwP with isolated psychosis, (2) a *negative*-symptom group for those endorsing isolated apathy, (3) a *mixed*-symptom group for PwP with both psychosis and apathy, and (4) a *none*-symptom group for those who had neither psychosis nor apathy. The cut-off scores to determine apathy and depression were as above.

7.3.1 Statistical analyses

As the scores of the different scale data were not normally distributed (determined through Kolmogorov-Smirnov test), we used the Mann-Whitney-U-test or the Kruskal-Wallis test, where relevant, to evaluate group differences. In order to determine statistically significant associations between SAS scores, demographic data, and non-motor outcomes we performed univariate analyses (Spearman's test) between the different assessments, as outlined above, and SAS scores. The significance threshold for all analyses was set at <0.05 and a Benjamini-Hochberg procedure (Benjamini & Hochberg, 1995) was used for multiple comparisons, where relevant; *post-hoc* analyses were performed for outcomes that remained significant after correction for multiple testing. All data were analysed using SPSS Version 27 (IBM SPSS Statistics for Windows (Version 27.0. Armonk, NY: IBM Corp.). Data are represented as mean ± standard deviation, median (25^{th}-75^{th} percentile), number (percentage) or *r*-value, unless otherwise specified.

A sample size of 41 psychosis and 34 non-psychosis within PD group achieves 80% power to reject the null hypothesis of equal PDQ8 score between the two groups. This sample size allows to detect a standardized effect size of ~0.65 (medium-to-large effect size). Type I error is set at 5%, and the power calculation is performed using a two-sided two-sample equal-variance t-test. Sample size calculation is conducted via PASS software (2022 Power Analysis and Sample Size Software (2022). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass.).

7.4 Results

Demographics, SAS scores, and other outcome measures for both PwP and healthy controls are provided in *Table* 6.1. In total, 75 PwP and 25 healthy controls were included in the current analysis. Overall, 56% of the PwP were classified as having clinical apathy, of whom 64.3% (36% of whole cohort) endorsed isolated apathy, while 54.7% of the cohort suffered from psychosis (*Table* 7.1). In terms of mood and anxiety, 22.7% of the cohort experienced clinical depression (HADS depression subscore $\geq$11(Mondolo et al., 2006)) and 56% endorsed clinical anxiety (HADS anxiety subscore $\geq$7 (Mondolo et al., 2006)), while 37.2% experienced both (*Table* 7.1).

7.4.1 Apathy and depression

In our cohort of PwP, depression scores were missing for one patient, and three patients had depression without apathy; these patients were not included for further analysis. In the remainder of the cohort, 29 patients had neither depression or apathy, 27 had apathy without depression, and 15 had both apathy and depression. Demographics and outcome measures for these groups are provided in *Table* 7.1; all groups were well-matched for age, sex, disease duration, LEDD, and HY stage ($p \geq 0.251$; *Table* 7.3). There was a statistically significant difference between the groups in relation to non-motor burden (NMSS total scores), with the highest scores in the group with both apathy and depression ($p=0.038$), although this difference was not observed after omission of NMSS domain 3 (mood/apathy) scores ($p=0.071$; *Table* 7.3). Other differences between groups included differences in NMSS domain 5 (cognition; $p=0.038$), and HADS anxiety and ESS scores ($p \leq 0.001$; *Table* 7.3). In addition, quality of life was significantly worse in those with apathy and those with both apathy and depression, compared to PwP with neither apathy nor depression ($p<0.001$; *Table* 7.3).

7.4.2 Apathy and psychosis

Clinical characteristics across psychosis subgroups are provided in *Table* 7.1. PwP with and without psychosis were well-matched for age, sex, disease duration, HY stage, LEDD, and years of education ($p \geq 0.063$; *Table* 7.1); however, in the cohort of healthy controls significantly more females were present compared to the PwP, and control participants tended to be slightly younger than the patients (*Table* 7.1).

We observed that SAS scores were significantly higher amongst PwP (15.5±8.1) compared to healthy controls (10.2±6.1) ($p=0.007$); the largest difference was observed between healthy controls and PwP with psychosis ($p<0.001$), but also the difference in SAS scores between patients without psychosis (12.8±7.5) and those with psychosis (17.8±8.0) reached statistical significance ($p=0.019$) (*Table* 7.1). Also, when comparing SAS scores between patients with no psychosis (NMSS domain 4 score <8), mild psychosis (NMSS domain 4 score 8-11), and severe psychosis (NMSS domain score ≥12), we found the highest apathy scores in those with severe psychosis ($p=0.043$; *Figure* 7.1). Moreover, we observed that quality of life was significantly worse in patients with psychosis compared to those without ($p<0.001$). Interestingly, despite the disparities in apathy scores, no differences in HADS depression scores were observed between PwP with and without psychosis ($p=0.116$).

Finally, we determined which symptoms were associated with apathy scores. We observed that the factors most strongly positively associated with SAS scores were HADS depression ($r=0.618$; $p<0.001$) and anxiety scores ($r=0.465$; $p<0.001$; *Table* 7.2). Similarly, we found a moderate positive association between apathy (SAS scores) and quality of life (PDQ-8) ($r=0.503$; $p<0.001$; *Table* 7.2).

7.4.3 Overlap of psychosis and apathy

We further analysed the distribution and differences among the *positive*-symptom (isolated psychosis), *negative*-symptom (isolated apathy), *mixed*-symptom (psychosis and apathy), and *none*-symptom groups (neither psychosis nor apathy). 20.7% had only *positive* symptoms with no *negative* symptoms, 15.5% endorsed only *negativ*e symptoms with no *positive* symptoms, 31% suffered mixed *positive* and *negative* symptoms, while 32.8% had none of the psychiatric symptoms explored here. Demographics were comparable across the symptom groups, except that the *positive* symptom-group were significantly older than the *none*-symptom group, and the *mixed*-group having markedly higher LEDD than the *none*-symptom group (*Table* 7.4).

Pairwise comparisons between either the *positive*-symptom or the *negative*-symptom group with the other groups yielded no statistically significant associations; however, this was not the case between the *mixed* group and the *negative* or the *none*-symptom groups.

Here, the *mixed*-symptom group had a significantly higher total non-motor burden as compared to the *negative*-symptom (*Table* 7.4, p=0.011) or *none*-symptom (*Table* 7.4, p<0.001) groups, which remained significant even after removal of domains 3 (Mood/Cognition) and 4 (Perceptual problems/hallucinations) from analysis. The *mixed*-symptom group also had significantly higher NMSS domains 2 (Sleep/Fatigue) and 5 (Attention/Memory) burden than both the *negative*-symptom (*Table* 7.4; NMSS Domain 2: p=0.032; NMSS Domain 5: p=0.003) and *none*-symptom (*Table* 7.4; NMSS Domain 2: p=0.040; NMSS Domain 5: p<0.001) groups. As compared to the *none*-symptom group, the *mixed*-symptom group is also associated with worse NMSS domain 1 (Cardiovascular including falls) scores (*Table* 7.4, p<0.01). In general, we observed a worse impact on quality of life from the *mixed*-symptom group, as compared to the *positive*-, *negative*- or the *none*-symptom groups.

As antipsychotics and antidepressants (particularly the SSRIs) may confound the results, a *post hoc* sensitivity analysis was performed, but pairwise comparisons are made only between the *mixed*-symptom group vs the *negative*-symptom and the *none*-symptom groups. Among the cohort,

12 were on SSRIs, 11 were on non-SSRIs, and 1 was on an antipsychotic medication. Data from these was removed from analysis and results were summarised in *Table* 7.5. Here, we observed that the *mixed*-symptom group no longer differed significantly in terms of total non-motor burden when compared to the *negative*-symptom group (*Table* 7.5, p=0.123), although there was still a significantly higher NMSS domain 5 (Attention/Memory) burden (*Table* 7.5, p=0.021). However, the earlier findings between the *mixed*-symptom group compared to the *none*-symptom group remained the same, with the former having worse total non-motor burden (*Table* 7.5, p<0.01), worse NMSS domain 1 (Cardiovascular/Falls) (p<0.01), domain 2 (Sleep/Fatigue)(p<0.05), and domain 5 (Attention/Memory) (p<0.001) scores than the latter. Overall, the *mixed*-symptom group was still associated with a worse quality of life than the *negative*- (*Table* 7.5, p<0.05) or *none*-symptom (p=0.001) groups.

***Table* 7.1. Demographics and apathy scores in patients with Parkinson's disease, both with and without psychosis, compared to healthy controls.**

	PD patients											
	Whole group (n=75)	**With psychosis (n=41)**	**Without psychosis (n=34)**	***p*1**	***p*1***	**Healthy controls (n=25)**	***p*2**	***p*2***	***p*3**	***p*3***	***p*4**	***p*4***
Age	66.2±10.9	68.6±9.7	63.4±11.6	0.035	0.063	61.2±9.9	0.035	**0.049**	0.032	0.078	0.005	**0.006**
Sex (M/F)	64.5%/36.0%	56.1%/43.9%	73.5%/26.5%	0.150	0.188	20.0%/80.0%	<0.001	**<0.001**	<0.001	**<0.001**	0.004	**0.005**
Education, yrs	15.0±4.8	14.7±4.3	15.4±5.3	0.596	0.701	14.4±4.3	0.639	0.639	0.588	0.672	0.755	0.755
Disease duration, yrs	9.8±5.6	9.6±5.5	9.9±5.7	0.924	0.924	-	NA	NA	NA	NA	NA	NA
HY	3.0 (2.0-3.0)	3.0 (2.0-4.0)	2.0 (2.0-3.0)	0.043	0.071	-	NA	NA	NA	NA	NA	NA
LEDD (mg)	875.9±655.6	1,022.4±753.9	699.3±464.9	0.046	0.071	-	NA	NA	NA	NA	NA	NA
NMSS	70.7±48.8	90.5±46.6	46.9±40.4	<0.001	**<0.001**	-	NA	NA	NA	NA	NA	NA
Domain 1	3.2±4.3	4.6±4.7	1.6±3.0	<0.001	**<0.001**	-						
Domain 2	14.6±11.5	18.1±12.2	10.4±9.3	0.006	**0.015**	-						
Domain 3	12.2±14.6	15.6±15.4	8.3±12.8	0.005	**0.014**	-						
Domain 4	4.4±6.6	8.2±7.0	0.0±0.0	NA	NA	-						
Domain 5	9.0±10.2	13.0±10.4	4.2±7.7	<0.001	**<0.001**	-						
Domain 6	7.2±8.3	8.3±8.1	5.8±8.6	0.077	0.110	-						
Domain 7	11.0±11.0	14.1±11.4	7.4±9.4	0.009	**0.018**	-						
Domain 8	1.8±4.8	1.6±4.5	2.1±5.1	0.776	0.862	-						
Domain 9	6.9±7.0	7.2±8.0	6.5±5.9	0.887	0.924	-						
HADS	15.1±8.2	17.5±7.8	12.0±7.8	0.004	**0.013**	9.8±5.8	0.007	**0.012**	0.283	0.377	<0.001	**<0.001**
Anxiety	7.9±4.5	9.5±4.3	5.9±4.0	<0.001	**<0.001**	5.8±3.5	0.063	0.074	0.965	0.965	0.002	**0.003**
Depression	7.2±4.3	8.0±4.2	6.1±4.4	0.087	0.116	3.5±3.2	<0.001	**<0.001**	0.017	0.068	<0.001	**<0.001**
ESS	11.7±6.9	13.6±6.3	9.3±6.9	0.007	**0.016**	5.3±4.1	<0.001	**<0.001**	0.039	0.078	<0.001	**<0.001**
PDQ8	12.3±7.0	15.6±5.9	8.3±6.0	<0.001	**<0.001**	-	NA	NA	NA	NA	NA	NA
SAS	15.5±8.1	17.8±8.0	12.8±7.5	0.019	**0.019**	10.2±6.1	0.007	**0.007**	0.191	0.306	<0.001	**<0.001**

*p*1: between PD with and without psychosis; *p*2: between whole group of PD patients and controls; *p*3: between PD patients without psychosis and controls; *p*4: between PD patients with psychosis and controls; NA: not applicable; yrs: years; *: Corrected for multiple testing using Benjamini-Hochberg procedure (not including SAS scores as this is the primary outcome). Data represented as mean±standard deviation, median (25th-75th percentile), or percentage.

***Table* 7.2 Association between SAS scores and quality of life, disease demographics, and non-motor variables in patients with Parkinson's disease (n=75).**

	ρ
Quality of life (PDQ-8)	0.503***
Age	0.212*
Disease duration	0.102
LEDD	0.249*
HADS anxiety	0.465***
HADS depression	0.618***
ESS	0.364***
NMSS	0.381***
Domain 1	0.196
Domain 2	0.191
Domain 3	0.468***
Domain 4	0.284*
Domain 5	0.343**
Domain 6	0.328**
Domain 7	0.106
Domain 8	-0.027
Domain 9	0.073

*: $0.05 \leq p > 0.01$; **: $0.01 \leq p > 0.001$; ***: $p < 0.001$

***Table* 7.3. Differences in people with Parkinson's disease with different apathy and depression profiles.**

Groups	**1**	**2**	**3**		
	No Apathy, No Depression (n=29)	**Apathy, No Depression (n=27)**	**Apathy & Depression (n=15)**	***p***	***p****
Age	65.1±10.5	66.8±12.0	66.7±10.2	0.437	0.639
Sex (M/F)	19/10	16/11	11/4	0.707	0.802
Disease duration (yrs)	9.2±5.5	9.6±5.4	11.4±6.5	0.526	0.714
HY	2.0 (2.0-3.0)	3.0 (2.0-3.0)	3.0 (3.0-4.0)	0.210	0.363
LEDD (mg)	727.2±638.5	1034.0±711.0	881.2±612.5	0.119	0.251
Education (yrs)	15.7±4.7	15.0±4.0	14.4±6.0	0.660	0.802
SAS scores	7.7±3.6	19.6±4.5	24.5±6.1	NA	NA
NMSS	52.9±38.7	71.3±43.6	108.3±56.9	0.008	**0.038[b]**
NMSS without domain 3	46.5±35.3	59.3±35.2	81.4±39.8	0.028	0.071
NMS1score	2.8±3.6	4.5±5.4	2.5±2.8	0.403	0.638
NMS2score	12.5±11.3	13.3±10.0	22.8±12.6	0.027	0.071
NMS3score	6.2±8.1	12.0±12.9	26.9±19.4	NA	NA
NMS4score	2.9±4.8	5.1±7.5	5.8±7.5	0.158	0.300
NMS5score	4.7±6.1	9.3±9.4	17.6±13.4	0.010	**0.038[b]**
NMS6score	4.8±7.3	6.6±6.6	12.7±11.7	0.030	0.071
NMS7score	10.1±11.7	11.0±10.5	11.3±10.6	0.837	0.837
NMS8score	1.6±3.9	2.4±6.3	1.3±3.5	0.773	0.815
NMS9score	6.0±5.4	7.3±8.7	8.4±7.6	0.718	0.802
HADS	10.1±5.6	14.0±6.2	25.1±5.4	NA	NA
Anxiety	5.6±3.4	7.9±4.3	12.0±3.7	<0.001	**<0.001[a,b,c]**
Depression	4.5±2.9	6.1±2.6	13.1±2.4	NA	NA
ESS	9.1±7.3	11.3±6.3	17.2±4.6	<0.001	**<0.001[a]**
PDQ-8	8.3±5.9	12.4±6.0	19.1±4.5	<0.001	**<0.001[b,c]**

yrs : years; *p**: *p*-value corrected for multiple testing using Benjamini-Hochberg procedure; NA: not applicable. Post-hoc analyses: **a**: $p<0.05$ between groups 1 and 2; **b**: $p<0.05$ between groups 1 and 3; **c**: $p<0.05$ between groups 2 and 3.

***Figure* 7.1. Starkstein apathy scores across different psychosis severity in Parkinson's disease patients (n=75).**

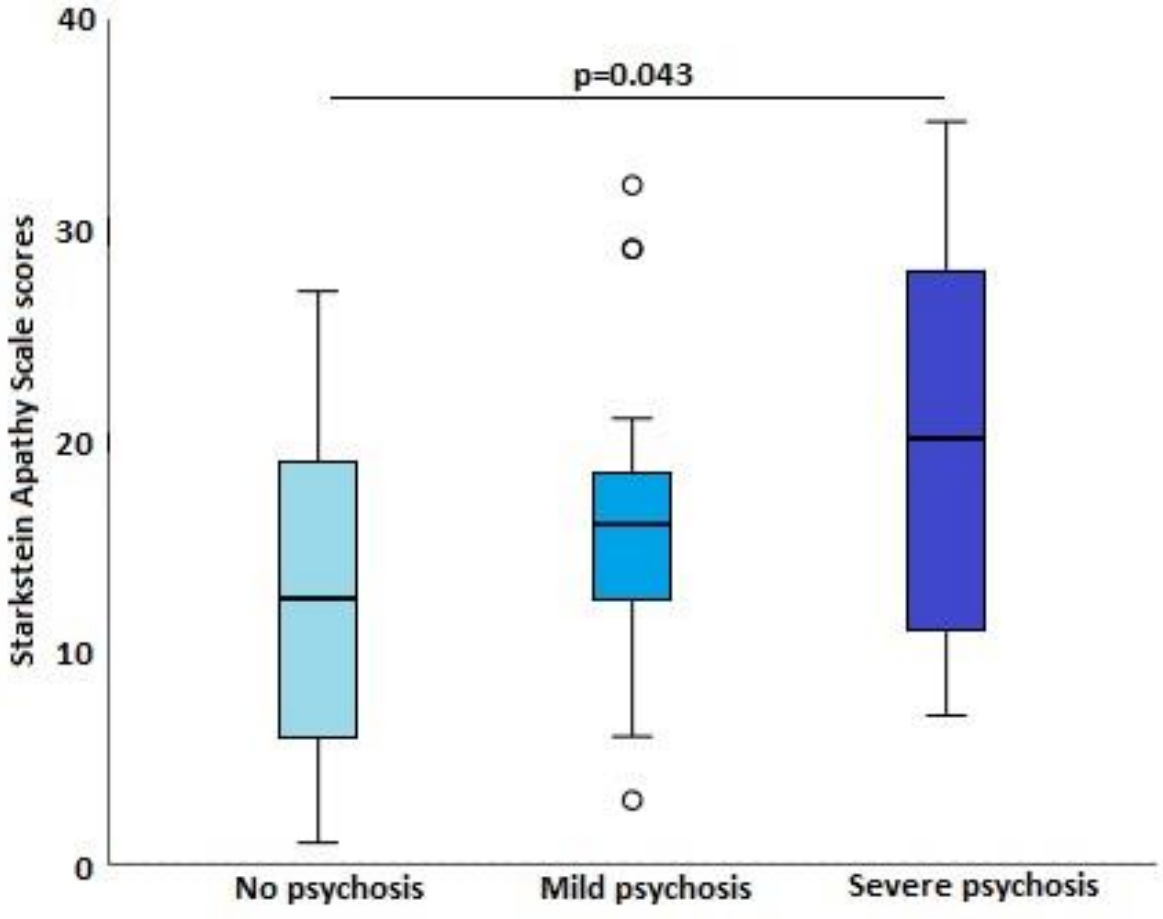

***Table* 7.4. People with Parkinson's disease presenting with apathy, but without depression, and the effect of psychosis.**

Symptom Groups	Group 1	Group 2	Group 3	Group 4	Groups 1 v. 2		Groups 1 v. 3		Groups 1 v. 4		Groups 3 v. 4		Groups 2 v. 3		Groups 2 v. 4	
	Positive **(psychosis without apathy) (n=12)**	***Mixed*** **(psychosis and apathy) (n=18)**	***Negative*** **(apathy without psychosis) (n=9)**	***None*** **(neither apathy nor psychosis) (n=19)**	*p*	*p**	*p*	*p**	*p*	*p**	*p*	*p**	*p*	*p**	*p*	*p**
Age	73.67±8.15	64.50±6.95	67.67±18.18	60.37 ± 8.60	0.029	0.464	0.354	0.629	<0.01	**0.01**	0.065	0.926	0.571	0.611	0.061	0.122
Sex (M/F)	8/4	10/8	6/3	13/6	0.543	0.764	1.000	1.000	0.919	0.919	0.926	0.926	0.580	0.611	0.420	0.560
Disease duration (yrs)	11.8 ± 5.97	8.28 ± 4.99	12.22 ±5.47	7.68 ± 4.38	0.111	0.484	0.943	1.000	0.044	0.117	0.794	0.926	0.084	0.192	0.703	0.762
HY	3 (2-4)	3 (2-3)	2(2-3)	2 (2-3)	0.121	0.484	0.215	0.430	0.299	0.435	0.458	0.926	0.331	0.467	0.172	0.250
LEDD (mg)	1000.74 ±760.74	1175.55 ± 781.01	750.90 ±459.41	590.05 ± 500.60	0.612	0.764	0.522	0.777	0.149	0.265	0.175	0.926	0.150	0.498	0.004	**0.011**
Education (yrs)	16.33 ± 5.07	14.67 ± 3.82	15.78 ± 4.60	15.21 ± 4.70	0.383	0.734	0.943	1.000	0.610	0.813	0.708	0.926	0.421	0.514	0.714	0.762
NMSS total without domain 3	62.75 ± 40.55	73.89 ± 27.41	30.56 ± 32.47	31.79 ± 29.01	0.459	0.734	0.081	0.323	0.027	0.10	0.844	0.926	<0.01	**0.011**	<0.001	**<0.001**
NMSS without domain 3 & without domain 4	55.58 ± 36.61	66.17 ± 24.53	30.56 ± 32.47	31.79 ± 24.47	0.373	0.734	0.126	0.336	0.063	0.126	0.844	0.926	<0.01	**0.020**	<0.001	**0.001**
NMS1score	4.33 ± 3.47	5.78 ± 5.89	2.00 ± 3.46	1.53 ± 3.15	0.764	0.764	0.101	0.323	0.017	0.090	0.734	0.926	0.033	0.088	0.002	**0.005**
NMS2score	16.17 ± 6.60	16.94 ± 9.59	6.11 ± 6.60	0.11 ± 8.18	0.641	0.764	0.080	0.323	0.187	0.300	0.310	0.926	0.010	**0.032**	0.018	**0.040**
NMS3score	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
NMS4score	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
NMS5score	7.33 ± 7.20	13.28 ± 8.89	1.22 ± 2.73	2.68 ± 4.28	0.075	0.484	0.0096	0.154	0.031	0.100	0.200	0.926	<0.001	**0.003**	0.000	**0.000**
NMS6score	5.08 ± 5.79	7.44 ± 6.60	4.89 ± 6.58	4.68 ± 7.88	0.392	0.734	0.971	1.000	0.805	0.919	0.881	0.926	0.311	0.553	0.091	0.146
NMS7score	15.42 ± 11.90	12.39 ± 10.90	8.11 ± 9.57	6.47 ± 9.66	0.418	0.734	0.175	0.400	0.047	0.107	0.395	0.926	0.351	0.562	0.085	0.146
NMS8score	1.67 ± 4.87	2.22 ± 5.19	2.67 ± 8.00	1.21 ± 2.76	0.724	0.764	0.534	0.777	0.868	0.919	0.632	0.926	0.437	0.619	0.628	0.762
NMS9score	5.58 ± 6.10	8.11 ± 9.74	5.56 ± 6.13	6.11 ± 4.81	0.731	0.764	0.858	1.00	0.667	0.821	0.552	0.926	0.754	0.754	0.890	0.890
PDQ-8	12.5 ± 6.49	15.22 ± 4.76	6.67 ± 3.94	6.11 ± 3.94	0.235	0.734	0.035	0.233	0.007	0.06	0.729	0.974	**<**0.001	**0.003**	0.000	**0.000**

Data represent as number, mean ± standard deviation, or median (25^{th}-75^{th} percentile);
Symptom groups: *Positive* : Psychosis (without Apathy & without Depression), *Mixed* : Psychosis + Apathy (without Depression), *Negative* : Apathy (without Psychosis & without Depression), *None* : No Psychosis (without Apathy & without Depression); yrs: years;
*: corrected for multiple testing using Benjamini-Hochberg procedure.
In bold : *p*<0.05

***Table* 7.5. People with Parkinson's disease presenting with apathy, but without depression, and the effect of psychosis (without antidepressants or antipsychotics)**

Symptom Groups	Group 1	Group 2	Group 3	Group 4	Groups 2 v. 3		Groups 2 v. 4	
	***Positive* (psychosis without apathy) (n=10)**	***Mixed* (psychosis and apathy) (n=12)**	***Negative* (apathy without psychosis) (n=6)**	***None* (neither apathy nor psychosis) (n=17)**	***p***	***p****	***p***	***p****
Age	72.9±8.76	68±8.28	71.00±19.29	60.41 ± 9.06	0.260	0.462	0.059	0.106
Sex (M/F)	7/3	8/4	5/1	12/5	0.457	0.511	0.822	0.822
Disease duration (yrs)	12.6 ± 6.22	6.83 ± 3.88	10.5 ± 5.82	7.71 ± 4.57	0.205	0.434	0.706	0.807
HY	2.5 (2-4)	3 (2-3)	2.5 (2-3)	2 (2-3)	0.371	0.511	0.246	0.328
LEDD (mg)	1111.884±772.63	1028.24 ± 713.88	711.93 ±543.93	593.59 ± 530.85	0.453	0.511	0.051	0.103
Education (yrs)	16.00 ± 5.54	14.83 ± 4.41	16.83 ± 4.12	15.35 ± 4.76	0.217	0.434	0.577	0.710
NMSS total without domain 3	64.5 ± 44.54	75.83± 23.51	33.17 ± 40.07	31.41 ± 25.45	0.031	0.123	<0.001	**0.003**
NMSS without domain 3 & without domain 4	57.5 ± 40.13	67.00 ± 23.65	33.17 ± 40.07	31.41 ± 25.45	0.06	0.161	0.003	**0.009**
NMS1score	48 ± 3.52	5.5 ± 3.92	1.33 ± 3.27	1.71 ± 3.29	0.019	0.100	0.003	**0.009**
NMS2score	17.6 ± 15.15	18.75 ± 10.43	7.50 ± 7.04	8.76 ± 8.61	0.039	0.123	0.017	**0.044**
NMS3score	NA	NA	NA	NA	NA	NA	NA	NA
NMS4score	NA	NA	NA	NA	NA	NA	NA	NA
NMS5score	7.8 ± 7.86	13.67 ± 6.29	1.33 ± 3.27	2.47 ± 4.20	<0.01	**0.021**	0.000	**0.000**
NMS6score	4.7 ± 6.27	7.44 ± 6.60	6.50 ± 7.69	4.76 ± 8.36	0.479	0.511	0.052	0.103
NMS7score	15.9 ± 13.09	10.83 ± 8.85	7.00 ± 10.56	7.00 ± 10.08	0.343	0.511	0.201	0.293
NMS8score	2.00 ± 5.31	3.33 ± 6.13	4.00 ± 9.80	0.88 ± 2.34	0.468	0.511	0.144	0.230
NMS9score	4.7 ± 6.27	6.33 ± 7.45	5.50 ± 7.53	5.82 ± 4.76	0.885	0.885	0.787	0.822
PDQ-8	12.2 ± 7.13	15.08 ± 4.89	6.50 ± 4.04	6.18 ± 4.10	**<0.01**	**0.025**	0.000	**0.001**

Data represent as number, mean ± standard deviation, or median (25^{th}-75^{th} percentile);
Symptom groups: *Positive* : Psychosis (without Apathy & without Depression), *Mixed* : Psychosis + Apathy (without Depression), *Negative* : Apathy (without Psychosis & without Depression), *None* : No Psychosis (without Apathy & without Depression); yrs: years;
*: corrected for multiple testing using Benjamini-Hochberg procedure.
In bold : $p<0.05$

7.5 Discussion

To our knowledge, while apathy has been identified in psychotic patients in a few studies (Santangelo G et al 2007; Omoto et al 2020), the current study represents the first in-depth analysis of the clinical profile of apathy and its associations with psychosis in a multi-centre cohort of non-demented PD patients, utilising standardised recommended and validated measurement scales.

The key primary findings were:

(a) Compared to either symptom alone, the co-occurrence of apathy and psychosis appeared to be associated with a higher non-motor burden and reduced quality of life in PwP.

(b) The *mixed*-symptom group, consisting of patients with concurrent apathy and psychosis was identified as a possible endophenotype associated with poor quality of life in PD, even when the influence of psychotropic medications was removed.

Secondary findings included:

(a) The overall prevalence of clinical apathy in PwP was 56% , with more than half experiencing isolated apathy (without depression).

(b) Psychosis was not uncommon in our PD cohort, with more than 50% experiencing psychotic symptoms.

(c) Clinical apathy seemed to occur more often in PwP with psychosis and was also associated with increased severity of psychosis.

The prevalence of clinical apathy in this PD cohort was found to be within the range of estimates (12% - 62.3%) reported in recent meta-analyses (den Brok et al., 2015; Mele et al., 2019), with 36% endorsing isolated apathy without depression. Our findings further support that

clinical apathy is not only common in PD, but can co-occur with psychotic symptoms, and is in fact more common among patients with *positive* symptoms of psychosis. Concurrent apathy appeared to be associated with more severe forms of psychosis, which might provide clues to the underlying neural substrates in pathogenesis.

Interestingly, we identified that endorsement of both psychosis and apathy (*mixed*-symptom) may be a specific behavioural marker of a worse outcome in PD, compared to the experience of either symptom alone. This finding is largely congruent with the known factors associated with poorer outcomes in PD such as impairment in the mood/apathy, sleep/fatigue, and cognitive domains (van Wamelen, Sauerbier, et al., 2021; Zhao et al., 2021) which are in line with the clinical associations of the *mixed*-symptom group in this study (*Table* 7.5).

With the removal of any potential influence of SSRI-induced apathy syndrome (Barnhart et al., 2004; Wongpakaran et al., 2007; Zahodne et al., 2012), as well as the possible effect of non-SSRI antidepressants and antipsychotics, our *post hoc* sensitivity analysis revealed little change in the results for the *mixed*-symptom group, which still endorsed a higher non-motor symptom burden, and a significantly reduced quality of life overall (*Table* 7.5).

Our findings need to be interpreted in the context of several important limitations. Firstly, this includes the cross-sectional design which does not allow for causality interpretations in any associations described. The use of NMSS to measure psychosis is not ideal, as elaborated earlier in Chapter 3 (page 116), as the single item question each for hallucinations and delusions of the NMSS are unable to capture the full spectrum of PD psychosis, and there is a narrow window for measuring clinical change. In addition, the self-rated Starkstein's apathy scale was used, without concurrent proxy-rated measures, which would likely introduce bias in apathy estimates. Our subgroup sizes were also unequal for comparisons. Nonetheless, the inclusion of a control

group and the standardised assessments offset some of these limitations. Moreover, we feel that our findings are clinically useful, and that the two cohorts represent real-world sample populations which provide a good platform for future research into apathy and psychosis in PwP.

7.6 Conclusions

In summary, clinical apathy is common in PD, and can exist independently of depression and psychosis. We identified a possible clinical phenotype comprised of mixed psychosis and apathy (or *positive* and *negative*) symptoms in PD which is associated with a poorer quality of life compared to others, although this will need verification in longitudinal studies. The clinical characterisation of neurobiological footprint of apathy in the *mixed*-symptom groups may provide the background for future studies to track the advancing dysfunction of neural networks resulting in more severe forms of PD psychosis.

Chapter 8
Conclusions & Future Perspectives

8.1 Overview

The research described in this thesis focuses on the clinical features of psychosis and apathy amongst patients with Parkinson's disease (PD) and aims to provide an in-depth analysis of their clinical correlates as well as associations with each other, in hopes to fine-tune a holistic approach to identify and manage both these debilitating neuropsychiatric symptoms. While the objectives may be too ambitious and beyond the scope of this academic project, I hope that it represents the first step towards building an international collaborative platform for research into clinical diagnostic or prognostic phenotypic biomarkers in PD, which may well encompass the array of neuropsychiatric symptoms. Such a foundation is possible with the resources and current work being undertaken by Prof. K. Ray Chaudhuri and his colleagues in London, as well as that by Prof. Eng-King Tan and his team in Singapore.

In Chapter 1, I provided an overview of the non-motor symptoms of Parkinson's disease, specifically that of psychosis and apathy in PD. In Chapters 2 and 3 respectively, reviews were conducted into the neuropsychiatric fluctuations in PD, as well as all existing scales used to measure psychosis severity in PD. In the latter, the psychometric attributes, strengths, and weaknesses of all such scales developed since 2008 were discussed.

These three chapters then provided the solid information background on which to introduce the Psy-PD in Chapter 6, a new instrument which I developed using standardised international scale validation guidelines, and accounting for the limitations of existing scales, with the guidance and experience of Prof. K. Ray Chaudhuri and his team at the King's Parkinson's Centre of Excellence in UK. The Psy-PD was analysed to be a feasible and reliable instrument for the comprehensive evaluation of psychosis severity in PD, with acceptable clinimetric properties.

Chapters 5 and 7 analysed data collected from the cohort studies that I conceptualized in UK and Singapore respectively, with appropriate comparisons made. In Section 1 of Chapter 5, I investigated for potential shared genetic risk variants between schizophrenia and bipolar disorder with PD by analysing four single nucleotide polymorphisms (SNPs) in a genome-wide association study (GWAS) of a local sample entirely in Singapore, to see if there was any modulation in the risk for PD in our cohort of Asian ancestry. Although no significant findings were found, the study still adds to the current genetic literature exploring the links between primary psychotic disorders and the neuropsychiatric disease of PD, with recommendations for future research.

Section 2 of Chapter 5 marks a unique and international collaborative research effort between UK and Singapore, where I investigated the influence of ethnic and geographic disparities on apathy in PD and demonstrated that no significant differences exist across the top three ethnic groups in London or in Singapore, although both cohorts endorsed clinical apathy overall. This finding further supports the notion that apathy is an intrinsic symptom of Parkinson's disease, which likely involves more non-dopaminergic disruptions.

The research described in Chapter 7 explored the differential clinical apathy burden among PD patients with psychosis in UK, their relationship with each other, as well as the associated impact on quality of life. The findings here showed that concurrent experience of *positive* (psychosis) and *negative* (apathy) symptoms are associated with poorer quality of life. The study also demonstrated that clinical apathy was associated with increasing severity of psychosis in PD, thus hinting at the overarching and intersecting neural circuits underpinning these two neuropsychiatric symptoms.

8.2 Conclusions

This thesis has demonstrated the challenges in the approach to both psychosis and apathy in Parkinson's disease, despite the devastating impact of both these symptoms on overall functioning and quality of life. I have introduced a novel, more comprehensive scale to assess psychosis severity in PD which is built on the limitations of existing scales. Future studies can be done in larger cohorts to further validate its utility and improve on its psychometric attributes. I have also demonstrated that psychosis and apathy are both independently common in PD, with their concurrent endorsement associated with a poorer quality of life. Finally, I demonstrated that clinical apathy is intrinsic in PD, irrespective of ethnic or geographical barriers. I hope that the findings from this academic endeavor can be used for future research to further our understanding of the neuropsychiatric symptoms of psychosis and apathy in tailoring a personalized holistic approach towards their identification and management.

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